Voice of the Patient Report

A summary report resulting from an Externally-Led Patient Focused Drug Development Meeting reflecting the U.S. Food and Drug Administration (FDA) Patient-Focused Drug Development Initiative

Spinal Muscular Atrophy (SMA)

Externally Led Public Meeting: April 18, 2017

Report Date: January 10, 2018

cure SMA

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The Voice of the Patient Report for Spinal Muscular Atrophy

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The Voice of the Patient

A report resulting from an Externally-Led Patient-Focused Drug Development Meeting corresponding to FDA's Patient-Focused Drug Development Initiative

Spinal Muscular Atrophy

Externally Led Public Meeting: April 18, 2017
Report Date: January 10, 2018

Hosted by:
Cure SMA

Submitted to:

Center for Drug Evaluation and Research (CDER) &
Center for Biologic Evaluation and Research (CBER)
U.S. Food and Drug Administration (FDA)

This report represents a comprehensive summary report composed by a patient advocacy organization as a result of an Externally-Led Patient-Focused Drug Development meeting; a parallel effort to FDA's Patient-Focused Drug Development Initiative. This report reflects the Cure SMA's account of the perspectives of patients and caregivers that participated in the public meeting.

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Introduction

On April 18, 2017, Cure SMA hosted an externally led Patient-Focused Drug Development meeting to share with senior officials at U.S. Food and Drug Administration and other SMA stakeholders (e.g., families, caregivers and individuals with SMA, industry and research institutions) the perspectives of people living with spinal muscular atrophy (SMA), its impact on their daily lives, and their expectations and priorities for current and future treatments for SMA. The meeting was conducted in accordance with the Agency's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systemically gather patients' perspectives on their condition and available therapies to treat their condition. In addition, the recently passed 21st Century Cures Act, has emphasized the importance of patient input in the regulatory process, mandating that regulators learn about which outcome measures matter to patients and to consider how patients weigh the balance of risks and benefits of a particular treatment. This meeting with the SMA community is the fourth externally led PFDD meeting to be granted.

More information on the FDA Patient-Focused Drug Development meetings can be found at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm.

Overview of SMA

Spinal muscular atrophy is a recessively inherited neurodegenerative disease caused by deletions or mutations in the survival of motor neuron 1 gene (SMN1). On average, one in every 50 people is a genetic carrier—and one in 11,000 infants is born with SMA (approximately 400 live births in the United States each year).

Most of the body's functional SMN protein is encoded by the SMN1 gene, the absence of which leads to progressive muscle denervation, axonal nerve deterioration, loss of spinal motor neurons and atrophy of skeletal muscle fibers. The clinical result is a debilitating and potentially fatal loss of muscle function, with deficits of mobility and weakness, as well as difficulty breathing, swallowing and, in some cases, speaking. The pattern of weakness is symmetrical, with proximal muscles affected first and to a greater extent than distal muscles. Muscle loss is progressive over time—often leading to loss of ambulation, and in severe cases, loss of fine motor skills. In the most advanced cases, loss of the control of most distal muscles, such as in the fingers—which are so important for using a computer mouse or to control one's wheel-chair—is jeopardized. There are also indirect consequences of skeletal muscle weakness, most commonly fatigue, orthopedic issues and bone health, may also become impaired. Individuals with SMA have normal cognitive abilities, however.

SMA is heterogeneous with respect to mode of inheritance, age of onset, achieved motor abilities, affected muscles, progression of the disease and survival. Given this heterogeneity, SMA has been classified into clinical subtypes based upon the age of onset (which is related to disease severity and survival) and the highest physical milestone achieved. The spectrum of severity has been associated with the copy number of the SMN2 gene, which is almost identical to SMN1 except that most of the SMN protein it encodes is truncated and rapidly degraded. While these 'types' of disease are not really separate entities, the burden of disease and the treatment and support needs of people with different subtypes of the disease (SMA type I and type II/III for the purposes of this meeting) are distinct and thus merit consideration on their own. Disease-altering treatments, such as the recently approved nusinersen, may alter the clinical presentation of SMA, as traditionally defined, by phenotype. With new evolving treatments for SMA, and access to newborn screening on the horizon to facilitate treatment, even pre-symptomatically, the traditional classification of this disease may need to be redefined, looking to copy number as a more accurate predictor of outcomes and highest function achieved.

SMA type I

Infants who have normal function at birth but who experience the onset of weakness before the age of six months are classified as SMA type I. They typically have two copies of the SMN2 gene (those with one copy of SMN2 are affected *in utero or at birth*). This is the most common type of SMA, affecting about 55 to 60% of people born with SMA. Most experience early morbidity and mortality. At the time of drafting this report, SMA type I was the number one genetic cause of death for infants. According to the Cure SMA database, the largest worldwide, 25% of patients currently living with SMA have SMA type I. Infants with SMA type I never achieve the ability to sit unaided, have severely reduced muscle tone and lose their ability to breathe and feed independently early in life.

SMA types II through IV

Infants and children with onset of weakness from six to 18 months of age and ability to sit independently are diagnosed as SMA type II. Roughly, 27% of those born with SMA are diagnosed as SMA type II. These individuals generally have three copies of the SMN2 gene. With proper supportive care, most people with SMA type II can survive well into the third or fourth decade. However, although they can achieve the ability to crawl and sit unaided, they never gain the ability to walk unaided. Independent sitting may be lost over time due to progressive muscle weakness. Because of this, most use a motorized wheel chair as an assistive mobility device.

Children with onset after 18 months of age and in their juvenile years, who acquire the ability to walk independently, typically have three or four copies of SMN2 and are diagnosed as SMA type III. Approximately 10-13% of those with SMA are diagnosed with SMA type III. Individuals with SMA type III reach most key developmental milestones, including ambulation, with muscle weakness developing over time. Fatigue is a hallmark symptom within this phenotype. Over time, most patients with SMA type III lose their ability to walk independently or require the assistance of walkers or scooters for mobility. Finally, about 1% of those diagnosed have an onset in adulthood and are classified as type IV. Typically, they have four or more copies of SMN2 and may see little weakness or loss of function until after the age of 30.

SMA treatment overview

This patient-focused drug development meeting had originally been planned to provide the FDA with patient perspectives on SMA treatment, partly in anticipation that the agency was going to be reviewing the new drug application of nusinersen (Spinraza™), the first pharmaceutical to attempt to address the underlying cause, rather than the symptoms, of SMA. Much to the satisfaction of the SMA community, the FDA approved the drug *before* the meeting—on the basis of solid data showing that it significantly improved motor function and halved the rate of mortality in treated patients with SMA type I.

The meeting took place almost four months after approval. However, while nusinersen has demonstrated benefit in infants and young children with SMA, it is not a cure for SMA. It likely will change the trajectory of the disease, but treated individuals will still experience many of the consequences of SMA; they will still be at risk of losing muscle strength and motor function, and will have ongoing unmet medical needs. In addition, nusinersen is intrathecally delivered, which presents challenges for administration.

With increased survival, there will be an increased need for multidisciplinary care from teams of specialists trained to manage SMA including neurologists, physical medicine and rehabilitation specialists, pulmonologists, orthopedic specialists, and gastroenterologists. Physical and occupational therapy, assistance with speech and swallowing, and respiratory and nutritional support are also key elements of helping people with SMA to maximize their functional ability. Mobility issues often require assistive devices or physical therapy regimens. Some individuals with SMA require support for breathing and

feeding, as well as pain management. Almost all individuals with SMA report the need to manage their fatigue and maintain stamina.

Future treatments may focus on improving muscle function, motor neuron survival and function, as well as developing other approaches and delivery methods to increase the levels of SMN protein. Treatments to address the secondary targets of SMN deficiency (skeletal muscle, bone or other systems) are also needed, which will not be treated with nusinersen.

Meeting overview

More than 400 individuals registered for the meeting (204 in person, 218 via webcast). Over sixteen members of the FDA attended the meeting to hear directly from the patients, caretakers, and other patient representatives about patients' experiences with SMA and the available treatments and management approaches. FDA attendees included Dr. Peter Marks, Director of the Center of Biologics Evaluation and Research (CBER), Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies (CBER), together with representatives from the Center for Drug Evaluation and Research (CDER), including Dr. William Dunn, Director of the Division of Neurology Products, and Dr. Jonathan Goldsmith, Associate Director for Rare Diseases, Office of Tissues and Advanced Therapies. The meeting also included presentations from clinical experts to provide a wider context on the mechanisms of disease and the experience of patients.

Approximately 50% (98) of the people who attended the in-person meeting were either individuals with SMA (17), or a parent/primary caregiver of a child or person with SMA (81). Of the 17 people with SMA in attendance, one was diagnosed with SMA type I, nine with SMA type II, and seven with SMA type III. Another 160 individuals with or representing people with SMA registered to attend via webcast. In addition, family and friends of people with SMA, and a broad cross-section of representatives from the pharmaceutical industry, academia and patient advocacy organizations also attended the meeting.

After an initial introduction, the first part of the meeting focused on the burden of disease and unmet needs in people with SMA and their families; while the second half of the meeting explored patient perspectives on current and future treatments, including treatment benefits they considered clinically meaningful and perspectives on how they balance the benefits versus risks of current and potential treatment options. Each topic was divided into two sessions, one on SMA type I and one on SMA type II/III, for a total of four panels, two on each topic.

Each session began with a table of panelists representing the spectrum of types, ages, and stages of SMA (there were twenty overall) who brought their voices and stories to depict the debilitating impact of SMA upon almost every aspect of their lives. Most panelists presented a slide show or video along with their narrative that helped to illustrate what it is like for the child and family to live with SMA.

After each round of panelists, a series of polling questions were posed to the participants at the meeting and, via a live streaming webcast, across the US and internationally; these were followed by a period of facilitated discussion. Participation in the polling questions was voluntary, and included a total of 144 respondents, 30 representing children with SMA type I, 69 for children or adults with SMA type II/III, and 45 individuals who did not designate their SMA type. The results were used as a discussion aid and to gain a better understanding of the full impact of the disease and should not be considered scientific data.

To supplement the input gathered at the meeting, Cure SMA posted a survey for patients and caregivers to provide additional feedback about their experiences. Eleven individuals completed the survey, including some from individuals who were physically unable to attend the meeting. Highlights

of the survey are integrated within the topic sections where they are pertinent and are further described in Appendix 4. Additionally, a Benefit-Risk Survey for SMA was sent out, fall 2017, to gain further insight as to how individuals and families with SMA would weigh different hypothetical benefits-risk equations that might come up during an FDA-review of new SMA therapies. The findings of the questionnaire were quantitatively analyzed and topline results are shared in the Benefit-Risk section, and the full survey and findings shared in Appendix 5.

Report overview and key themes

This report summarizes the input provided by the patients, and caregivers during the meeting. It also includes a summary of comments submitted to the post-meeting survey. To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences reflect the words used by in-person participants and language used in submitted survey responses. There may be symptoms, impacts, treatments, or other aspects of SMA that are not included in the report. This report follows the structure of the meeting.

Topic 1: Burden of disease in SMA

The first section focused on the burden of disease in SMA. Several key themes emerged:

- SMA is a devastating and debilitating disease—life-threatening in individuals with SMA type I and II—with a wide range of symptoms and complications that can have detrimental effects on the day-to-day life of people with SMA (regardless of type) and their families.
- Muscle weakness and immobility in an infant with SMA type I are painfully conspicuous, often causing parents to seek out diagnosis within the first six months of life, and leading to the child's complete dependence upon them. Once caregivers come to terms with their child's diagnosis, life-threatening respiratory symptoms (such as difficulty breathing, inability to clear secretions, lung infections and respiratory failure) become over-riding concerns and require constant vigilance to keep airway passages clear and dependence on equipment for survival. Historically, only about 20% of children with SMA type I live beyond two years. As children grow, communication difficulties are very common, making the tasks of caregiving more challenging. Difficulty swallowing forces families to make difficult decisions weighing the risks and benefits of surgical interventions such as gastrostomy tubes and tracheotomy.
- Severe scoliosis is very common in individuals with SMA type II (though it can also occur in individuals with SMA type I who survive childhood and some people with SMA type III who experience early disease progression). Scoliosis emerges in nearly all non-ambulatory SMA patients with severe progression, and it remains one of the major problems for orthopedic therapy in SMA. In severe cases, scoliosis can make it extremely difficult to sit without pain and may interfere with normal breathing. Consequently, many children and young adults with SMA have multiple surgeries to implant growing rods that prevent scoliosis and spinal fusion to correct it; post-surgical infections, and wound complications are not uncommon among many who undergo these procedures. The time spent in the hospital presents other risks to the health of these individuals, and takes time away from their school and social lives.
- Additionally, the development of upper and lower extremity contractures, largely due to limited motion, is experienced in most patients with SMA types I and II, and in type III patients who are non-ambulatory.
- Young adults with SMA type II attending the meeting shared their passion for life despite dealing with severe limitations on physical activity and their ability to independently perform activities of daily living. A constant worry for anyone with SMA is further losses of functional ability—with the loss of ambulation being a pivotal event in the lives of those with SMA type III.

- Caregivers described the delay and trauma of receiving a diagnosis of SMA for their child, and then adjusting to the burdens of managing complicated medical care and equipment at home. They spoke of their fear of respiratory complications, particularly in children with SMA type I, and the threat of imminent death. SMA has profound economic, emotional and psychosocial consequences on individuals, caregivers and families. Having and caring for a child with SMA type I or II can be more than a full-time commitment that involves careful planning of events for the child, and scheduling of therapists, nursing help and night-time help.
- People with SMA type II and type III described how they strategize and reserve energy to get through the activities of daily life, as well as their efforts to retain as much independence as possible for as long as possible. Both those with SMA type II and SMA type III described how an ever-increasing amount of effort was required for simple actions, making fatigue a constant part of their lives.
- For caregivers as well as patients, anything that increases or decreases the child's or individual's independence is acutely meaningful.

Topic 2: SMA patient perspectives on Treatment Options

The second section of the meeting focused on SMA patient perspectives on current and future treatment options. Although patients receive extensive treatment and care to manage the symptoms of SMA, prior to first FDA-approved treatment for SMA, nusinersen (Spinraza™), approved on December 23, 2016, there were no therapies available to treat the underlying cause of the disease. Several key themes emerged from this section of the meeting:

- There is a sense of optimism about an FDA-approved treatment for SMA that improves survival and leads to some gains in strength and function, though it is expected that some disease symptoms will still exist in treated individuals. In fact, in clinical trials with nusinersen, 32% of infants with SMA type I still reached the combined endpoint of death or permanent ventilation and only 51% achieved greater motor function (compared to zero in the placebo). In addition, SMA type II patients had a 4-point increase on the motor function scale in clinical trials, which, though significant, still only represents gaining about 2-4 (partially scored) items on a 33-item scale. Patients in the control group lost one point on average.
- Although the new drug is approved for all people with all types of SMA, the intrathecal route of administration, cost, lack of trial data, and lack of clinical expertise using the treatment in adults can limit access to treatment for some individuals with SMA.
- Management of the consequences/symptoms of SMA requires multidisciplinary care and multiple medical and nondrug supportive care therapies, surgical interventions, braces and equipment. Much time was devoted to discussing these interventions that patients undergo to alleviate or manage the most debilitating symptoms (respiratory failure, dysphasia, secretion clearance, contractures, etc.), provide comfort and improve quality of life. However, administering and/or receiving these treatments can be quite burdensome, uncomfortable and time-consuming for both patients and caregivers. Furthermore, these treatments only help to manage the symptoms and clinical consequences but not the underlying causes of SMA (decreased SMN protein levels and motor neuron loss that leads to muscle denervation and atrophy).
- In light of nusinersen treatment, caregivers to children with SMA type I expressed a desire for future treatments that lead to increases in strength and functional ability, even if those gains are small. Small changes that provide greater independence in activities of daily living are also hugely significant to children and adults with SMA type II/III—but safe treatments that simply stabilize the disease course and prevent further functional losses would be valued as well.
- Caregivers and patients expressed a heightened interest in clinical trial participation, due in part to

the positive experiences in the nusinersen and gene therapy trials. However, trial designs will likely be altered by the approval of nusinersen, depending upon the population. For instance, trials for those with SMA type I benefitting from nusinersen may require a standard-of-care arm rather than placebo, and there is considerable interest in trial designs of combination therapy comparing new treatments added to the standard of care (nusinersen) to the standard of care alone. If the benefits of treatment prove to be more limited in patients with SMA type II and III, it may be possible to conduct randomized- or even placebo-controlled trials of new treatments.

Benefit-Risk overview

In a departure from other Voice of the Patient reports, a section is included before the conclusion summarizing the benefit-risk findings of the meeting and the topline findings on a Benefit-Risk (B-R) Survey conducted after the meeting, to gauge the tradeoffs that patients and caregivers with SMA would make when considering the benefits (clinically meaningful outcomes) versus the risks of a given therapeutic. In brief, the Benefit-Risk survey results may reflect the current optimism of the community regarding the newly approved treatment for SMA. In a context where treatment is expected to produce clinically meaningful benefits with a low risk-profile, there may be less of a tolerance for taking major risks to access other potential treatments that may become available. As more experience is gained on the limitations of existing treatment, across the entire spectrum of SMA, and specific sub-populations identified who may be refractory or intolerant to treatment, it is expected that perceptions about risk- benefit may shift.

Finally, the appendices include the meeting agenda, polling questions, the post-meeting questionnaire and B-R survey results and other materials. Additional information on the meeting has been posted on the Cure SMA website: http://www.curesma.org/news/sma-voice-of-the-patient.html. The archived webcast has also been posted online: https://www.youtube.com/playlist?list=PLQVcp9RApBmwvAJJHkIBkUsUV_xlqxeFf.

Topic 1, SMA type I: Most significant symptoms and their impact on daily life

The first discussion topic focused on the experiences of caregivers and the patients with the symptoms of SMA type I as well as the impact and burden of the disease upon their daily lives. The session began with a panel of four parents (and caregivers) to children with SMA type I, and included:

- Panelist 1: "*Time is not a luxury*," said the first panelist, father of a thirteen-month-old girl with "*an infectious smile*." He had become concerned about his daughter after he witnessed her missing key developmental milestones, such as holding her head up and rolling. Now, she is completely dependent on her parents to eat, breathe, manage her secretions, and move. He said that she has recently started on nusinersen and that he was hopeful that it will help her achieve some gains in function, however small.
- Panelist 2: "*Her protection and care are who I am now*," said the second panelist, a one-time pediatric registered nurse who now spends all her time caring for her three-year-old daughter with SMA. Despite her considerable expertise as a professional caregiver, anxiety over risks posed by infections to her daughter's life and "*anticipatory grief*" have been overwhelming at times, to the point where she has developed post-traumatic stress disorder.
- Panelist 3: The third panelist, mother to a three-and-a-half-year-old boy said that ever since a near-death experience, her son requires an around-the-clock team of home-care nurses and a full schedule of in-home therapy, though her son's life-threatening respiratory infections have decreased since he had a tracheotomy. "*We make endless adaptations*," she said, including acquiring a 'telepresence' robot that he uses to attend pre-school.
- Panelist 4: "*You have to be your child's greatest advocate all the time*," said the final panelist, mother of a seven-year-old boy. This mother shared a video of a day in the life of her son who is unable to breathe, eat and swallow without supportive equipment. He has lost almost all ability to move, with the exception of his eyes, and cannot speak to communicate his needs.

The panelists painstakingly recounted how this severe form of SMA had mercilessly robbed their children of the strength and ability to move, eat or breathe unassisted. Parents also emphasized the all-consuming nature of caring for a child with SMA type I, and the tremendous physical, emotional, psychosocial and financial burdens tied to providing full-time care to children who are entirely dependent upon them for care. The need for special medical equipment, mobility aids, and home adaptations that allow patients with SMA to live and participate more fully in everyday life, also contributes to the financial burden of managing SMA.

These themes were reiterated during the facilitated discussion (and in responses to the post-meeting questionnaire) by other meeting participants. More than one shared how they watched helplessly as their children first failed to reach simple developmental milestones and then lost what little muscle strength was left. Some had lost children to the disease. Their testimonials are summarized below.

SMA type I: Perspectives on symptoms that matter most to patients and their caregivers

In a polling question before the wider group discussion, (Appendix 3, question 11), participants at the meeting and online were asked to identify up to four symptoms that currently have the most significant impact on the lives of patients, their caregivers and family.

Although SMA results in an evident loss of strength and mobility, the symptoms that caregivers and patients were most worried about represented threats to the ability to breathe, eat or swallow and communicate. Nonetheless, muscle weakness and related loss of mobility affected both patients' and their caregivers' lives in multiple ways. (Full polling results can be found in Appendix 3.)

A. Respiratory Symptoms

"Keeping him breathing is priority number one"

Taken as a whole, the respiratory complications of SMA were the most distressing to the caregivers as these could very rapidly lead to death. For children with SMA, the weak muscles in the upper chest (intercostal muscles) make breathing extremely difficult. As a result, they can have a number of respiratory problems including lung underdevelopment and weak cough; increased difficulty with infection, including viral infections and pneumonia; swallowing problems and aspiration; and sleep problems with hypoventilation.

- **Breathing difficulties:** Respiratory problems are the leading cause of illness for children with SMA. There can be a range of breathing disorders in children with SMA type I, ranging from rapid 'belly' breathing (tachypnea) to weak or shallow breathing (hypoventilation), typically during sleep.

  "*When he was first born, I thought he was having trouble breathing*." Obsessing over their child's respiratory distress typically becomes a constant worry: "*You've got your daily stresses of 'is my child breathing?'"*

- **Inability to cough/clear lung secretions:** The weak intercostal muscles in children with SMA type I make it very difficult for them to cough and clear their own airways of mucus secretions that obstruct breathing. Caregivers said that the clinical consequences of this disability can quickly override other concerns:
  "*We went from fearing our daughter would never dance, play a physical sport or even walk. Now we fear our daughter might not be able to cough up her own secretions*."

  One of the panelists provided a graphic example: "*One evening our daughter stopped breathing. Her pulse oximeter numbers dropped to dangerous levels. I flipped her over… and began working her body to get her to start breathing. Thankfully, the mucus plugging her lungs leaked out and she began breathing again. Sadly, less than a few days later, we were not so lucky and had to call 911*."

- **Respiratory failure requiring assistive devices:** Eventually, the respiratory muscles become too weak to sustain a child's breathing particularly when there is an obstruction. In one case: "*Another plug had formed, one we could not remove. With her already weakened state, we chose to intubate her so that we could transfer her to specialized doctors in Chicago. This was the last time she was able to breathe without the help of a ventilator*."

- **Respiratory infections:** Caregivers described how viral or bacterial respiratory infections are a grave threat to children with SMA type I and, as such, must be avoided fastidiously. "*What is only a cold to others may cause him to need respiratory treatments every four hours or a week-long hospital stay, or worse. Before any visitors are allowed to come into our home, we require that their entire household be free from illness."* Said another: "*A cold for our daughter means around the clock treatments, a potential weeks-long PICU stay, strength loss and worst of all, it can mean respiratory failure and death.*"

B. Feeding/ swallowing difficulties

"The most crippling symptom is his inability to swallow. It turns simple [activities] into choking threats."

For infants with SMA type I, difficulty eating may begin shortly after birth with poor latching and tiring during breastfeeding. Difficulty swallowing (dysphagia) may follow, which can increase the risk of choking and aspiration of liquids or food into their lungs. In addition, food and saliva that have not been properly swallowed may be inhaled and introduce bacteria into the lungs, increasing the risk of respiratory infections.

As children become unable to tolerate oral feeds, the placement of gastrostomy tube becomes necessary for nutritional support and to prevent the risk of aspiration. *"Our son has lost his ability to swallow, so he is strictly tube-fed. He's fed through a G-tube, which is inserted in his stomach*."

Children with SMA type I who survive infancy may sorely miss the ability to eat. During the discussion session, one caregiver described how her granddaughter with SMA type I was so obsessed with food that she would ask to watch her grandmother eat: "*I've always wished and prayed… that she could get her swallow back."*

C. Muscle weakness leading to complete loss of mobility

"He has lost a lot of strength since his diagnosis [including the] ability to move his arms… The bigger your child gets, the weaker he gets."

The hallmark of SMA is progressive muscle weakness that prevents the development of, or leads to, rapid progressive functional loss that robs children of their mobility. In some infants who were normal at birth, SMA type I presents precipitously, with low muscle tone (hypotonia) and weakness. This is followed by a predictable overall decline in motor function. Some of the parents of SMA type I children at the meeting reported observing these symptoms at birth: "*Right at birth, he did not come out kicking and screaming. He did not move a lot. We were told that he was just a floppy baby and that he would outgrow whatever he had."*

Others remarked noticing their children were too weak to reach the earliest developmental milestones: "*She wasn't getting into the crawling position and having enough strength in her legs to hold a standing position like regular, typical babies do at around five, six months."* Another caregiver said his daughter "*was missing simple milestones, such as holding her head, rolling over and crawling. She hated tummy time, screaming and crying, never looking to turn her head. Her whole body would only go limp, especially in her legs."* Early signs of weakness are first observed in the neck: "*When my son was one month old, we noticed that he couldn't lift his head during tummy time.*" Another family said they watched their son lift his head only once, and then, never again.

Over time, weakness extends to the muscles of the face. Parents were unequivocal about the pain of watching their children with SMA type I gradually lose their smile*: "I had watched her lose the ability to eat, talk, move… and eventually her smile, which was incredibly difficult."* Another said: "*Her muscles continued to atrophy at rapid pace, and she'd even lose her ability to smile, as SMA would rob that too."*

D. Communication difficulties

"I hope that one day he may have the muscle dexterity to speak."

Due to the severe muscle weakness and other factors not fully understood, many children with SMA type I never speak, and thus, have difficulty expressing their needs or feelings to their caregivers and the world around them. In response to a polling question (Appendix 3, question 11), 72% of SMA type I meeting participants selected the inability to communicate as one of the most significant symptoms of the disease.

The inability to speak is a source of worry and frustration for both caregivers, and the child. According to one panelist: "*Our son doesn't articulate words but he can vocalize syllables with proper inflection. I try to translate the best I can."* One caregiver wrote in the post-meeting survey that the inability to *"adequately communicate needs and desires" limited social relationships for their daughter.*

E. Other symptoms

During the discussion, a few caregivers mentioned some other symptoms that can occur in children with SMA type I who survive to an older age such as scoliosis and difficulty drawing blood.

SMA type I: Impact on daily life of patients and their caregivers

Throughout the session, participants discussed the consequences of the disease on their child's daily life, as well as the exhausting daily routine to keep children with SMA type I alive and comfortable. This, as one caregiver said had "*taken a toll on our family financially, emotionally, and socially*." Another parent stated, "*sleep is also sparse, as our daughter requires frequent turning and positioning. As you can imagine, we are very, very tired."*

A. Complete Dependency

"She requires 24/7 one-on-one care… 365 days a year."

Children with SMA type I are entirely dependent upon their caregivers to meet their most basic needs—to breathe, eat, move, communicate and perform any activities of daily living. In a polling question (Appendix 3, question 12), caregivers and patients were asked to name the four most important activities to them or their loved ones or that the child was unable to do because of SMA type I. The most common responses were the lack of independence and mobility (as perceived by most caregivers) followed by not being able to feed oneself, to engage in social activities/build relationships and or to spend time alone/be independent."

Some parents stressed that they can never leave their child unattended: "*Because they can't move for themselves, you really have to have an eye on them at all times, so that means your eye can't be on anything else.*"

One parent of an infant with SMA type I remarked, "*Our greatest fear is [that] we won't be able to give [her] the life that she and all other SMA children deserve a life of independence."* Another said: "*About a third of our day is keeping him alive. The rest focuses on teaching him how to live as completely and as independently as he can.*"

B. The psychosocial and emotional impact on patients, caregivers and family:

"A lot of parents, like us, need intense therapy and counseling to move through this, but it's expensive and not covered by insurance."

Another polling question asked patients and caregivers about their psychosocial experiences trying to cope with SMA in their family (Appendix 3, question 13). The top responses were anxiety, depression and social isolation; however, quite a few caregivers also had troubled relationships or were unable to maintain employment as a consequence of caregiving. Several participants in the discussion characterized what they were experiencing as either post-traumatic stress disorder or 'anticipatory grief.'

- **Post-traumatic stress disorder:** Some meeting participants said they were traumatized by their child's diagnosis, repeated respiratory arrests, and, in some cases, their child's near-death experience. The diagnostic journey itself caused prolonged distress. One caregiver described as "*a long road of trying to convince doctors that something was wrong and they did not believe us."* Getting the diagnosis sometimes took months; and then, once they received the diagnosis, they were given absolutely no hope. Caregivers were told things like: "*Take him home; love him; take a lot of pictures. There's nothing you can do."*

  The distress resulting from the diagnostic journey is followed by traumas dealing with recurrent respiratory arrests and other life-threatening emergencies. One parent noted how, after one respiratory crisis: "*My son had to be emergently intubated and resuscitated with CPR and three shots of epinephrine. Two days later he got his [tracheotomy] and G-tube. My son's near-death experience showed me just how quickly he could be overwhelmed if his respiratory system is compromised or if he is left unattended."*

- **Depression and 'anticipatory grief':** Many parents and caregivers spoke of the difficulty coming to terms with lost expectations and unrealized dreams they once had for their child. Others described the sorrow caused by their constant fear of losing their child at any time as 'anticipatory grief.'

- **Anxiety/fear:** As one parent explained: "*I leave the house every day in fear that I might come home and my son might not be there. That is a fear that I've had since diagnosis."* One father stressed that his daughter's previous respiratory emergencies taught him to be anxious; now: *"Any time [her oxygen levels] dip lower even slightly, anxiety and fear begin to take hold that another mucus [plug] event could take her life."*

- **Isolation and other impacts on relationships: "***Life as an SMA family can be very lonely and isolating*," one panel member said. When children become dependent upon equipment, "*It's hard to leave the house."* A constant consideration, again, is the risk that the child might pick up an infection: *One caregiver said she was "so worried about illness and that's keeping us very isolated."* Sometimes, these concerns lead caregivers to take what their family sees as drastic measures to keep their child safe: "*One holiday, we cut short a large family gathering because a cousin started coughing. We sent them all home."*

- **Inability to work/keep a job:** The time commitment required for care and taking their child to appointments—roughly 62% of polling respondents reported taking their child to care more than 10 times a year—makes it difficult to keep regular employment. According to one panelist: "*Hours were put into finding the appropriate doctors and specialists. Countless days and missed work and scores of hours lost to health care visits take their toll."* Another said: "*I am unable to work, as good quality nurses are hard to come by and filling nursing hours is nearly impossible*."

C. Good day/bad day

"Your best days and your worst days are sometimes the very same day."

Some meeting participants described what constituted a good versus a bad day for their children with SMA type I. According to one of the panelists, a good day is when *her child's "extensive morning routine" of treatments and therapy go well. "On a bad day, he has come down with a cold or allergies. Allergy season gives us a lot of bad days, airway clearances that we normally do every two to three hours have to be done every 15 minutes around the clock, in order to help clear out his lungs of any mucous, to clear out the airway.*"

According to another caregiver, "*Your ideal day is a nurse showing up on time; your night nurse showing up, so maybe you got a few hours of sleep. The physical therapist showing up, and just being able to see small gains—just little things. A bad day: anything as tragic as a hospital stay or having to call 911 is devastating. It affects every aspect of your life from work to your relationships. And then, just seeing your child struggle and you're helpless.*"

One caregiver in the audience with two grandchildren with SMA type I said "*My worst day was when I've had to revive one of them twice and one of them once."*

D. Financial and insurance issues

"It's all about the kid. You will do anything at any cost for that child."

Particularly as new treatments are being approved, insurance and payer issues are becoming increasingly important. In response to a polling question, almost half of the caregivers of SMA type I patients said that they currently have private or commercial health insurance, 41% have Medicaid and 11% have Medicare. But there are also out-of-pocket costs associated with the medical care and equipment that children with SMA type I need for day-to-day life. In response to a question about the estimated annual SMA-related

expenses or costs that patients or their families pay directly, including co-pays, deductibles, for prescriptions, medical supplies, adaptive vehicles and mobility devices, a third said that they were spending between $5,000 to $14,999 annually, but another 10% were paying between $15,000 to $19,999, while another third were paying between $20,000 to $49,999 per year.

Topic 1, SMA type II/III: Most significant symptoms and their impact on daily life

The next session focused on the experiences of patients with SMA type II/III and their caregivers, with descriptions of the symptoms of the disease and the impact it has upon their daily lives. A much larger percentage of type II/III SMA survive childhood, but they then must deal with the gradual loss of strength, energy and functional abilities. Wheelchairs are part of life for those with SMA type II, while the loss of ambulation is a critical milestone for SMA type III patients. The voices of both ambulatory and non-ambulatory cases were heard in this session, launched with the testimonies of two caregivers, and four individuals with SMA type II or type III:

- Panelist 1: "*Perhaps the most difficult part of life with SMA is the unknown of it all*," said this caregiver who represented two children: one, a three-year-old son, living with SMA type II and, the second, a five-year-old daughter with SMA type III. Her daughter took steps but never walked—on her best days now she can climb up and down stairs. Her brother is somewhat weaker and needs more support, especially when ill. "*The loss of strength is basically our only guarantee. We're anticipating another period of decline to come*," she said.
- Panelist 2: "*One day when [our son] was about five months, he stopped meeting his milestones,*" said the second panelist, a mother to a thirteen-year-old boy with SMA type II. About a month later, her son was diagnosed with SMA described as being on the spectrum between a strong type I, or a weak type II. At the time, she and her husband were told that he might not live past the age of two. "*We have seen him stop breathing and watched his heart stop several times. I can never let down my guard,*" she said.
- Panelist 3: "*The biggest thing I've had to deal with is the degenerative aspect of SMA*," said the third panelist, a 23-year-old man (and recent college graduate) with SMA type II. He spoke about how the disease was robbing his strength and making it difficult for him to perform basic tasks, such as eating or drinking. Despite physical challenges, this young man is an accomplished writer who has "*never allowed SMA to keep [him] from fully living [his] life.*" However, he fatigues, and said "*there are times when I feel like a burden to the people I depend on. I felt like both my parents and I were trapped*."
- Panelist 4: A 29-year-old ambulatory woman with SMA type III served as the fourth panelist. She said that she was always aware of her weakness and lack of coordination, but wasn't diagnosed until the age of 10. Now she deals with "*unpredictable fatigue that can last a few days or even weeks*" and fears having a hard fall that might break her bones and lead to increased muscular atrophy. She also spoke about her personal struggles with the stigma that society holds against people with disabilities.
- Panelist 5: "*Having SMA requires me to have additional planning, structure, support and time to my daily routine,*" said the next panelist, a 42-year-old man with SMA type III. Although he can still walk short distances, he increasingly needs assistance from family, co-workers or strangers. Now it requires additional planning, structure, support and time to get through his daily routine. Travelling can be very difficult: "*I often have a lot of anxieties. I think about the unknowns I may encounter,*" he said.
- Panelist 6: "*While having SMA is a very constant experience, there are little subtleties that can completely change the trajectory of my day,*" said the final panelist, a 29-year-old woman with SMA type II. Though she is completely dependent on her caregivers for all the activities of daily living, she "*has a life full of love, traveling, and rewarding work*." Although she worries that further muscular degeneration could rob her of all that she enjoys—even her life—she looks forward to cutting the cake at her upcoming wedding.

Panelists explained how various symptoms of SMA can develop with age and impact them or their loved ones. Many of the panelists described the unrelenting progressive loss of function that they or their loved ones had experienced. Others described feeling like they had achieved a 'plateau,' only to realize that they had been experiencing almost imperceptible but cumulative losses that were noticeable to friends over time. In some, surgeries, bad falls and other life changes had precipitated unexpected health crises such as a sudden life-threatening loss of weight. Participants online and at the larger group meeting communicated further experiences adding complexity to the picture of how SMA can present and evolve over the years across the wide spectrum of disease.

SMA type II/III: Perspectives on symptoms that matter most to patients and caregivers

A polling question (Appendix 3, question 11) asked participants to identify up to four out of a list of symptoms that currently have the most significant impact on their lives. By far, the two most common responses were fatigue (71.6%) and muscle weakness (66.7%) followed by joint contractures (tight muscles and tendons) and/or severe scoliosis—although, if taken together, respiratory related symptoms were also commonly selected. A number of respondents also noted that symptoms such as falls and sleep problems significantly impacted their lives. The range of symptoms discussed by panelists as well the participants in the larger discussion is described below.

A. Fatigue

"Most recently, I have experienced long periods of fatigue that make me feel as if every muscle has a 100-pound weight attached to it."

As the muscle weakens, activities require ever greater exertion, which leads to increasing fatigue that make it difficult to perform normal tasks. As one caregiver reported, her ten-year-old daughter with SMA type II would sometimes grow too fatigued to eat: "*She's dying to eat but she is just too tired."* Even the simplest tasks can become ordeals, as one panelist with SMA type III pointed out: "*Something simple like doing laundry becomes a draining and exhausting task. This unpredictable fatigue can last a few days or even weeks and it's probably the most debilitating part of my disease*."

B. Muscle weakness (affecting mobility and functional abilities)

"The loss of strength is basically our only guarantee."

Muscle weakness in SMA can manifest in a variety of ways throughout the body, spreading out from the muscles proximal to the spinal cord and increasing until even the most distal muscles are affected. According to one audience member with SMA: "*For five years, you are using 80 percent of your muscle strength to do one task; and then the next five years, you're using 90 percent. [Finally, a point is reached when] we can no longer perform that task [which] could be walking or lifting an arm."*

- **Loss of upper body strength:** As one panelist said: "*Immobility might seem like the most obvious or the most impactful effect of SMA—to me that's just life. What does stand out is the complete lack of strength in my upper body and my core.*" Another agreed that lack of arm and upper body strength was *"more of a burden than my inability to walk. Before I started to lose it, I didn't even think much about my disability. Now I exert massive amounts of energy just moving my arms a few inches."* This affects activities essential to life and spirit, as one 14-year-old young woman stressed: "*Every single time I attempt to eat a bowl of soup or reach my canvas while painting a picture, I know I am getting weaker."*

- **Problems with balance:** A young woman with SMA type III, still able to walk, said that her ability to balance herself, once secure, "*now leaves me feeling as if I am standing on the top of the Eiffel Tower ready to fall at any moment*."

- **Problems with mobility:** Although individuals with SMA type II achieve the ability to sit, and may be

relatively mobile in their wheelchairs and power chairs, many places are not wheelchair accessible, and it can be very difficult to travel with or navigate their environments.

For individuals with SMA type III, threats to their mobility become pronounced over time. For instance, a young woman with SMA type III, who was still ambulatory, said that she had reached all of her milestones early. "*There was a time I could walk more than a half of a mile without my muscles giving out*," she said, but not any longer. Some people lose ambulation with disease progression and must adapt to using a power chair/wheelchair for mobility. Others can still walk for short distances or with aid of mobility devices (such as a cane, scooter, etc.) as adults—but need to strategically plan how they will get from point A to point B ahead of time.

- **Difficulty chewing/smiling:** Muscular atrophy can spread from the neck to the jaw and the face. One panelist—a mother of a seven-year-old boy with SMA type II—said that, in an effort to compensate for the gradual loss of jaw strength, her son uses his arm to support his chin and to help himself chew.

C. Joint contractures (tight muscles and tendons) and/or severe scoliosis

"Contractures and scoliosis are central factors that affect the quality of life of a person with SMA."

Joint contractures and/or severe scoliosis were the third most commonly selected category of symptoms currently having the most significant impact on respondent's lives. However, the experiences of ambulatory and non-ambulatory patients differ significantly with regards to these complications. Joint contractures in the hands and wrist can make it difficult to use anyone's hands and fingers, while contractures in the ankle or leg can increase the risk of falling in the ambulatory. Contractures in the hip may make it difficult to stand or make it painful to sit in one's wheelchair. As one panelist with SMA type III noted, "*the muscle contractures and twitching have also gotten worse over the years with no solution or relief."*

Scoliosis was emphasized by individuals with SMA type II (or their caregivers) as one of the most serious complications with which they must contend. As muscles in the back grow weaker, the spine can begin to curve very rapidly, making it difficult to sit in a wheelchair, and, sometimes, making it difficult to breathe. In response to another polling question (appendix 3, question 18), about half of the meeting participants with or representing those with type II or SMA type III had undergone scoliosis surgery (the majority of these were likely to be type IIs). Elaborating on this, one meeting participant with SMA type II said that she had been having a lot of pain that her doctors dismissed, but when they finally sent her for an x-ray, it revealed that she had "*a 90-degree curvature in my lower spine and somewhere between 45 and 50-degree curvature in my upper spine. My spine was literally bent into an 'S' [shape]."* She and similar cases required, often, multiple surgeries. Some caregivers also reported proactively choosing for their children with SMA type II to undergo surgeries to insert growing rods to keep the child's spine straight, while others only went for or planned to have surgeries after scoliosis developed. These surgeries, including spinal fusion, often cause their own complications—including making it difficult or impossible to receive Spinraza™, which is intrathecally injected (see Patient perspectives on treatment).

D. Respiratory Symptoms

"Another symptom that has a severe daily impact for me is the respiratory weakness."

- **Breathing difficulties:** Some weaker children with SMA type II may lose the ability to breathe on their own when they are as young as two years old and require tracheotomies and ventilators. In older patients, scoliosis, weight or muscle loss can make breathing difficult. One participant said that when her weight had fallen under 50 pounds, "*the toll that took on my body and the fatigue that I felt—it was a struggle just to breathe.*"

- **Inability to cough/clear lung secretions:** Caregivers of weaker children with SMA type II also described how life-threatening the inability to clear lung secretions could be. One said she almost lost her son many times when he would "*choke on his own secretions and stop breathing."* Even older individuals with SMA type II can have challenges coughing: *"I need physical help because I don't have the strength to cough. My mom or somebody [has to] push on my stomach,"* said a young woman with SMA type II during the discussion.

- **Respiratory failure requiring assistive devices:** Many of the patients had had respiratory failure and need assistive devices such as BiPAP, ventilators, etc., (see treatment section), particularly while sleeping or during episodes of respiratory infection.

- **Respiratory infections:** People with SMA type II are also at risk for respiratory infections. One caregiver spoke about how her daughter "*was hospitalized from a cough. She never had a fever. She had a cold. She ended up hospitalized with a bronchoscopy and we left with a G-tube*." Another said, "*We have seen our son stop breathing and watched his heart stop several times when he has had the flu and RSV.*"

  One of the panelists, a woman with SMA type II, said that this had happened to her once when she was 11 after surgeries and weight loss led to a respiratory distress situation: "*I basically died at my best friend's house at her garage sale down the street. I had the whole 'out-of-body' experience and everything*."

E. Other symptoms: Panelists and participants at the meeting listed other significant symptoms, including falls and fear of falling: *"I used to be able to get up and walk up and down stairs but haven't been able to since I broke my leg 8 years ago from a fall that was a result of my leg strength,*" said a panelist with SMA type III. Pain is also a complaint, caused by contractures, scoliosis, improper positioning, or sores from being on a spot for too long. "*Improper positioning leads to unbearable pain in my hips and pressure points under my elbows,"* said a panelist with SMA type II. A 14-year-old with SMA type II added, *"Every day I am in pain and recently it is getting worse."*

SMA type II/III: The daily impact on patients and their caregivers

Individuals with SMA type II and type III represent a very diverse population with different functional abilities. Nevertheless, they all must deal with the effects of muscular degeneration in their bodies on a daily basis. Many individuals with SMA type II, and some non-ambulatory patients with SMA type III, have grown accustomed to using wheel/power chairs, but are gradually losing upper limb mobility. Other people with SMA type III are struggling to maintain the ability to walk, though those who present symptoms after 18 months and before three years of age, typically lose the ability to walk earlier than those who present after three years of age. Caregivers and patients from across the spectrum of SMA type II/III provided rich details about the impact of the disease on their daily lives.

A. Decreasing functional abilities and the loss of further independence in activities of daily living

"The littlest of tasks are monumental."

In one polling question (appendix 3, question 12), caregivers and patients were asked to name the four most important activities to them or their loved one with SMA or that the individual was unable to do because of SMA type II or III. The top response was being able to go to the restroom by oneself. Other very common responses included the ability to transfer (to and from wheelchair/scooter to bed or toilet) by oneself, being able to turn in bed, the ability to dress oneself, attend to personal hygiene independently, go to school and engage in physical activities. However, a very wide range of daily challenges to the independence of people with SMA were highlighted in the larger group discussion.

- **Being able to go to the restroom by oneself:** A number of ambulatory people with SMA type III said that the loss of the ability to use the toilet by oneself was one of their greatest fears, while others who had already lost mobility and other functional abilities highlighted toileting as being particularly important. Many with SMA type II lose the ability to go to the restroom alone while they are quite young: "*Toileting is near impossible since he has gotten bigger.*" Some caregivers noted that this was a great source of humiliation for the children. One said her six-year-old daughter would cry when she had to ask someone at school, *"for help wiping herself after toileting."* Another said, "*She says, 'I'm sorry,' every time she asks for help to go to the bathroom*."

- **Being able to transfer (to and from wheelchair/scooter to bed or toilet) by oneself:** Several times a day, many individuals with SMA depend upon someone to help them transfer, although some patients lose this ability earlier than others. As a caregiver to one 14-year-old boy with SMA type II noted *"as soon as puberty hit, it was like he was physically a different kid. [He had been] able to help bear weight a little bit but within two years he was unable to transfer himself. Just getting in bed and moving around in bed had become more difficult."*

  Even a person with SMA type III who is still ambulatory may need help transferring from a seated to standing position. For instance, one male panelist with SMA type III noted challenges getting up from chairs and desks but highlighted how this affected his ability to use the restroom: *"When I get up for work, the first thing I do is use the bathroom because I know that I will not be able to use the restroom at work as I'm not able to stand up from a toilet without assistance or without using a bench or a chair to push up on*."

- **Being able to turn in bed:** A male panelist with SMA type III also spoke about how problems turning in bed impact his life, "*I don't sleep well because I have difficulty rolling over in bed due to the weakness in my upper body and core. Unfortunately, I have to wake my wife up a few times each night to have her help me reposition in bed*." This has a major effect on caregivers—one at the meeting, a caregiver to two teenagers with SMA type II, said that she and her husband are *"up rolling [their children] all night."*

- **Being able to dress oneself:** SMA patients become increasingly reliant upon others to help themselves dress. One caregiver said that on most days, her seven-year-old daughter with SMA type III "*needs help. She asks for help getting dressed, fixing her hair,*" but every day her four-year-old daughter who is a weak type II *"is dependent on others for much of her basic needs: toileting, transferring, dressing."*

  Others lose the ability to dress themselves much later. According to one audience member with SMA type III: *"from 27 to 30, I was unable to essentially dress myself anymore*." Dressing oneself can also present challenges to ambulant individuals. One male panelist with SMA type III explained that after showering "*I need help from my wife or one of my sons to help me get on my pants, socks and shoes. Because of the weakness in my core, I cannot bend over and put them on myself. Even having the arm strength to button my pants is often a problem*."

- **The need for independence is acutely meaningful:** Participants with SMA type II and III stressed that they wanted to maintain independence and the ability to engage in social activities and relationships were extremely important. Several panelists highlighted the cumulative effect of all various abilities that they had lost.

  The 29-year-old panelist with SMA type II said that there were many routine tasks she missed being able to do: "*I can only imagine now being able to feed myself (or as I joke, binge eat in secrecy), scratch*

an itch, defend myself from insects, change a tampon, cook meals, nurture the people that I care about, clean my house, dress myself, do my own hair and makeup; and I want to hug people. I want to reach out and cuddle with my fiancé."

She and other participants added that losing their remaining fine motor skills or ability to communicate would be devastating to them. "*I don't want to lose strength in my hand because then I will lose the independence to drive my own wheelchair. If I lose the ability to speak, I won't be able to work," s*he said. Others voiced similar concerns with typing in a computer, using a joystick, etc.

B. The psychosocial and emotional impact on patients, caregivers and family:

"The psychological burden of SMA is sometimes more tricky and convoluted physical disease itself."

In response to another polling question (Appendix 3, question 13), most respondents said that they had experienced anxiety, social isolation and depression due to their or their loved one's SMA, although troubled relationships were also quite common.

- **Anxiety/Fear:** Anxiety is common among caregivers and patients. Frequently, this is due to internalized fear that their child might be exposed to a life-threatening respiratory infection: "*Wherever I am, when someone sneezes, the panic that just pulses through me is really intense and it's come to also affect my unaffected 11-year-old. She hears someone sneeze and she's like, 'Who was that? Where did that just come from?'"*

  Some anxiety reported among individuals with SMA was related to worries about how to mitigate the day-to-day social and physical consequences of their condition. As one caregiver said about her 11-year-old with SMA type III, who had just recently lost the ability to walk: "*She apologizes daily and… has a lot of anxiety as she tries to plan ahead and decide what she needs for school from her caregivers at school also*." Other anxiety may be due to misplaced guilt, as one adult panelist remarked: *"I have this constant sense of not accomplishing enough—I feel like I should justify why I need so much help from other people*."

- **Social isolation and the impact on relationships:** SMA has a considerable impact on the social lives of those affected and their families. Even though people with SMA II/III are well integrated into society, they are regularly limited by the activities in which they can become involved. Parents/caregivers have less time, money and energy for social lives of their own. Fear of infection can also lead caregivers and people with SMA to avoid social situations. Older participants with SMA type II and III also stressed that fatigue can limit their ability to enjoy their social life. "*Even socializing can be difficult because of a lack of energy,"* said one panelist with SMA type II. Another panelist with SMA type III said, *"I hate feeling so fatigued on certain nights that I must stay in and not participate in everyday activities that allow me to live my life to the fullest*."

- **Depression:** Meeting participants with SMA cited a number of causes for depression. According to one, people with SMA often work out ways to compensate for lost abilities—but as the disease progresses, they realize that this is not always possible: "*I thought that I would figure out something and then I just got depressed by not being able to.*" Frustration about the lack of treatment options can also be a factor. As one panelist said: "*You're constantly praying that you hope there is a cure out there. It led, for me, to become very sad and very depressed because I didn't understand why there were no treatments and why God hadn't found a cure."* Then, once a new treatment finally was approved, he learned that, much to his frustration, it wasn't readily accessible to him.

- **A great time commitment is required for care:** The struggle to access necessary care can take a considerable amount of time. On another polling question (appendix 3, question 9), respondents

reported that they or their loved one had either sought emergency care or had been admitted to a hospital due to SMA at least once or twice in the past year, while about 10% percent said they had gone to the hospital three to five times, and a few said six or more times. Time spent at the doctor's office or specialty clinic was even more common, with about 40% having reporting more than 10 routine visits in the last year.

C. Good Day/Bad Day

A few of the participants with SMA II and III spoke about what constituted a good versus a bad day for them. A panelist with SMA type III said that on a good day, she could perform routine tasks for herself, such as being about *"to get out of a chair."* On her worst days, she was unable to do any of those tasks and felt defeated and not "*good enough or ever capable of success."* A young man with SMA type II said *that "On a really bad day, I get overtly frustrated by my lack of arm strength and struggle to get anything done. This can result from something as seemingly minor as being incorrectly positioned in my chair or not getting enough sleep the night before."*

D. Financial and insurance issues

In response to the polling question on insurance (appendix 3, question 23), a little over half of the respondents said they have private or commercial health insurance, a little over a third have Medicaid, and about 10% have Medicare.

There are also many other associated costs that must be paid out-of-pocket to help people with SMA type II and III lead as independent a life as possible. When asked about the estimated annual SMA-related expenses or costs that patients or their families pay directly—including co-pays, deductibles, for prescriptions, medical supplies, adaptive vehicles and mobility devices—more than one third of the respondents said that they spent $5,000 to $15,000, about half of the remaining responders spent less and half spent more. However, a small percentage paid close to or more than $100,000 per year in out-of-pocket costs.

One mother to a daughter with SMA type II described how these costs can accrue. First, her family decided that they needed to build a new fully handicapped-accessible house with an elevator: "*Just to add the elevator to our house is an extra $50,000."* Then, they realized that the child also needed a power chair but that they would be unable to afford both the power chair *and* a vehicle that could transport it between home and school.

Topic 2, SMA type I: Patient and caregiver perspectives on treatment

The second topic focused on current and future approaches to treatment, as well as supportive care and medical devices used to help manage SMA type I. A panel of four caregivers to children with SMA type I led off the session:

- Panelist 1: The first panelist was a mother to a 10-month-old boy with SMA type I who said that she believed she has seen some improvement in her son in the three months since starting nusinersen. Nonetheless, her son still needs multidisciplinary care from a team of specialists, as well as equipment to assist with breathing, suctioning and feeding. One of the hardest parts of treating her son, she said "*is how few of the possible treatments, especially for secondary symptoms, are backed by evidence of success*."
- Panelist 2: "*He is completely and forever dependent on machines in order to survive*," said the second panelist, caregiver to an 11-year-old boy who needs a ventilator and other respiratory assistance to breathe. She described her family's decisions to have him receive a tracheotomy when he was 16-months old, and to also address his scoliosis early with a series of surgeries. "*My focus has and always will be to choose a treatment plan which will provide the best quality of life for my son,*" she said.
- Panelist 3: "*She's become so strong over the years*," said the third panelist, whose three-year-old daughter with SMA type I started nusinersen at the age of three months via an open-label clinical trial. Her improvements—which include decreasing dependence on respiratory and suctioning equipment—are in stark contrast to what happened to her first daughter with SMA type I who passed away at seven months of age. "*Every little gain or even just maintaining the current level of strength is welcome improvement and amazing to celebrate*," she said.
- Panelist 4: The final panelist was the mother of a child with SMA type I who passed away when she was three-and-a-half years old. She later had another daughter who was diagnosed with SMA type I when she was eight weeks old. Painfully aware of her daughter's prognosis without treatment, she said that within 24 hours of receiving her daughter's diagnosis, "*my husband began to research any and all clinical trials.*" She reported that this child is now 20 months old and has been having a good response to treatment in the gene therapy trial.

Panelists described the various caregiving routines used to help their children manage the symptoms of SMA, and how and why they made certain difficult treatment decisions. A few could explain their experiences with the first therapies to address the underlying causes of SMA—and what is most important for future treatments to address or deliver. Finally, they shared their positions on enrolling their children into clinical trials.

Participants at the meeting and online were then asked to respond to polling questions about treatments and multidisciplinary care for SMA—with a particular focus on respiratory and surgical interventions—as well as to questions about future treatments and participating in clinical trials. They were then asked to expand on their responses in a facilitated group discussion.

SMA type I: Experiences with prescription treatments and supplements

In the first polling question, participants were asked about any of the medications and supplements that had ever been prescribed either by a doctor or through a clinical trial to an individual with SMA type I in the family. The responses showed that most commonly prescribed drug was inhaled albuterol, followed by nusinersen, carnitine, albuterol liquid, valproic acid (VPA), while a few had had experience with steroids, sodium phenylbutyrate and creatine. However, the only substantial discussion concerned the recently approved nusinersen.

Nusinersen/Spinraza™

"I can say with 100 percent certainty that, had the drug not been approved so quickly for us, our daughter would not be here today."

Nusinersen has given hope to caregivers of children with SMA type I. *"For nearly half of his life, we've been able to parent him as a child with a serious, long-term disability, rather than a terminal illness,"* one parent said.

However, at the time of the meeting (only a few months after the drug had come to market), only 11 out of 108 poll respondents had accessed it—mostly through the clinical trials and the expanded access program. Those present at the meeting reported positive experiences on treatment. Panelists and other participants taking the drug described their children getting stronger, achieving milestones that they never expected them to reach with sustained treatment over time, and needing fewer respiratory treatments or other support. According to one panelist, after approximately a year of doses, her daughter *"no longer needed the coughing treatments... She has never needed the BiPAP that has sat in the house for over three years now, which was completely unexpected after her diagnosis*." In addition, she had recovered much of the muscle control she had lost. *"She seems to gain strength and stamina daily*," the caregiver said.

Some parents had lost earlier children, or had to provide supportive, complex care for older children with SMA type I. For instance, one spoke about her five-year-old boy with SMA type I who had difficulty breathing and swallowing from a very early age, and after a near-death event had to have a tracheotomy. When she learned through an amniocentesis that her next child also had SMA, they did everything possible to get their child into a trial—traveling from Wisconsin to Baltimore when he was just six days old, despite the fact that she had had a C-section. Her second son, who had started nusinersen when he was just 12 days old, through a clinical trial, was now 14 months old, and had not required much respiratory care, until recently developing a cold, after which he needed BiPAP for sleeping.

However, panelists and participants made it clear that nusinersen is not a cure and that the clinical responses are not complete. Also, not every treated child responds as well to the drug. One mother who spoke positively about the drug also stressed that her daughter still has significant problems with swallowing. Another described how her son was able to sit up more now but this put stress on other muscles. Finally, one family described their joy at seeing their son getting a little bit stronger after receiving three loading doses of the drug—even swallowing more and reaching out to grab toys—only to then have a medical emergency that almost took his life. *"There are still a lot of symptoms, even when you have a kid who's a great responder to the drug,"* his mother said.

[*Note, clinical trial data reported after this meeting strongly supports that there is an age dependent effect in response to nusinersen, with a markedly superior rate of response in those treated within the first twelve weeks of the disease compared to those who have had the disease for more than 12 weeks before starting treatment*].

There was also one parent/caregiver who said that they are cautious about starting it in their older child with SMA type I (aged 11), being concerned about possible side effects, and the burden of going to a hospital to have the drug administered intrathecally at a time while he is mostly stable clinically.

SMA type I: Experiences with multidisciplinary care to treat the symptoms of SMA

The next polling question asked caregivers and patients about other types of interventions and therapies they used to treat SMA symptoms. Therapy for respiratory maintenance and clearance was most commonly used, followed by mobility equipment, physical therapy, nutritional support and orthotics

support. However, the responses reflected the wide spread of multidisciplinary care needed to support infants and young children with severe SMA—with many patients receiving speech therapy, occupational therapy and orthopedic support as well. As one panelist said, *"About a third of our day is about keeping [my son] alive…. for now, that includes 10-18 hours a week with doctors and therapists, nearly 15 hours of preventative respiratory treatments. He has three physical therapists, two occupational therapists, a swallow specialist, a speech specialist, a dietician, a deeply involved pediatrician, and six specialist doctors, [a] neurologist, urologist, cardiologist, pulmonologist, orthopedic and endocrinologist, who each focus on what seems to be a single organ."*

A. *Respiratory assistance treatments*

"He is unable to clear his airway—so we had to do coughing, suctioning. Also, we have an extensive morning routine, where we have to do an albuterol treatment, chest PT, cough assist and suctioning."

All of the respondents said that some respiratory support was needed—most commonly suction to remove secretions, followed by cough assist devices, chest physiotherapy (CPT) for clearance/comfort. Non-invasive ventilation (NIV), such as BiPAP, invasive ventilation/mechanical ventilator (with tracheotomy) and high frequency chest wall oscillation devices had also been used by a substantial proportion of the patients with SMA type I represented in the polling (see Appendix 3, question 17).

- **Suction to remove secretions:** Almost 95% of the SMA type I caregivers who participated in the polling reported using suctioning devices for respiratory assistance. Caregivers at the meeting described suctioning secretions often, particularly in infants: "*Approximately… 20 or more times [per day] in her first year of life."* Though not as frequently, older children with SMA type I continue to need suctioning but it can be difficult to get them to ask for it*: "He hates that!*" said one of the panelists. Being dependent upon these devices (and other equipment) puts constraints on families' lives and makes travel difficult: "*If he needs airway clearance, we have to pull over in order to suction him,*" Another caregiver said that their device had a weak battery, so they had to be "*within five feet of an outlet any time we're out of the house for more than 10 minutes*."

- **Cough assist devices:** "*Shortly after [diagnosis], we started twice daily treatment protocol to help our daughter cough and her lungs to expand with a cough assist,*" one caregiver said. Another said that, at three months of age, her daughter also needed "*to use the cough assist twice a day—and more frequently when sick*."

- **Chest physiotherapy (CPT):** CPT involves treatments to improve breathing by removing mucus from the breathing passages, using a cupped hand or a mechanical chest vest to help loosen the mucus. CPT is performed by physical therapists and respiratory therapists, or by parents after training. Roughly, 67% of poll participants reported using CPT and about 50% use the high frequency chest wall oscillation (VEST©) as part of their respiratory regime.

- **Non-invasive ventilation such as BiPAP:** BiPAP is used by many children with SMA to help with sleeping: "*He's on BiPAP only at night, during naps, and in the car,*" said one caregiver. Others use it to forestall having to resort to more invasive forms of ventilation.

- **Invasive ventilation / mechanical ventilator (with tracheotomy):** Many parents are very reluctant to have a tracheotomy performed on their child, seeing it as a negative milestone in the disease. One caregiver said, *"My husband and I were very against traching [but] after you resuscitate your child so many times and see them gray and blue and lifeless, you'll do everything."* Fifty percent of poll respondents reported their child had to use invasive ventilation / mechanical ventilator (with tracheotomy) for respiratory assistance.

B. Nutritional support (nasogastric tube, nasojejunal (NJ) tube, gastrostomy (G) tube)

"Shortly after her diagnosis, her swallow [started] to weaken. She started to cough while nursing, which can very easily lead to aspiration pneumonia. So, we made the tough decision to put a feeding tube in her body."

Since children with SMA type I lose the ability to swallow, almost all of the participants in the poll said that children with SMA type I in their families had required some form of nutritional support—generally through G-tubes. One panelist, a father, described how, not long after diagnosis, his daughter "*suddenly stopped swallowing. You could see she didn't trust formula to go down her throat… We needed to quickly get her the nutrients she needed. Within a few short days we were in the hospital again to have a G-tube surgically placed into her abdomen.*"

C. Physiotherapy / physical therapy (PT)

"To postpone the progression of the disease, we started physical therapy five days a week."

Most participants in the poll also said that physical therapy was a routine part of care for their child with SMA type I. One caregiver said that their family had even made adaptations to their home to *"create a physical therapy space."*

D. Mobility equipment (adaptive strollers, wheelchair, scooters, adaptive tricycles, crutches, walkers):

"He recently got his third power wheelchair, which helps him not only with independence but also with controlling his own positioning."

Over 70% of the poll participants said that their child with SMA type I used some form of mobility equipment. One said that her daughter on nusinersen could now, *"propel herself in a wheelchair."* Another remarked that if her 11-month-old son retained his strength in his wrists and hands, he might one day be able to drive his own power chair.

E. Orthotics support and scoliosis surgery (growing rods or spinal fusion)

"My daughter does not have a curve yet. We have decided that in the case that she does have one that is impacting her breathing, that we will be proactive and will get surgery done."

With weakening muscles in the limbs and spine, most children with SMA type I require some form of orthotics support and in some cases surgery. Again, more than 70% of the responses said that they had used some form of support, either braces, neck collars or splints, among others. Scoliosis surgery is a particularly invasive intervention that about a quarter of the poll respondents (see Appendix 3, question 18), said their child had required. As children with SMA type I live longer on treatment, however, surgery will more often become a consideration.

F. Other supportive therapies and interventions included speech therapy to help children express their needs, occupational therapy and communications devices such as the 'eye gaze' for children with SMA type I who can no longer speak, and the BEAM telepresence robot to help children attend and interact in school while remaining at home, especially in the flu season when children are more vulnerable to respiratory infections.

SMA type I: Perspectives on future treatments and considerations in treatment decisions

In light of nusinersen's recent approval, a drug that improves survival and other outcomes in children with SMA type I, patients and caregivers were about what they were looking for in future SMA therapies. In response to a multiple-choice polling question (Appendix 3, question 19), two-thirds of the respondents indicated they would prefer a treatment that provides gains in function (e.g., increased strength, energy, doing something the patient was unable to do before), while some said that they would be satisfied with treatment that would lessen symptoms and improve quality of life. Only a few chose the option of slowing or stopping disease progression (without improvements in quality of life). No one selected the outcome of prolonging life on its own. The discussion offered more insight into these responses.

Gains in function and strength, however small

"It doesn't have to be a huge gain…"

While some would of course like a treatment that could "*cure the disease" or "strengthen the legs and allow these children to walk*," most stressed that *"little changes are very significant to this community*." A number of the panelists and caregivers at the meeting described the sort of gains in function and strength that they would want from a future treatment:

- "*To get to use a finger that had lost its movement or gain back their ability to smile means more to us than the big things,"* said one caregiver.
- *"We want to help him hold up his head and support his own back, [and] develop a grasp so he can hold a marker and color a picture,"* said one parent.
- *"I hope that one day he may have the muscle dexterity to speak*," said one of the panelists.

SMA type I: Perspectives on benefit-risk analyses

Another question (Appendix 3, question 20) asked about factors that would influence decisions regarding whether to use or stop a given treatment. The most common response, chosen by (77%) of all SMA type I respondents, was if there are significant risks of serious side effects such as cardiac or kidney toxicity. This level of risk-tolerance is very much reflected in the choices made by close to 300 affected individuals and families (of all types) who participated in the Benefit-Risk Survey for SMA, the fall of 2017. The other common choices were the burden of administration—such as the need for anesthesia, radiation exposure, surgical procedure, etc.—followed by the cost of treatment.

However, caregivers to children with SMA type I expressed a willingness to accept a risk of side effects in exchange for treatment that could improve the chance of their child's survival or quality of life. "*Incremental improvements are worth the risks*," one of the panelists said. *"We believe our job is to give our kids the best life possible, even if it's shorter than we would like. Our kids will get over the pain of the shot or headache."*

In the case of SMA type I, even a significant risk of serious side effects could be seen as counterbalanced by the risk that the disease presents: "*SMA works fast. It can take away any ability overnight. The possibility of any improvement from the drug or therapy makes it worth it to me. There would have to be a very large chance that a serious side effect would happen for me to not have my child try it."*

SMA type I: Perspectives on clinical trials

To develop future treatments, participation in clinical trials will be required, so a pair of polling questions (see Appendix 3, questions 21 and 22) asked about the meeting participants' experiences with clinical trials. A little less than half of the caregivers responded that their child had participated in a clinical trial. Most of those who had not been in a trial had tried to enroll in a clinical trial but did not qualify—some were however able to access treatment in an expanded access program.

Caregivers were then asked to select up to four factors that they would rank as most important to their decision about whether to participate in a clinical trial to study an experimental treatment (Appendix 3, question 22). The top response was 'how the treatment might prevent further disease progression or improve their loved one's health,' followed closely by 'the risk of rare but serious side effects.' Other common responses were 'the reputation of the study's primary investigator' and 'the promise of receiving open label therapy at the end of the trial.'

During the testimonies and discussion, caregivers of children with SMA type I expressed a desire to get into clinical trials to access treatment that could potentially benefit their child: *"Please know that we would have done whatever it took to get our daughter into a trial,"* said one panelist. Others' views had changed

after their child had suffered a major functional loss—and as a result of hearing about the positive outcomes on nusinersen and gene therapy. One of the panelists said she had previously been very much against her son participating in clinical trials: *"Look how far we got because of these great parents who did put their kids in these clinical trials. I'm very grateful."*

Some caregivers elaborated on how clinical trial design had or could affect the decision to enroll their child.

Placebos

"The deciding factor for us was the placebo."

Some caregivers had had a choice in clinical trials to participate in. According to one of the panelists had lost an earlier child to SMA type I, when she was presented with the choice between the nusinersen controlled study, or the gene therapy trial, her family realized: "*Time… wasn't on our side and that gene therapy [trial] did not have a placebo. In the end, we know first-hand what is to come if we don't try something. We knew [she] would die sooner than later."*

Combination therapy and other SMA enhancing drugs

"Add them all on. Whatever gives these kids strength. Give it to us. We're ready."

With the approval of nusinersen, there is now a standard of care treatment for children with SMA type I, so a placebo-controlled study in this particular population would no longer be considered ethical, unless the child cannot tolerate nusinersen or appears to be failing treatment. However, there are still unmet medical needs and a need to develop further treatments.

Consequently, caregivers of children with SMA type I expressed an interest in whether experimental treatments with other mechanisms of action or routes of administration could be combined with the standard of care, nusinersen, in upcoming clinical trials, rather than taking a risk of their child being randomized to an ineffective or less effective treatment. Some parents asked whether it would be possible to combine nusinersen and gene therapy. According to one of the principal investigators attending the meeting, gene therapies for SMA and nusinersen increase SMN protein production in different ways. "*There's at least a reason to think there might be some complementarity there, but there's nothing proven to say that*," he said.

Some meeting participants were concerned about possible interactions between the two therapeutic approaches. *"My daughter is getting nusinersen so, would it interfere with that?"* asked one, suggesting they are worried about stopping nusinersen to become involved in other trials.

Others are actively seeking out the option of having their child studied on the combination. *"We contacted everybody we possibly could to see if maybe my child could be the first to have both,"* said one father. *"We're doing our due diligence to make sure that side effects may not harm or disrupt what she's currently on, but in the same vein, I'm looking at a daughter who severely lost everything so quickly, that I need to be a little more aggressive like some people have been in the past, to give her that opportunity."*

Topic 2, SMA types II and III: Patient and caregiver perspectives on treatment

Individuals with SMA types II and III, who typically survive childhood, and their caregivers have somewhat different perspectives than those with SMA type I on current and future treatment approaches, and have different supportive care needs and medical devices experience. Six panelists, including three caregivers and three individuals with SMA type II or III, led this session, describing how they manage the condition:

- Panelist 1: The first panelist is mother to an 8-year-old boy with SMA type II who uses a power wheelchair that "*stands him up like a transformer*" to navigate his environments. She worries that he will lose critical fine motor functions that would make it harder for him to chew or generate a cough when he becomes ill. She is hopeful now that he is receiving Spinraza™ and taking VPA. Even so, she said, "*we're always hoping for another drug to come along that can improve our child's strength*."
- Panelist 2: The next panelist was an 18-year-old young woman with SMA type II, with limited mobility and respiratory weakness, who leads a very busy life as a high school student. She said that for her to make time for a treatment to be administered, it would have to be "*guaranteed to be extremely effective in helping the actual core symptoms of SMA, not just working on the surface level*," For her, that meant something that would help her maintain lung function and current mobility. Mostly she said she just wants to lead a normal life—and pass her advanced Calculus III course.
- Panelist 3: A mother providing care to two children with SMA: a five-year-old son with SMA type II and a four-year-old daughter with type SMA III was the third panelist. Her son has regained some muscle strength on nusinersen but she believes his disease is still progressing. Meanwhile, her daughter is ambulatory but has many emerging difficulties, requiring assistance to keep from falling. Providing the multidisciplinary interventions her children need, can be extremely time-consuming, she said: "*Management of the 'almighty schedule' becomes its own full-time job."*
- Panelist 4: A 27-year-old young man with SMA type III, who is a research specialist for the Muscular Dystrophy Association, served as the fourth panelist. He lost ambulation at the age of 12 and underwent a spinal fusion at the age of 22 but believes his disease has now plateaued. Even so, he said SMA affects almost every aspect of his life. Though he never wanted to get his hopes up about treatment, he is interested in nusinersen and frustrated that his care provider knows little about it.
- Panelist 5: The fifth panelist was a caregiver to two daughters with SMA, one a seven-year-old with SMA type III who still walks independently, and a four-year-old with SMA type II who is 100% wheelchair dependent. Both have had good responses to nusinersen, but she said, *"they are still incredibly affected by their disease*." For instance, her seven-year-old suffers from over-exertion after active days at school. She also thinks there should be more research focused on managing complications that may present later in life. *"SMA forces a sedentary lifestyle. How can we protect the cardiac function of people living with SMA?"* she asked.
- Panelist 6: The final panelist was a 14-year-old high school student with SMA type II who has spent her entire life in a wheelchair. She has taken sodium phenylbutyrate, and has had twelve spinal surgeries over the years—including having VEPTR rods installed and more recently a spinal fusion—and takes respiratory treatments. She is hoping for a treatment that stops her progression so that she can keep doing the things she loves. She would also like "*something that would better help regulate my pain without having to constantly take pain medications.*"

The caregivers described the approaches to managing SMA in children with differing degrees of mobility, some ambulatory and some not. A common refrain was that they must spend hours on physical therapy and respiratory treatments. At least some of the children have been able to access either nusinersen or

other experimental drug via clinical trials. Caregivers reported nusinersen had been very beneficial, but that they had seen some disease progression continue despite treatment. Symptoms seem to be managed best in those with the earliest exposure to the drug. The patients with SMA on the panel described the procedures that they have undergone over the years, and stressed that they want treatment that would allow them to carry on the activities of life that they enjoy. However, they are also cautious about getting their hopes up about treatments that may not work for them, or that might disrupt their lives for minimal benefit.

After a series of polling questions about prescribed treatments, multidisciplinary care for SMA, and their views on future treatments and participation in clinical trials, meeting participant expanded on these themes during the facilitated group discussion.

SMA type II and III: Experiences with prescription treatments and supplements

The first polling question asked participants about medications and supplements prescribed either by a doctor or through a clinical trial to manage SMA type II or III. Once again, the most commonly prescribed drug was inhaled albuterol, but individuals with type II and type III had more experience with a wider range of therapies than the children with SMA type I. The same number had been prescribed nusinersen and carnitine, followed by VPA, creatine, albuterol liquid, and steroids, while some had experience on albuterol tablets, sodium phenylbutyrate and hydroxyurea. Several responded that they had used other treatments that were not listed in the question. For instance, some individuals with fractures had received either ibandronate or zoledronic acid for bone strengthening.

Nusinersen/Spinraza™

"The drug has had a positive impact on their SMA but they are still incredibly affected by their disease."

Most of the discussion again centered on nusinersen/Spinraza™. At the time of the meeting, which was only several months since FDA-approval, access to the drug was not yet uniform across children with SMA types II and III—and few adults had yet tried the drug.

Many of the caregivers with children on nusinersen reported seeing profound improvements while their children were on the drug. One panelist whose 5-year-old son with SMA type II had been on it for the past three years saw "*measurable and valuable improvements in his function and movement,*" one of the most impactful of which "*is his ability to give a tight hug and really squeeze on. Other improvements for him include increased muscle control, stamina, and fine motor strength*."

According to another caregiver whose son has only been on treatment a short while, they "*have seen subtle but important improvements in his physical abilities. Two weeks ago, he reached for a few Legos on his shelf by turning his trunk and reaching out his arm, something he could not have done before. He has also been able to chew about half of his meals [by] supporting his chin with his arm and he can sit unsupported for over two minutes while holding a small object in front of him.*"

Others reported their children were less fatigued after just a couple doses. Another panelist who has a daughter with SMA Type II and another with SMA Type III who were both in nusinersen trials said, "*their lives have been dramatically altered. [Her youngest daughter's] increase in head control and arm strength from the past year on the drug has given her independence and confidence*." Her elder daughter with SMA type III, who's been on nusinersen via an open-label trial for the past four years, has benefitted by gaining large motor function. She can now climb steps, jump, and kick a soccer ball.

- **Ongoing/unmet medical needs:**

However, "*many symptoms of SMA remain and that every aspect of her day is still affected by SMA*," said

one panelist with a daughter on nusinersen. One problem is that, *"after 10 minutes of active play, her daughter on nursinersen reaches muscle tolerance and exertion."* Other parents also saw limits to the treatment effects on nusinersen, "*SMA symptoms do still appear. A progression in spinal curvature and scoliosis, hip issues, and fatigue are the latest as he grows older, taller, and heavier*," said one caregiver.

Other parent/caregivers described challenges getting access to the drug. *"Despite the wide approval that the FDA granted the drug (for SMA of any type), older individuals with SMA have had particular challenges getting access to the drug. In some cases, this has been because of lack of provider knowledge about the drug*." One of the adult panelists made an appointment with his regular neurologist to see if he could try the drug, but found: "*My doctor has not prescribed it to any adults with SMA. She doesn't really know much about the drug; doesn't really know if the side effects are going to harm me, or if they are actually going to approve me because I'm 27 years of age*." This patient wants a study to provide more information about the drug in an adult population, even though the drug's approval places no restriction on age or subclass of SMA.

- **Challenges in administration of Spinraza™ with a spinal fusion:**

Another challenge for many older patients is that the administration of an intrathecal drug can be difficult if they have had spinal fusion. According to one meeting participant, "*I have contacted a few physicians in the area, both pediatric and adult, and no one I talked to is willing or interested in looking into administration of it because I have a spinal fusion. I'm the one that's having to do the research and searching for other patients' experiences. It's hard when the physicians I am trying to get information from aren't knowledgeable and don't seem very motivated to investigate and research more*."

One caregiver said her daughter's full spinal fusion was definitely a problem: "*We're fully approved by our insurance; our hospital is dosing. We've had labs drawn. We've had a CT scan, and then found out that there are no openings*." Others share the same fear: *"I am concerned about my spinal fusion and how that's going to play into whether or not Spinraza™ is going to be an option for me*."

This is an issue that individuals getting a spinal fusion will need to consider in the future. Some surgeons working with multidisciplinary teams are already taking it into consideration though. One caregiver to a son with SMA type I said that he had his back fused this summer, and the surgeon, "*left a spot so that he could get spinal injections knowing that this was coming down the pipeline.*"

SMA type II/III: Experiences with multidisciplinary care to treat symptoms

The next polling question (see Appendix 3, question 16) asked about other types of interventions and therapies used to manage SMA type II and III symptoms. The most common response for these mostly older individuals was mobility equipment, followed by respiratory maintenance, physiotherapy / physical therapy, orthotics support, aqua therapy and occupational therapy. Close to 60% of all polling participants reported the use of orthopedic support (e.g., orthotic support, Braces, standers, etc.), while 30% (mostly with SMA type II) reported the use of invasive nutritional support (either a nasogastric tube, nasojejunal (NJ) tube, or G-tube).

Mobility equipment

"Power wheelchairs are all many kids have to stay healthy and access the world. It is very important that the latest equipment be brought to the government channels faster."

Many of the panelists and participants spoke about how important mobility equipment was to their lives, from quite an early age. One caregiver to a four-year-old daughter with SMA type II said, "*she's 100 percent wheelchair dependent*." A young woman with SMA type II said, "*My whole life I've been in a wheelchair. Not until my 8th grade year did it really occur to me that being in a wheelchair was actually different."* Another caregiver said her son's wheelchair allowed him to "*torture the shop owners, just like any middle schooler should do."*

A couple of non-ambulatory adults with SMA type II and III mentioned being more independent with the aid of equipment such as robotic arms. "*I was able to acquire a robotic arm in 2015 and this device gives me tremendous independence and allows me to perform basic physical functions such as eating and drinking*," said a young man with SMA type II.

But meeting panelists and participants also described downsides of needing to rely on often multiple pieces of mobility equipment (manual and electronic). One issue was the expense, which is compounded by the fact that new appropriate equipment is needed as children grow older. "*For us to try to find adaptations and equipment that fit him just right, that are at the right height, that are safe for him to use and don't take tremendous effort to get approved by insurance is a lot of work for us," said one caregiver.* Many caregivers stressed how inaccessible many places are to strollers and wheelchairs. One caregiver said that after one trip, she *"was completely drained and… physically exhausted from picking them up, carrying them, pushing their strollers, wheelchairs through grass, gravel, sand and whatever activity they were trying to do."* As one adult with SMA III who is wheelchair dependent said, *"transportation is never that easy when you are in a wheelchair*."

Finally, equipment requires maintenance, and can break or malfunction. "*Equipment failures can also exasperate the SMA experience. An uncharged ventilator battery, a broken joystick, a malfunctioning suction machine, then, I can't leave my house*," said a 29-year-old panelist with SMA type II.

Respiratory maintenance treatments

"Equipment is so important [including] cough assist machines to suction machines."

Many of the respondents reported the use of some form of treatment to support breathing. In response to a polling question about the types of respiratory support, most said they had used a cough assist device, followed by non-invasive ventilation (NIV), such as BiPAP, then chest physiotherapy (CPT) for clearance/comfort, suction to remove secretions while high frequency chest wall oscillation devices and postural drainage had also been used by a substantial proportion of the patients. Only a few said that they used invasive ventilation or mechanical ventilation with a tracheotomy.

A. Cough assist devices: A number of participants said that after learning how to use cough assist devices at home, visits to the hospital became less common. One family felt that using the cough assist device routinely helped keep their daughter with SMA type III's lungs strong**,** but when they stopped, her lung function went from 100% to about 70%. "*We have increased it back to every night in hopes that her lung function will increase again*."

B. Non-invasive ventilation such as BiPAP: One caregiver at the meeting said her seventeen-year-old son with SMA type II is "*on BiPAP at night: We had a flu bout about a year and a half ago and after that he has to sleep on the BiPAP.*" A fourteen-year-old with SMA type II said that she also uses a BiPAP machine every night *"to keep my lungs strong*."

C. Invasive ventilation/mechanical ventilator (with tracheotomy): Although only a few people said that they or their child had had a tracheotomy and used mechanical ventilation, a couple panelists commented upon it. One adult woman said that getting a tracheotomy was "*the biggest decision of my life. I was a teen-aged girl and I liked boys and I didn't want a tube because that's gross. But I gained all my weight back, all my energy back, and I've never had a respiratory issue since then*." There are downsides though. One adult with type II cited constant concerns with "*Keeping my trach and airway clear, managing and maintaining the medical equipment*."

Physiotherapy / Physical therapy

"Keeping up my strength and [staying] on top of my health requires physical therapy at least once a week and as often as five times a week to stop any contractures and other muscle joint issues."

Several meeting participants said physical therapy was helpful to them. One meeting participant said that if she didn't exercise or do her physical therapy, she would begin to experience *"fierce progression."*

Physical therapy can be time consuming, however. According to a teenaged panelist with SMA type II, as her life became busier with school activities, "*fitting in time for therapy became more and more difficult."* In addition, she felt that "*physical therapy does not necessarily improve the symptoms that affect my daily life, it just temporarily removes some tension and prevents my muscles from getting even tighter*."

Orthotics support (Braces [AFOs, KAFOs, TLSO], neck collar, splints)

"We feel it was a big help to us and our daughter"

A number of caregivers reported positive experience using orthotic supports. According to one caregiver, "*My daughter uses Ultraplex splints, knee and ankle orthotic type device to help manage the contractures of the knee and the ankle which at one point in her life were severe enough that they were going to stop her mobility."* Another father said that they began using the TLSO brace before their daughter started developing scoliosis, when most parents wait till the scoliosis sets in. "*We started with the brace really early. She's four now. Her scoliosis [is] still setting in, but it's not as severe as what we expected it to be or what we've heard in the past*."

Scoliosis surgery (growing rods or spinal fusion)

"My scoliosis required me to undergo spinal fusion as an adult at the age of 22. Overnight I grew three inches and was able to breathe better as my ribcage was no longer crushing my lungs."

In response to another polling question (see Appendix 3, question 18), about 46% of the respondents had undergone scoliosis surgery (this is most commonly necessary for people with SMA type II and III who are non-ambulatory). According to the mother of the panelists with SMA type II, "*It was a very difficult choice to go against doctor recommendations when they said she's eight and her spine should be fused because of severe scoliosis, but we chose not to intervene at that point. We were able to a year later get her in the VEPTR rods which were great because they enabled her grow, but the result of that was 12 back surgeries and putting a kid in and out of the hospital has compromised lung capacity, everything."*

Surgery can be fraught with complications and recovery difficult. One participant with SMA type III, who described experiencing pain in the torso associated with her severe scoliosis. She decided to have surgery to put in rods, and fuse her spine from the cervical vertebras to the throat vertebras. The recovery period should have been nine months, but her insurance company refused to cover rehabilitation so it took much longer. She became wheelchair dependent afterwards.

A caregiver to a teenage boy with SMA said that she allowed him to have a say in the decision, and he chose to have a spinal fusion. However, *"his recovery… was very long."* She said that at one point, he said, *"I don't think I made the right decision. I'm in so much pain now all the time*." The whole family was distressed by the pain, but after another six months, it subsided. Now they believe it was the right choice.

Aqua therapy

"Aquatic therapy to improve stamina and endurance."

While some respondents reported greatly benefited from aqua therapy, one has to have access to a pool. A high school student noted that, like other physical therapies, it takes time that she no longer had.

Nutritional support (either a nasogastric tube, nasojejunal (NJ) tube, or G-tube)

"[Getting] a feeding tube that I used overnight… was a really tough decision for me as it was a real clear

milestone of decline that I didn't really want to think about. [But] it has improved my quality of life."
In cases of severe SMA progression, invasive nutritional support is sometimes necessary. One panelist's son, a strong type I/weak type II, completely lost his ability to swallow when he was 13 months old, and then required a feeding tube. Another caregiver said his teenage son with SMA II had a series of illnesses that led to him getting a G-tube, and now, *"if he doesn't like what I cook for dinner, he puts it in his tube."*

SMA type II/III: Perspectives on future treatment / considerations in treatment decisions

In response to a multiple-choice polling question (Appendix 3, question 19), 63% of the respondents indicated that they would prefer a future SMA treatment that provides gains in function (e.g., increased strength, energy, doing something the patient was unable to do before), and close to 28% said they wanted a treatment that could stop or slow down disease progression (even if it does not provide lessening of symptoms that would improve quality of life and/or enhance activities of daily living). More insight into these responses was offered during the group discussion.

Gains in function and strength

"Improved fine motor strength like the ability to hold a spoon or write and lower extremity strength are not well addressed in current treatment."
Meeting participants were passionate about the sort of gains in function they would like treatment to achieve. One, a high school student with SMA type II, desired treatments that could help her *"maintain or improve my mobility and lung functions.*" Another adult panelist with SMA type III said, "*just being able maybe to dress myself, or just do a transfer in and out of the bed or from and to the toilet—that would be huge, to not have to rely on someone 24 hours a day."*

A caregiver to two children, one with SMA II and one with SMA III, said an ideal treatment for SMA in the future would address the root cause of the disease, "*limiting or preventing muscle wasting and allowing for functional improvements in strength. Everyday wins would be things like improved respiratory function, skills for life improvement, like being able to pull up the blanket to cover yourself in bed, independently use the toilet. To put your own shoes on, and keep up with peers without excessive fatigue."*

As another caregiver said, *"We want to see treatments that can slow this awful disease, or better yet, reverse some of the symptoms… being able to chew [on his own] might seem meaningless [to you] but in the picture of a healthy, happy life, it means the world*."

"It would be great if the future treatment would better address arm and leg strength," one caregiver said, before she mentioned how difficult scoliosis, contractures, and a decreased ability to breathe can be. *"Meaningful improvements for a future drug could be as simple as slowing the progression of such co-morbidities or improving the strength in one of those areas."*

Stopping or slowing down disease progression

"I simply want to live my life to the fullest and I hope that future treatments will help me do that."
Other people with SMA types II and III are happy with their present lives, but aware of the progressive nature of the disease, would be satisfied with a treatment that allows them to continue what they love doing. One participant said that while she'd like to see improvements, *"it is important to remember that SMA is a progressive disease. It's ugly over time. Even if the current treatment doesn't offer much in terms of strength gained, a slowing of the progression of SMA is extremely meaningful."*

"A*s much as I don't want to disrupt the life I have,"* one adult with SMA type II said *"I don't want to lose more strength because losing more would disrupt my life just as much as any treatment would."* According to an adult with SMA type III: *"For me an ideal treatment for SMA would be to maintain and improve my strength so that I can continue to walk and perform daily activities independently."*

"*Once we…can no longer perform that task, … that could be walking, lifting an arm... that's probably, for me, when I would search out for treatment*," said another participant with SMA type III. "*If the next milestone means I'm no longer able to drive myself somewhere. I would probably seek out treatment."*

"Some of us have older teenagers who have been stronger and been able to do things on their own, and are now getting older and their bodies are continuing to grow, but they get weaker," said one caregiver to a 14-year-old with SMA type II. *"For myself and some other families who have similar-aged children, even if we don't gain anything, it is for them not to lose anything more than they already have."*

As one father to two daughters with SMA said, "*You go from hoping they'll walk to hoping they'll stay out of the hospital, to hoping that life would become just a little easier."*

SMA type II/III: Benefit-risk

"SMA can be an awful disease. When I look at the potential benefits versus risk factors, the risks have to be high to not consider the treatment or clinical trial if the drug showed it can help."

Another polling question (Appendix 3, question 20) asked about factors that would influence decisions to use or stop using a given treatment. The most common response (~90%) was whether there are significant risks of serious side effects such as cardiac or kidney toxicity. Other common responses were the cost, the burden of administration (such as the need for anesthesia, radiation exposure, surgical procedure, etc.) followed by the time that it would take away from daily activities, job, school, etc.

Many caregivers and patients explained that they were concerned with serious side effects but not common side effects such as nausea or headache. *"Potential benefit would always outweigh common side effects, and only more serious life-threatening or life altering and well-documented risks would be any kind of a deterrent,"* said one caregiver to two children with SMA, one with type II and one with type III.

A young man with SMA type II stated, *"I consider things like headaches and nausea pretty minor if it means stopping the progression of my disease. However, if there are more serious side effects like infections and blood or liver damage, then I would be much more skeptical about a treatment."*

An important caveat is that adolescent or adult patients with SMA tended to be more conservative about side effects than caregivers to children with SMA. For instance, one of the panelists, a non-ambulatory young man with type III, said that he might accept some side effects in exchange for greater independence, but added, *"I've accepted my disability, and if any treatment would shorten my life or cause me pain then maybe I would not consider taking it. I rely on others for my independence and it can be limiting at times, but not life threatening and I don't have any pain."*

Perspectives on clinical trials

Two more polling questions asked about clinical trials. Only about 28% of the respondents had participated in clinical trials, but most (56%) had tried to enroll but either did not qualify or the study was closed.

Patients and caregivers then reported up to four factors that they would rank as most important to their decision about whether to participate in a clinical trial of an experimental treatment (Appendix 3, question 22). The top response was how the treatment might prevent further disease progression or improve their or their loved one's health, followed by the risk of rare but serious side effects, the promise of receiving open label therapy at the end of the study, and the availability of safety data.

During the discussion, a number of caregivers and people with SMA type II and III indicated they were quite enthusiastic about previous trial engagement.

"*We made the choice to get her in drug trials right away,*" said one mother to a teenager with SMA type II—and the teenager who was at the meeting, said that she was grateful. Others said they were quite happy to have been able to participate in the nusinersen trials.

"*More and more families, with and without spinal muscular atrophy, are curious about clinical trials and these treatments are not just huge for the SMA community patients but are also creating wonderful ripple effects of hope,"* said one of the adult panelists with SMA who counsels other patients about clinical trials.

Placebos and other clinical trial design issues

There was less discussion about aspects of clinical trial design that might affect decisions about trial participation for children and adults with SMA type II and III. It should be noted, though, that while nusinersen is approved for all types of SMA, the limited data and expertise on its use in SMA type II and III means that there is some clinical equipoise about its use in this population. It should be noted that gene therapy and Sprinraza both aim to increase SMA protein levels; and, as there has not been a direct comparison of the two therapeutic approaches to date. Since there is less great risk of early mortality in people with SMA type II and III, it may be possible to perform a randomized clinical trial that compares the two approaches in this population.

Similarly, it may also be possible to perform a placebo-controlled study in this population, though patients have generally expressed a preference for the use of natural history comparators or active comparators controls. However, comments from some of the people with SMA type II and III suggested a degree of altruism about engaging in clinical trials that provide clear answers about whether a treatment works.

For instance, the panelist with SMA type III who counsels others said: *"I've never participated in a clinical trial, but [if there was a study in adults], I would jump on it immediately. I want to move it along for those patients who are adults that do want it, and also for those patients that are on the fence about it or feel like they have accepted their disability—because I had definitely accepted my disability but it is wonderful that we now have this new thing to look forward to that we never had before."*

Benefit-Risk survey for SMA

Through this meeting and Cure SMA's previous efforts to collect and further understand the SMA patient / caregiver experience with SMA, much has been learned about the multifaceted burden of the disease, clinical meaningful changes/desired outcomes by SMA type, attitudes toward clinical trials and perspectives on ideal treatment. Following the Voice of the Patient meeting, Cure SMA felt there was a need to better characterize how SMA patients and families would weigh specific risks for specific gains expected from a potential therapy. Thus, in order to more systematically (quantitatively) learn about risk-tolerance in SMA, Cure SMA conducted an IRB-approved Benefit-Risk survey in the fall, 2017 that was opened to all members in the SMA database with current contact information. A summary can be found in Appendix 5.

Topline results were as follows:

- A total of 298 affected individuals (18 or older), and caregivers to children and adults (unable to independently complete survey), of all SMA types, and a confirmed diagnosis of SMA responded to the survey.
- To most accurately understand and assess risk tolerance in SMA, the following factors were analyzed and correlated with individual responses (a) SMA type (I-IV)/disease severity, (b) stage of disease (progression) at the time of survey, (c) respondent type (parent vs. affected individual), (d) risk-taking attitude, (e) gender and (f) rated quality of life, including rated level of independence, and expectations for improvements in quality of life in a future treatment.
- Overall, survey respondents consistently rated the following as the <u>most tolerable risks</u> regardless of the benefit of the treatment:
    - Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.)
    - Possible need for general anesthesia to administer treatment
    - Side effect of dizziness (may increase risk of falls)
    - Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.
- Conversely, respondents consistently rated the following as the <u>least tolerable risks</u> regardless of the benefit of the treatment:
    - Life-threatening allergic reactions
    - 1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure
    - Worsening in "quality of life" (possibly due to drug's side effects, worsening condition, etc.)
- To Cure SMA's surprise, no strong correlation was found between risk-tolerance and SMA types, stage of disease, respondent type, quality of life, or rated levels of independence at the time of survey. Gender or risk-taking attitudes did not appear to influence their choices of risk-benefit tradeoffs.

These findings may be specific to this unique moment in the evolution of SMA therapy, where there is a sense of great optimism, and yet, limited experience with a newly approved treatment with a low risk profile. As the benefits and limits of treatment across the spectrum of SMA types and in older patients become more clearly characterized, it is anticipated that sub-populations of SMA patients who are refractory or intolerant of treatment may emerge and that perceptions about risk-benefit will continue to evolve.

Incorporating patient input into a benefit-risk assessment framework for SMA

Over the past several years, FDA has developed an enhanced structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework involves assessing five key decision factors: Analysis of Condition, Current Treatment Options, Benefit, Risk, and Risk Management. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision.

In the Framework, the Analysis of Condition and Current Treatment Options rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision-making, including valuable information for weighing the specific benefits and risks of a particular medical product under review.

The input provided by patients and patient representatives through the SMA Patient-Focused Drug Development meeting and docket comments will inform the understanding of the Analysis of Condition and Current Treatment Options for this disease.

The information in the top two rows of the sample framework for SMA, below, draws from various sources, including what was discussed at the SMA Patient-Focused Drug Development meeting held on April 18, 2017. This sample framework contains the kind of information that, it is anticipated, could be included in a framework completed for a drug under review for SMA. This information is likely to be added to or changed over time based on a further understanding of the condition or changes in the treatment armamentarium.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• SMA is a rare inherited neurodegenerative disease caused by mutations in the survival of motor neuron 1 (SMN1) gene. Without the SMN protein, individuals with SMA experience progressive muscle denervation and the atrophy of skeletal muscle. The clinical results are a loss of muscle function, limiting mobility, and causing difficulty breathing, swallowing and, in some cases, speaking. • Due to production of a limited amount of SMN protein by a redundant gene, there is a spectrum of severity in SMA. The amount of SMN determines the age of onset, milestones achieved, disease progression and life expectancy—features used to classify the disease. Symptom severity is now classified from type I (most severe and lethal of subtypes to SMA type IV, its mildest form) based on highest motor milestone achieved. - SMA type I is 90% fatal or leads to ventilator dependence by the age of two, and those who survive are entirely dependent upon caregivers. Those with SMA type II are wheelchair-dependent, gradually lose other abilities and independence, and do not live long into adulthood. SMA type III may achieve most developmental milestones, but face a life of functional loss, including ambulation. For those with SMA type IV, symptoms present after the age of 30. • Symptoms range from an almost complete absence of motor functions and mobility, dysphagia respiratory complications and, communication difficulty, to gradual loss of mobility, contractures, scoliosis, fractures—and related pain and fatigue. • SMA also has a profound effect on caregiver and families' economic, emotional, social, and psychological health. Families are often socially isolated, coping with post-traumatic stress, depression, and anxiety.	SMA is a rare, progressive neurodegenerative disease that is often fatal (in types 1 and 2) and that causes wide-ranging complications that have devastating impacts on patients and their families' lives. Cases that are non-life threatening (e.g., type III or type IV) must nonetheless deal with the loss of the ability to live independently and functionally perform daily tasks without assistance. Individuals with SMA have complex treatment needs for therapies that address both the cause of the disease, and its consequences.
Current Treatment Options	• There is a sense of optimism about an FDA-approved treatment for SMA that improves survival and leads to some gains in strength and function, though disease progression still occurs. • Although the new drug is approved for all people with all types of SMA, the intrathecal route of administration, cost, and lack of clinical expertise using the treatment in adults, as well as, lack of treatment access due to spinal fusions in older children and adults, limits access to treatment for many people with SMA. • Management of the consequences/symptoms of SMA requires multidisciplinary care and multiple medical or nondrug supportive care therapies, surgical interventions, braces and equipment. These treatments only manage the symptoms and clinical consequences and not the underlying causes of SMA (muscle denervation and atrophy) • Participants expressed a desire for treatments that lead to increases in strength and functional ability —even small changes—but safe treatments that prevent further functional losses would be valued as well. Traditionally, parents of individuals with types I and II SMA have been willing to take significant risk to improve the quality of life or overall survival of their children — however, in light of recently approved treatment, there is reduced risk tolerance as long as treatment is working. Adults with type II and III with independent lives have a much lower tolerance for risk, in fear of worsening the current state of their disease or risk further dependence on others. The SMA B-R survey results showed that worsening in quality of life was most feared, of all the risks rated by people across the spectrum of SMA types. See the *Voice of the Patient* report for a more detailed narrative.	There continues to be an unmet need for more effective and tolerable FDA-approved therapies to treat SMA, especially those with more convenient routes of administration, particularly needed by those with spinal fusions or milder forms of the disease. The availability of a treatment with some efficacy increases the urgency of early diagnosis and treatment. It also will have bearing on the ethical design of clinical trials of new treatments. Additional more effective and tolerable treatment options are needed for the symptoms and complications of SMA—as well as more rapid access to state of the ART equipment.

Conclusion

This meeting emphasized the urgent need for increased awareness, early diagnosis, and treatment for SMA. A presentation by a renowned SMA clinician researcher provided insight into the complex issues faced by clinicians and scientists in developing better treatments for this disease. Furthermore, the FDA was provided with a unique opportunity to hear in great detail directly from patients at this Patient-Focused Drug Development meeting and to better appreciate the all-encompassing physical and emotional burdens related to living with spinal muscular atrophy.

Some of the key themes, as summarized by an FDA official at the end of the meeting, included:

- The diagnostic journey
- The impact of respiratory complications in SMA
- The impact of the loss of the ability to swallow in SMA type I
- The importance of mobility issues
- Difficulties with the activities of daily living
- The impact of fatigue, weakness and muscle pain across the spectrum
- The complications and benefits of surgical intervention
- The challenges of managing complicated medical care at home
- The impact on caregivers and those affected of prolonged hospitalizations
- The impact of frequent medical visits, including transportation of patient and equipment
- The impact on the family, including social isolation and mental health issues
- The importance of equipment, such as ventilators for home use
- The use of computer technology, including for communication
- Advancements in robotics, wheelchairs and other assistive technology
- The community's views on new treatments and those under development
- Individual and collective thought processes when a new treatment comes out
- How families make individual decisions to best fit their unique needs

The recent FDA approval of a treatment for SMA was a landmark one for the community and is having a major impact on the disease, particularly when treated early. Even so, there are still many unmet needs when addressing the complexities and burden of this multi-systemic disease. During the discussions, caregivers and patients explained that small changes in function could make a big difference in their life—while additive, incremental changes would be critical to achieving greater overall function and enhanced quality of life. New treatments or combinations of treatments that improve respiratory function, swallowing and reduce fatigue would have significant impact on daily living activities. Caregivers and people with SMA would welcome treatments that could provide greater independence, particularly improvements in activities such as toileting, grooming, and feeding that would increase patient's dignity and ability to participate in society.

The positive experiences of those who participated in the nusinersen and gene therapy trials has heightened interest in enrolling in clinical trials, although trial designs may need to be adapted to suit the needs of the population. For instance, trials for those with SMA type I benefitting from nusinersen may require a standard-of-care arm rather than placebo, and there is considerable interest in trial designs comparing combination therapy with new treatments added to the new standard of care (nusinersen). In SMA type II and III, on the other hand, there is more clinical equipoise, and thus randomized- or even placebo-controlled trials may find eager participants. The perspective on benefit-risk has also evolved with nusinersen's approval—the former high tolerance for risk is reduced among those who are seeing or anticipating seeing a response to the recently approved treatment.

Cure SMA is grateful to the patients and their representatives and to the physicians and scientific experts who participated, and to the FDA for their support, participation and for bringing this initiative to life. It is hoped that this information will be used to guide approvals of much needed future therapies in SMA.

Appendix 1: Meeting Program, Includes Agenda and Discussion Questions

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Make today a breakthrough.

PATIENT-FOCUSED DRUG DEVELOPMENT MEETING FOR SPINAL MUSCULAR ATROPHY (SMA)

PUBLIC MEETING | APRIL 18, 2017

MEETING AGENDA

7:15am – 8:15am	**Registration** A light breakfast will be served from 7:00-8:00 am
8:15am – 8:20am	**Welcome Remarks** Kenneth Hobby, *President*, Cure SMA
8:20am – 8:45am	**Background on SMA** John W. Day, M.D., Ph.D. *Professor of Neurology, Pediatrics and Pathology; Director, Division of Neuromuscular Medicine,* Stanford University School of Medicine
8:45am – 9:05am	**Opening Remarks** Wilson Bryan, M.D., *Director, Office of Tissues and Advanced Therapies,* CBER, OMPT, FDA
9:05am – 9:15am	**Goals and Objectives for the Meeting and Overview of Discussion Format; Participant Polling of Demographic Questions** James E. Valentine, J.D., M.H.S., *Moderator*

Session 1: Type I SMA Patient Voice

9:20am – 9:40am	**Panel #1 (Topic 1) - SMA Symptoms & Daily Impact** A panel of **SMA type I** patients/caregivers will provide comments to start the discussion
9:40am – 10:35am	**Participant Polling & Large-group Facilitated Discussion on Topic 1**
	SMA type I patients/caregivers in the audience and online are invited to add to the dialogue
10:35am – 10:55am	**Break**

Session 2: Type II/III SMA Patient Voice

10:55am – 11:25am	**Panel #2 (Topic 1) – SMA Symptoms & Daily Impact**
	A panel of **SMA Type II/III** patients/caregivers will provide comments to start the discussion
11:25am – 12:20pm	**Participant Polling & Large-group Facilitated Discussion on Topic 1**
	SMA type II/III patients/caregivers in the audience and online are invited to respond to polling questions and add to the dialogue
12:20pm – 1:20pm	**Lunch Break**

MEETING AGENDA

Session 3: Type I SMA Patient Voice

1:35pm – 1:55pm	**Panel #3 (Topic 2) – Current and Future Approaches to Treatment**
	A panel of **SMA type I** patients/caregivers will provide comments to start the discussion
1:55pm – 2:50pm	**Participant Polling & Large-group Facilitated Discussion on Topic 2**
	SMA type I patients/caregivers in the audience and online are invited to respond to polling questions and add to the dialogue
2:50pm – 3:10pm	**Break**

Session 4: Type II/III SMA Patient Voice

3:10pm – 3:40pm	**Panel #4 (Topic 2) – Current and Future Approaches to treatment**
	A panel of **SMA type II/III** patients/caregivers will provide comments to start the discussion
3:40pm – 4:35pm	**Participant Polling & Large-group Facilitated Discussion on Topic 2**
	SMA type II/III patients/caregivers in the audience and online are invited to respond to polling questions and add to the dialogue
4:35pm – 4:50pm	**Closing Remarks** Jonathan Goldsmith, M.D., *Associate Director for Rare Diseases, Office of New Drugs*, CDER, FDA
4:50pm – 5:00pm	**Next Steps** Jill Jarecki, Ph.D., *Chief Scientific Officer*, Cure SMA

WELCOME LETTER

Dear PFDD Participants,

Welcome to the externally led Patient-Focused Drug Development Meeting for spinal muscular atrophy! Cure SMA, and its collaborating partners, are very pleased to have all of you in attendance. We are excited to have representation from all the key SMA stakeholders at this meeting – senior leaders from the Food and Drug Administration (FDA), industry professionals, members of academia, clinicians, patient-advocacy organizations, individuals affected with SMA and their families and caregivers, across the United States and worldwide. We thank all of you for coming together today to show your support and let your voices be heard!

Bringing the patient's voice to guide the evaluation of future therapeutics for SMA and enhancing the FDA's ability to assess the benefits and risks of a particular therapy is directly connected to the mission of Cure SMA, which is to lead the way to a world without spinal muscular atrophy. We fund and direct comprehensive research that drives breakthroughs in treatment and care, and we provide families the support they need for today.

We especially want to recognize the participating panelists for selflessly giving their time and generously and vulnerably sharing their lives with each of us. We also want to thank the patients, families, and caregivers for coming out today and speaking up about the realities of your lives with SMA; for sharing your hope for you and your loved ones, and your expectations and desires for future treatments in SMA. Your voices will impact the future of SMA and without your contribution this meeting would not have been possible!

We also want to thank the honorable FDA speakers, Dr. Wilson Bryan, MD, Director, Office of Tissues and Advanced Therapies, CBER, OMPT, FDA and Dr. Jonathan Goldsmith, MD, Associate Director for Rare Diseases, Office of New Drugs, CDER, FDA, for their time and support of this meeting, and all senior leaders attending this meeting today. Our entire SMA Community is grateful for your support through the years.

Last, we would like to take this opportunity to thank the Muscular Dystrophy Association and SMA Foundation for their partnership and support of this initiative on behalf of the SMA Community.

Finally, Cure SMA thanks each of you for your ongoing commitment to finding a treatment for this devastating disease. We know that each and every participant in the SMA community plays an essential role in our mission of a world without SMA.

Sincerely,

Kenneth Hobby
President

Jill Jarecki PhD
Chief Scientific Officer

Rosángel Cruz, MA, BS
Associate Research Director of Clinical Affairs

ABOUT THIS PATIENT-FOCUSED DRUG DEVELOPMENT MEETING

The Patient-Focused Drug Development Initiative is part of FDA's commitments under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V), which aims to more systematically obtain the patient's perspective on the burden of specific diseases and current treatments available.

Through this Patient-Focused Drug Development Meeting, the FDA provides a forum where SMA patients, families, and caregivers are invited to share their unique insight on the impact of SMA on their day-to-day lives. The FDA is also interested in gathering the SMA community's perspective on available treatment options and how well these may help to treat their symptoms, strategies for managing their SMA, and expectations for approved treatments for SMA, among other important topics.

At today's meeting, 20 panelists, representing all types, ages and stages of SMA, will bring their voices and stories to depict the real and specific ways in which their lives are impacted by SMA. Each round of panelists will be followed by polling questions and a period of facilitated discussion with participants here in Washington DC, and from across the US via our livestreaming webcast. The goal of this meeting is to increase the FDA's understanding of how patients, families and caregivers manage SMA, and the factors that are taken into account when a treatment is chosen. This in turn, will inform the FDA regarding the benefit-risk balance of treatment options, the severity of the condition, and the urgency of unmet medical needs. Ultimately, your voice and feedback will directly inform decisions made about the drug development process, and the overall assessment of current and future therapies for SMA.

Instructions for Polling Questions

Each session in today's meeting will include a series of polling questions on SMA and its impact on your family's life. In-person attendees are encouraged to use their mobile phones to participate in these polling questions.

Text **2017PFDD** to **22333** to register your device, then follow the instructions below to answer each question when it is presented. If your phone does not accommodate short number texting, please text **2017PFDD** to **747.444.3548.**

For In-person Audience

1. Text and send the letter (A, B, C…) corresponding to your answer to the question on screen.
2. For questions allowing more than one answer, simply type each letter separated by a space and, after all of your choices have been selected, press send.
3. To change/undo your answer Text Clear or Undo.

Standard message and data rates apply.

PANELISTS' BIOS

Gina Cannady | Parent to Emma and Ruby Cannady, SMA type III & II, respectively

Gina lives in Philadelphia, Pennsylvania, with her husband and their three daughters. She is a strong advocate for inclusion and she's been caught calling her Congress members instead of calling for pizza when decisions that affect her family are being made. Gina cherishes her role as mom and works to ensure that her family lives a life full of brightness and joy, despite the significant diagnosis of SMA that affects two of her daughters.

Debbie Cuevas | Parent to Dylan Cuevas, SMA type II

Debbie is the President of the Cure SMA Greater NY Chapter. She took over responsibilities of the Chapter after her son, Dylan, was diagnosed with SMA in 2004. Debbie is a very active advocate for people with disabilities in the New York area. She is also 1st Vice President of the Riverside PTA and also serves on the Reach For a Star Committee. Family is by far the most important thing in Debbie's life. She resides in Rockville Centre, NY with her husband, Ron and their three children, Dylan, Heather, and Nicholas.

Scott Ellis | Parent to Alexandria Ellis, SMA type I

Scott lives with his family, in Lisle, Illinois just 35 minutes outside of Chicago. While Scott and his wife have lucrative careers in marketing and finance, they enjoy spending their downtime with their beautiful daughter Alexandria and her furry siblings (dogs), Bruce and Roxy. Scott's family goal is to continue improving Alexandria's quality of life through her regular treatments while educating and advocating for her disease, Spinal Muscular Atrophy.

Kristen M. Farrell | Parent to Braeden and Kernan Farrell, SMA type II and III, respectively

Braeden (SMA Type II), age five and Kernan (SMA Type II) age four. Kristen is a nationally certified American Sign Language Interpreter, and a board member of the Cure SMA New England Chapter. She enjoys spending time with the kids along with her husband, Jim. She especially loves the beach and loves running.

Christine Getman | SMA type II

Christine is 29 years old and lives with her fiancée in Portland, Oregon. She was diagnosed with SMA type II just after her first birthday. Christine studied Public Health and Psychology at Portland State University. Her career involves program development, volunteer coordination, curriculum implementation, and grant writing. Currently, Christine serves as Ms. Wheelchair Oregon and provides fundraising and development for Magic Wheelchair and The Wheel To Walk Foundation.

Grace Grutter | Parent to Nella Grutter, SMA type I

Grace Grutter is a pediatric registered nurse, turned stay at home medical mom, who resides in Kansas City, Missouri. She is married to her college sweetheart, Baron, and they have two children, Bowen and Nella, and a baby due in August. Since Nella's SMA type I diagnosis, Grace has made it her personal mission to advocate for Nella and all those affected by SMA, including pursuing adding SMA to the newborn screen in Missouri.

Kelly Jankowski | Parent to William Jankowski, SMA type I

Kelly works as a communications executive at Edelman, specializing in executive coaching and corporate positioning. Kelly and her husband Chris are parents to William, an 11-month old with SMA Type I. William began receiving treatment with the first approved drug for SMA via an Expanded Access Program at 6.5 months old. Kelly and Chris live in Philadelphia, both work full time and split care of William 50/50 with help from a full-time nanny and a nurse.

Patti Kemp | Parent to Adalyne and Madison Kemp, SMA type I

Patti Kemp is a wife and mother to four beautiful girls and resides in Birmingham, Alabama. Two of her daughters were diagnosed with SMA type I. Patti is a full time stay at home mother and makes her family her primary focus. Any free time she has, she enjoys running, working in the yard and watching her oldest daughter play travel softball.

Rio Landa | Parent to Mateo Landa, SMA type II

Rio is the mother of Mateo, a smart, fun and outgoing eight year-old boy, with (weak) SMA Type II. Rio lives with her husband Israel in Holly Springs, NC. North Carolina. They are expecting a baby girl due in July. Rio is a nurse and is currently pursuing a graduate degree in nursing. As a family they love animals, traveling, and food.

Kristen Lasko | Parent to Max Lasko, SMA type I

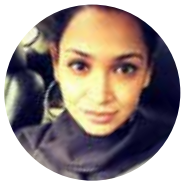
Kristen Lasko worked for six years as an elementary school teacher before becoming a full-time caregiver for her son, Max, (SMA, type I). Now she coordinates a team of homecare nurses, doctors, therapists, and educators keeping Max physically healthy and intellectually stimulated. She and her husband grew up in Montgomery County, Maryland; they now live in Rockville. If seen outside their home, she is most likely dancing at a local Zumba studio.

Jungin Angie Lee | SMA type II

Angie is an 18-year-old, senior in high school, who lives in Naperville, Illinois. She was diagnosed with Spinal Muscular Atrophy Type II at 15 months old. Angie is a co-founder of Angie's Hope, a local nonprofit that hosts annual fundraisers to raise awareness and fund research for a cure for SMA. Angie's Hope has raised over $250,000 towards Cure SMA. Angie plans to study English after high school, and is currently deciding between attending Harvard University or Stanford University. In her free time, she loves singing, writing, and serving the community.

Kathryn McBride | Parent to TJ Maclean, SMA type I

Kate is the proud mom to 11-year-old TJ Maclean, who has SMA type I. Kate is a wife, mother, caregiver and care coordinator, full time special education teacher in an urban district, and is even pursuing her doctorate in Educational Leadership. Kate and her family live in Connecticut and seek treatment for TJ at Connecticut Children's Medical Center in Hartford, CT and Morgan Stanley Children's Hospital at Columbia Presbyterian Hospital in NYC.



Christina Murray | Parent to Omar Hardy, SMA type I

Christina Murray is the mother of Omar Hardy who is a seven year-old boy with SMA type I, diagnosed when he was 6 months old. Omar enjoys watching Sponge Bob, and Disney movies, also spending time with his family. They live in Stroudsburg, Pennsylvania.

Bradley A. Nunemaker | SMA type III

Brad lives in Elmhurst, Illinois with his wife and two sons. Brad is Chief Financial Officer for Aon Hewitt Outsourcing. He graduated with a Bachelor of Business Administration from University of Michigan. Brad was diagnosed with SMA type III when he was 10. Brad serves as Treasurer on the Board of Directors of Cure SMA.

Kevin Schaefer | SMA type II

Kevin is a freelance writer and podcaster. After graduating from North Carolina State University in 2016 with an English degree, Kevin is focused on his writing and disability advocacy. He writes comic book scripts, movie reviews and is the co-host of an entertainment podcast. He is the youngest of three, and lives with his parents in Cary, North Carolina.

Danyelle Sun | Parent to Ruby and Landon Sun, SMA type III & II, respectively

Dany lives in Milwaukee, Wisconsin, with her two kids, Ruby and Landon; her husband Terence; mother, Margie; and their dog, Max and fish, Gooey. Dany is a social worker who works with adults with mental illness; and Terence works in small business sales. As a family, they love to take walks, try new restaurants, and go on weekend adventures! Landon and Ruby are best friends who love to play pretend together and have "tickle wars."

Hugo Trevino | SMA type III

Hugo is a first generation Mexican American who loves his family that consists of one sibling with SMA and two able bodied siblings. Hugo's passion for education and travel has inspired him to obtain a Master's Degree in International Higher Education. He also works for MDA which has allowed his other passion in life, helping people in the healthcare world, to flourish. Hugo envisions obtaining a second master's or a PhD in Public Health. Hugo loves working with people and cannot wait to see where that will take him.

Lyza Weisman | SMA type II

Lyza Weisman is a fourteen years-old, straight A student enrolled in Honors and Advanced Placement classes. A budding painter, aspiring writer, accomplished skier and newly certified scuba diver she stays busy. Lyza enjoys her duties as Colorado's MDA Ambassador, volunteering at the food bank, and working toward her Gold Award in Girl Scouts.

Brynne Willis | SMA type III

Brynne is employed as a coordinator for the Pediatric Neurology division at Johns Hopkins Hospital. She is also pursuing her Masters in Clinical Mental Health at Johns Hopkins University with the intent of tailoring her career around addressing the mental health needs of individuals with disabilities. In her spare time, Brynne enjoys reaching out to the community as the MDA Greater Baltimore Ambassador and trail riding with her horses.

Jessica White | Parent to Madison and Bailey White, SMA type I

Jessica White and her husband Randy have had 2 children with SMA type I. Madison passed away in 2012, at seven months of age, and Bailey is now three years old. Jessica spends her days at home caring for Bailey and is the Family Support Chair for the Virginia Chapter of Cure SMA. Her family loves getting outside when they can and snuggling up for a movie when they have to stay in.

SPEAKERS BIOS

John W. Day, MD, PhD

Dr. Day is a Professor of Neurology & Neurological Sciences Director, at Stanford Neuromuscular Disorders Program. He has over 25 years of experience in diagnosing, treating, and supporting patients with Spinal Muscular Atrophy and other neuromuscular diseases. Dr. Day graduated from the Albert Einstein College of Medicine and completed his Residency and Fellowship at University of California Medical School in San Francisco. Dr. Day is Board Certified in Neurology by the American Board of Psychiatry and Neurology.

Jonathan Goldsmith, MD

Dr. Goldsmith is Associate Director of the Rare Diseases Program at CDER's Office of New Drugs. He earned his medical degree from New York University, received his post-graduate training in Internal Medicine at Vanderbilt, and completed specialty training in hematology at the University of North Carolina. He has had an extensive career in academia as a tenured professor, in regulated industry focusing on clinical drug development, and with rare disease foundations.

Wilson Bryan, MD

Wilson Bryan graduated from the University of Chicago Pritzker School of Medicine. He served on the faculty of the University of Texas Southwestern Medical School, where he was an investigator for clinical trials in neuromuscular disorders, including amyotrophic lateral sclerosis and spinal muscular atrophy. Dr. Bryan joined the FDA in 2000, and now serves as Director of the Office of Tissues and Advanced Therapies in the Center for Biologics Evaluation and Research.

James E. Valentine, JD, MHS| Moderator

James Valentine is an Associate at Hyman, Phelps & McNamara, where he assists medical product industry clients in a wide range of regulatory matters, including new drug and biologic development and approval issues. Before joining the firm, James worked in FDA's Office of Health and Constituent Affairs where he facilitated patient input in benefit-risk decision-making and served as a liaison to stakeholders on a wide range of regulatory policy issues.

SMA PATIENT FOCUSED DRUG DEVELOPMENT – TOPIC QUESTIONS

Topic 1: SMA Symptoms and Daily Impacts

1. What symptoms have the most significant impact on you/your child's day-to-day life (please focus on the top 1-3 symptoms of greatest impact on the life of you/your child)?

2. How does SMA affect you/your child's daily life on best days/on worst days? Describe a best day and worst day for your child and your family.

3. Are there specific activities that are important to you/your child that you/your child cannot do at all or as fully as you would like because of SMA?

4. How have your/your child's symptoms changed over time? How has your/your child's ability to cope with symptoms changed over time? (may apply to patient or caregiver/family of patient)

5. What do you fear most as the disease progresses and you/your child get older? What worries you most about your/your child's condition? What frustrates you the most about your/your child's condition?

Topic 2: Current and Future Approaches to Treatment

1. What are you currently doing to help treat your/your child's SMA/SMA symptoms? (Examples may include prescription medicines, over-the-counter products and other therapies including non-drug therapies)
   a. What specific SMA symptoms do your treatments address?
   b. How has your/your child's treatment regimen changed over time, and why?

2. How well does your current treatment regime treat the most significant symptoms of your/your child's SMA?
   a. How well do these treatments improve your your child's ability to do specific activities that are important to you in your daily life?
   b. What activities that matter to you/your child are you still unable to do?

3. What are the most significant downsides to your/your child's current treatments and how do they affect your/your child's daily life? (Examples of downsides may include bothersome side effects, going to the hospital for treatment, restrictions on driving, etc.)

4. Assuming there is no complete cure for SMA, what specific things would you look for in an ideal treatment for SMA?

SMA PATIENT FOCUSED DRUG DEVELOPMENT – TOPIC QUESTIONS

Topic 2: All SMA Types

1. Which of your/your child's symptoms are not addressed as well by your current treatment regimen?

On an ideal treatment

2. What issues/symptoms would you like a potential treatment to address?

3. What would you consider to be a meaningful improvement (for example symptom improvements or functional improvements) in your/your child's condition that a treatment could provide?

4. How well have these treatments worked for you as your condition has changed over time? Examples of down-sides may include going to the hospital or clinic for treatment, time devoted to treatment, etc.)

On treatment selection

5. What factors do you take into account when making decisions about selecting a course of treatment?

6. What information on the potential benefits of these treatments factors most into your decision?

7. How do you weigh the potential benefits of these treatments versus the common side effects of the treatments? (Common side effects could include headache, nausea, injection site reactions.)

8. How do you weigh potential benefits of these treatments versus the less common but serious risks associated with the treatments? (Examples of less common but serious risks are infections, cancer, liver damage, kidney damage, birth defects, blood disorders, differences in views on near-term serious risks vs serious risks that may emerge many years after treatment)

ABOUT OUR PARTNERSHIPS

The SMA Industry Collaboration is a multi-faceted partnership that brings together pharmaceutical companies, Cure SMA, and other nonprofit organizations, to share information, ideas, and data. The SMA Industry collaboration works together to address scientific, clinical and regulatory topics that are critical for the broader SMA community.

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Appendix 2: FDA, expert, and meeting panel participants

As of 4/10/2017, **422** individuals had registered for this meeting; this included representation from SMA patients, caregivers, patient advocacy organizations, key FDA staff and industry partners. Of these:

- **204** were registered to attend in person (& 218, via webcast).

  Of those registered to **attend in person**,

A. Three (3) FDA officials within CBER, and CDER provided the opening and closing remarks

1. Billy Dunn MD, Director, Division of Neurology Products, CDER, FDA
2. Jonathan Goldsmith, MD, Associate Director for Rare Diseases, OND, CDER, FDA
3. Wilson Bryan, Director, Office of Tissues and Advanced Therapies, CBER

Thirteen (13) others prominent leaders attended, among them,

4. Dr. Peter Marks, MD, PhD, Director, CBER
5. Dr. Eric Bastings, MD, Deputy Director, Division of Neurology Products, CDER, FDA
6. Julienne Vaillancourt, R.Ph., M.P.H., Regulatory Review Committee Chair, CBER, FDA
7. Richard Klein, Director, Patient Liaison Program, Office of Health and Constituents Affairs FDA
8. Salina Prasad, MBA, Patient Liaison Program, Office of Health and Constituents Affairs at FDA
9. Sara Eggers, PhD, Office of Strategic Programs, CDER, FDA
10. Meghana Chalasani, Patient Liaison Program, Office of Health and Constituents Affairs, FDA
11. Pujita Vaidya, MBA, Patient Liaison Program, Office of Health and Constituents Affairs, FDA
12. Shanon Woodward, Patient Liaison Program, Office of Health and Constituents Affairs, CBER, FDA
13. Francis Kalush, PhD Health Program Coordinator, CDER, FDA
14. Elise Nguyen, Office of strategic Programs, CBER, FDA
15. Dr. Lei Xu, MD, PhD, Office of Tissues and Advanced Therapies, CBER
16. Diane Maloney, J.D., Associate Director for Policy, CBER, FDA

B. 27 Industry members, including representation from the following companies:

- Astellas Pharmaceuticals, Inc. (2)
- AveXis, Inc. (4)
- Biogen, Inc. (5)
- Cytokinetics (4)
- Genentech (2)
- F.Hoffmann-La Roche (2)
- Ionis Pharmaceuticals, Inc. (1)
- Novartis Pharmaceuticals (3)
- BioMarin Pharmaceutical Inc. (2)
- Pfizer, Inc. (1)
- Shire (1)

C. 31 were from Patient Advocacy organizations, including:

- MDA (2)
- Fighting for Kaiden Foundation, Inc. (2)

- Wheel to Walk Foundation (1)
- Spinal Muscular Atrophy, Malaysia (1)
- PPMD (1)
- Myotonic Dystrophy Foundation (1)
- SMA Foundation (2)
- Cure SMA (19)
- Jett Foundation (1)
- VSN - The Dutch Neuromuscular Diseases Association (1)

D. Six (6) Scientists/SMA Specialists

- Boston Children's Hospital (1)
- Columbia University Medical Center (1)
- Children Hospital of Philadelphia (CHOP) (1)
- Stanford University (1)
- University of Pennsylvania (1)
- University of Wisconsin (1)

E. Ninety-eight (98) were either, individuals diagnosed with SMA, a parent of a child with SMA or a primary caregiver with a child with SMA (other than a parent); a total of **258** in this category are registered, including webcast participants)

Of these,

- 17 were individuals diagnosed with SMA, (a total of 86/422 individuals with SMA, I-IV, are registered, including webcast participants)
    - One SMA type I
    - Nine SMA type II
    - Seven type III
- 79 were a parent(s) of a child/children with SMA 1-IV (a total of 164/422 are a parent of a child with SMA, including webcast participants)
    - 25 type I
    - 39 type II
    - 15 type III
    - 0 type, *unspecified*
- 2 were primary caregivers of a child with SMA (other than parents; **8/**422 are primary caregivers, including webcast participants)

F. Ten (10) had someone close to them who has/had SMA (a total of **29**/412 were registered under this category, including webcast participants)

G. Panelists' Recruitment: 20 panelists had been recruited to share their stories/journeys with SMA at this meeting. An outstanding group of candidates of all types, ages and stages of SMA were chosen to represent the voices of the SMA community on April 18. Of those,

- Eight are SMA type Is (ages, 1-11 years, parent of a child)
- Six are SMA type IIs (5-29) (patients and parents)
- Six are SMA type IIIs (5-41) (patients and parents

H. Registered Individuals included representation from 40 states and 27 different countries, who had registered to attend the meeting in person and via webcast.

Appendix 3: Polling Questions and Results (SMA type I-III)

Total number of participants: 144; Type I: 30; Type II: 69; Unknown: 45

Date of participation	Number of participants (%)	Type I n (%)	Type II/III n (%)	Unknown n (%)
04/18/2017	120 (83.3%)	26 (86.7%)	52 (75.4%)	42 (93.3%)
04/20/2017	1 (0.7%)			1 (2.2%)
04/21/2017	17 (11.8%)	3 (10.0%)	12 (17.4%)	2 (4.4%)
04/22/2017	2 (1.4%)	1 (3.3%)	1 (1.5%)	
04/23/2017	2 (1.4%)		2 (2.9%)	
04/25/2017	1 (0.7%)		1 (1.5%)	
04/27/2017	1 (0.7%)		1 (1.5%)	

Response Method	Number of participants* (%)	Type I	Type II/III
Text	80 (55.6%)	20 (66.7%)	45 (65.2%)
Web	64 (44.4%)	10 (33.3%)	24 (34.8%)

1. Where do you live?	Number of participants* (%)	Type I	Type II/III
Within Washington, D.C. metropolitan area (including Virginia and Maryland suburbs)	14 (14.7%)	4 (17.4%)	8 (12.7%)
East Coast (outside the Washington, D.C area)	31 (32.6%)	8 (34.8%)	20 (31.8%)
Midwest	29 (30.5%)	7 (30.4%)	20 (31.8%)
West Coast	9 (9.5%)	.	8 (12.7%)
Northwest	3 (3.2%)	.	3 (4.8%)
Outside of the U.S. (international participants)	9 (9.5%)	4 (17.4%)	4 (6.4%)

2. Do you live in:	Number of participants* (%)	Type I	Type II/III
A city	26 (26.3%)	10 (38.5%)	14 (21.2%)
A rural area	10 (10.1%)	2 (7.7%)	7 (10.6%)
A suburban area	63 (63.6%)	14 (53.9%)	45 (68.2%)

3. Which of the following best describes you?	Number of participants* (%)	Type I	Type II/III
I have SMA (Type 1, 2, 3, 4)	18 (19.0%)	2 (8.0%)	16 (23.9%)
I am the parent or caregiver to someone with SMA (Type 0, 1, 2, 3, 4)	77 (81.1%)	23 (92.0%)	51 (76.1%)

4. Have you/your loved one been diagnosed with any of the following SMA types?	Number of participants (%)	Type I	Type II/III
SMA type 0	.	.	.
SMA type 1	30 (30.3%)	30 (100%)	.
SMA type 2	45 (45.5%)	.	45 (65.2%)
SMA type 3	24 (24.2%)	.	24 (34.8%)
SMA type 4	.	.	.
Unknown	.	.	.

*Includes Unknown Type of SMA

5. What is the length of time since your/your loved one's diagnosis?	Number of participants*	Type I	Type II/III
Less than 1 year ago	9 (9.3%)	5 (17.9%)	4 (6.0%)
1 year ago to less than 2 years ago	2 (2.1%)	2 (7.1%)	.
2 years ago to less than 5 years ago	21 (21.7%)	6 (21.4%)	15 (22.4%)
5 or more years ago	65 (67.0%)	15 (53.6%)	48 (71.6%)
I am not sure	.	.	.

6. What is your/your loved one's age?	Number of participants*	Type I	Type II/III
≤ 2 years	9 (9.1%)	8 (30.8%)	1 (1.5%)
3-12 years	43 (43.4%)	13 (50.0%)	28 (41.2%)
13-17 years	12 (12.1%)	.	12 (17.7%)
18-34 years	29 (29.3%)	5 (19.2%)	22 (32.4%)
35-49 years	3 (3.0%)	.	3 (4.4%)
50-65 years	3 (3.0%)	.	2 (2.9%)
Older than 65	.	.	.

7. You are/your loved one is:	Number of participants*	Type I	Type II/III
Male	41 (40.6%)	17 (58.6%)	22 (32.4%)
Female	60 (59.4%)	12 (41.4%)	46 (67.7%)

8. On a day to day basis, *primary* caregiving for me/my loved one is provided by:	Number of participants*	Type I	Type II/III
Parent(s)	77 (75.5%)	23 (79.3%)	51 (76.1%)
Partner/Spouse	11 (10.8%)	.	10 (14.9%)
Grandparent(s)	1 (1.0%)	.	.
Sibling/other family member	2 (2.0%)	1 (3.5%)	1 (1.5%)
Nurse or other professional caregiver	10 (9.8%)	5 (17.2%)	4 (6.0%)
Other (friend, nanny, other relative)	1 (1.0%)	.	1 (1.5%)

9. In the past year, how often have you/your loved one had to go to the hospital, for emergency care or inpatient hospitalization due to your/your loved one's SMA?	Number of participants* (n=110)	Type I (n=25)	Type II/III (n=68)
None in the past year	58 (52.7%)	12 (41.4%)	40 (58.8%)
1-2 times	32 (29.1%)	7 (28.0%)	17 (25.0%)
3-5 times	13 (11.8%)	4 (16.0%)	9 (13.2%)
6-10 times	3 (2.7%)		2 (2.9%)
More than 10 times	4 (3.6%)	3 (12.0%)	.

*Includes Unknown Type of SMA

10. In the past year, how often have you/your loved one had to go to a doctor or a specialty provider for routine care, or follow up of your/your loved one's SMA	Number of participants* (n=96)	Type I (n=21)	Type II/III (n=65)
None in the past year	1 (1.0%)	.	1 (1.5%)
1-2 times	13 (13.5%)	2 (9.5%)	10 (15.4%)
3-5 times	24 (25.0%)	3 (14.3%)	20 (30.8%)
6-10 times	18 (18.8%)	1 (4.8%)	15 (23.1%)
More than 10 times	40 (41.7%)	15 (71.4%)	19 (29.2%)

11a. Which of the following symptoms currently has the most significant impact on you/your loved one's life? Select TOP 4	Number of responses* / Percent of participants (n=108)	Type I (n=25)	Type II/III (n=66)
Breathing difficulties (shallow, rapid, depressed breathing, etc.)	24 (22.2%)	13 (52.0%)	8 (12.1%)
Communication difficulties	19 (17.6%)	16 (64.0%)	2 (3.0%)
Inability to cough/clear lung secretions	35 (32.4%)	11 (44.0%)	20 (30.3%)
Feeding/swallowing difficulties	24 (22.2%)	10 (40.0%)	11 (16.7%)
Muscle weakness (facial, neck, arms, forearms, hips, legs)	66 (61.1%)	8 (32.0%)	44 (66.7%)
Breathing/lung infections (e.g. pneumonia, viral infections, etc.)	27 (25.0%)	6 (24.0%)	16 (24.2%)
Respiratory Failure requiring assistive devices (BiPAP, Ventilator, etc.)	16 (14.8%)	8 (32.0%)	7 (10.6%)
Joint contractures (tight muscles and tendons) / severe scoliosis	37 (34.3%)	2 (8.0%)	26 (39.4%)
Fatigue	57 (52.8%)	1 (4.0%)	47 (71.2%)
Falls	22 (20.4%)		16 (24.2%)
Sleep problems	21 (19.4%)	2 (8.0%)	13 (19.7%)
Bone fractures/Hip dislocation	18 (16.7%)	1 (4.0%)	12 (18.2%)
Other	5 (4.6%)	1 (4.0%)	3 (4.5%)
Paralysis	.		

Not everyone selected 4 choices

*Includes Unknown Type of SMA

11b. Which of the following symptoms currently has the most significant impact on you/your loved one's life? Select TOP 4	Number of responses*	Type I	Type II/III
Respiratory Difficulties (breathing difficulties, inability to cough/clear lung secretions, breathing/lung infections, and respiratory failure)	102	38 (48.1%)	51 (22.7%)
Communication difficulties	19	16 (20.3%)	2 (0.9%)
Feeding/swallowing difficulties	24	10 (12.7%	11 (4.9%)
Muscle weakness (facial, neck, arms, forearms, hips, legs)	66	8 (10.1%)	44 (19.6%)
Joint contractures (tight muscles and tendons) / severe scoliosis	37	2 (2.5%)	26 (11.6%)
Fatigue	57	1 (1.2%)	47 (20.9%)
Falls	22	.	16 (7.1%)
Sleep problems	21	2 (2.5%)	13 (5.8%)
Bone fractures/Hip dislocation	18	1 (1.3%)	12 (5.3%)
Other	5	1 (1.3%)	3 (1.3%)
Paralysis	.	.	.

12. What specific activities that are most important to you/your loved one are you/your loved one not able to do because of SMA? Select TOP 4	Number of responses* / Percent of participants (n=101)	Type I (n=23)	Type II/III (n=61)
Independence in mobility (around the house, to work, to school)	44 (43.6%)	13 (56.5%)	25 (41.0%)
Feed oneself	25 (24.8%)	11 (47.8%)	10 (16.4%)
Ability to spend time alone / be independent	24 (23.8%)	12 (52.2%)	11 (18.0%)
Engage in social activities and building relationships (playdates, dining out, dating, hugging my partner)	34 (33.7%)	12 (52.2%)	18 (29.5%)
Attend work or school	16 (15.8%)	8 (34.8%)	7 (11.5%)
Engage in physical activities (playing sports, going to the gym)	25 (24.8%)	4 (17.4%)	18 (29.5%)
Transferring (from wheelchair/scooter to bed, toilet, etc.)	42 (41.6%)	5 (21.7%)	29 (47.5%)
Attend to personal hygiene independently	25 (24.8%)	3 (13.0%)	16 (26.2%)
Dress oneself	39 (38.6%)	3 (13.0%)	27 (44.3%)
Going to restroom by oneself	51 (50.5%)	4 (17.4%)	35 (57.4%)
Turning in bed	39 (38.6%)	4 (17.4%)	27 (44.3%)
Other	2 (2.0%)	1 (4.3%)	1 (1.6%)

Not everyone selected 4 choices

*Includes Unknown Type of SMA

13a. Which of the following have you experienced as a result of coping with your/your loved ones SMA? Select ALL that apply	Number of responses	Percent of participants (n=105*)
Depression	64	61.0%
Anxiety	83	79.0%
Social isolation	67	63.8%
Loss of job	26	24.8%
Troubled relationships	52	49.5%
Other	25	23.8%

13b. Which of the following have you experienced as a result of coping with your/your loved ones SMA? Select ALL that apply	Type I responses (25 participants)	Type II responses (41 participants)	Type III responses (22 participants)	Combined Type II/III responses (63 participants)
	n (%)	n (%)	n (%)	n (%)
Depression	13 (52.0%)	22 (53.7%)	15 (68.2%)	37 (58.7%)
Anxiety	13 (52.0%)	22 (53.7%)	15 (68.2%)	48 (76.2%)
Social isolation	21 (84.0%)	30 (73.2%)	18 (81.8%)	40 (63.5%)
Loss of job	15 (60.0%)	27 (65.9%)	13 (59.1%)	13 (20.6%)
Troubled relationships	5 (20.0%)	10 (24.4%)	3 (13.6%)	32 (50.8%)
Other	11 (44.0%)	21 (51.2%)	11 (50.0%)	15 (23.8%)

14. What is the estimated annual SMA-related expenses/costs you and your family pay directly including copays, deductibles, prescriptions, medical supplies, adaptive vehicles, and mobility devices? Select ONE option	Number of responses* / Percent of participants	Type I	Type II/III
<$500	4 (3.5%)	.	3 (4.5%)
$500-$999	11 (9.6%)	3 (11.5%)	6 (9.0%)
$1,000-$1,999	1 (0.9%)	2 (7.7%)	.
$2,000-$2,999	5 (4.5%)	.	4 (6.0%)
$3,000-$4,999	15 (13.4%)	2 (7.7%)	12 (17.9%)
$5,000-$14,999	35 (31.3%)	8 (30.8%)	22 (32.8%)
$15,000-$19,999	9 (8.0%)	2 (7.7%)	5 (7.5%)
$20,000-$29,999	7 (6.3%)	3 (11.5%)	3 (4.5%)
$30,000-$39,999	5 (4.5%)	3 (11.5%)	2 (3.0%)
$40,000-$49,999	2 (1.8%)	1 (3.9%)	1 (1.5%)
$50,000-$79,999	4 (3.6%)	.	2 (3.0%)
$80,000-$100,000	4 (3.6%)	.	2 (3.0%)
>$100,000	1 (0.9%)	.	1 (1.5%)
Unknown	7 (6.3%)	1 (3.9%)	4 (5.6%)
Not applicable (N/A)	2 (1.8%)	2 (7.7%)	.

*Includes Unknown Type of SMA

15a. Have you/ your loved one ever been prescribed (either by your doctor or through a clinical trial) and taken the following medications? Select ALL that apply	Number of responses	Percent of participants (n=89)
Albuterol (inhaled)	52	58.4%
Albuterol (liquid)	20	22.5%
Albuterol (tablet)	7	7.9%
Carnitine	24	27.0%
Creatine	15	16.9%
Hydroxyurea	3	3.4%
Steroids	16	18.0%
Valporoic Acid (VPA)	20	22.5%
Sodium Phenylbuterate	6	6.7%
Riluzole	.	
Nusinersen/Spinraza	27	30.3%
Other	14	15.7%

15b. Have you/ your loved one ever been prescribed (either by your doctor or through a clinical trial) and taken the following medications? Select ALL that apply	Type I responses (18 participants)	Type II responses (37 participants)	Type III responses (19 participants)	Combined Type II/III responses (56 participants)
	n (%)	n (%)	n (%)	n (%)
Albuterol (inhaled)	11 (61.1%)	27 (73.0%)	5 (26.3%)	32 (57.1%)
Albuterol (liquid)	4 (22.2%)	6 (16.2%)	2 (10.5%)	8 (15.3%)
Albuterol (tablet)	2 (11.1%)	1 (2.7%)	3 (15.8%)	4 (7.1%)
Carnitine	5 (27.8%)	9 (24.3%)	4 (21.1%)	13 (23.2%)
Creatine	0	10 (27.0%)	2 (10.5%)	12 (21.4%)
Hydroxyurea	0	3 (8.1%)	0	3 (5.4%)
Steroids	2 (11.1%)	4 (10.8%)	5 (26.3%)	9 (16.1%)
Valporoic Acid (VPA)	2 (11.1%)	8 (21.6%)	4 (21.1%)	12 (21.4%)
Sodium Phenylbuterate	1 (5.6%)	2 (5.4%)	1 (5.3%)	3 (5.4%)
Riluzole	.	.	.	
Nusinersen/Spinraza	9 (50.0%)	7 (18.9%)	8 (42.1%)	15 (26.8%)
Other	6 (33.3%)	4 (10.8%)	4 (21.1%)	8 (14.3%)

16a. What are you currently doing to help treat your/your loved one's SMA/SMA symptoms? Select ALL that apply	Number of Responses	Percent of participants (n=98)
Respiratory Maintenance (may include Chest PT, suctioning, airway clearance, cough assistance, breathing support, devices, etc.)	66	67.3%
Nutritional support (nasogastric tube, nasojejunal (NJ) tube, gastrostomy (G) tube)	41	41.8%
Physiotherapy /Physical Therapy (PT)	64	65.3%
Aqua Therapy	41	41.8%
Occupational Therapy (OT)	45	45.9%
Speech Therapy	23	23.5%
Mobility equipment (adaptive strollers, wheelchair, scooters, adaptive tricycles, crutches, walkers)	86	87.8%
Orthotics' support (Braces [AFOs, KAFOs, TLSO], neck collar, splints, etc.)	59	60.2%

16a. (continued)		
Orthopedic support (Stander)	32	32.7%
Approved therapy (Spinraza)	30	30.6%
Investigational product (clinical trial)	9	9.2%
Other	14	14.3%

16b. What are you currently doing to help treat your/your loved one's SMA/SMA symptoms? Select ALL that apply	Type I responses (17 participants)	Type II responses (40 participants)	Type III responses (23 participants)	Combined Type II/III responses (63 participants)
	n (%)	n (%)	n (%)	n (%)
Respiratory Maintenance (may include Chest PT, suctioning, airway clearance, cough assistance, breathing support, devices, etc.)	15 (88.2%)	34 (85.0%)	4 (17.4%)	38 (60.3%)
Nutritional support (nasogastric tube, nasojejunal (NJ) tube, gastrostomy (G) tube)	14 (82.4%)	17 (42.5%)	2 (8.7%)	19 (30.2%)
Physiotherapy /Physical Therapy (PT)	13 (76.5%)	26 (65.0%)	14 (60.9%)	40 (63.5%)
Aqua Therapy	5 (29.4%)	18 (45.0%)	11 (47.8%)	29 (46.0%)
Occupational Therapy (OT)	8 (47.1%)	19 (47.5%)	10 (43.5%)	29 (46.0%)
Speech Therapy	10 (58.8%)	8 (20.0%)	1 (4.3%)	9 (14.3%)
Mobility equipment (adaptive strollers, wheelchair, scooters, adaptive tricycles, crutches, walkers)	12 (70.6%)	39 (97.5%)	19 (82.6%)	58 (92.1%)
Orthotics' support (Braces [AFOs, KAFOs, TLSO], neck collar, splints, etc.)	12 (70.6%)	27 (67.5%)	10 (43.5%)	37 (58.7%)
Orthopedic support (Stander)	5 (29.4%)	15 (37.5%)	3 (13.0%)	18 (28.6%)
Approved therapy (Spinraza)	10 (58.8%)	8 (20.0%)	8 (34.8%)	16 (25.4%)
Investigational product (clinical trial)	3 (17.6%)	3 (7.5%)	3 (13.0%)	6 (9.5%)
Other	4 (23.5%)	3 (7.5%)	6 (26.1%)	9 (14.3%)

17. Which of these do you/your loved one use for respiratory assistance? Select ALL that apply	Responses / Percent of participants (n=83*)	Type I (n=18)	Type II/III (n=50)
Chest physiotherapy (CPT) for clearance/comfort	41 (49.4%)	12 (66.7%)	17 (34.0%)
Postural Drainage	20 (24.1%)	6 (33.3%)	6 (12.0%)
High frequency chest wall oscillation (VEST ©)	32 (38.6%)	9 (50.0%)	17 (34.0%)
Cough Assist Device	70 (84.3%)	15 (83.3%)	42 (84.0%)
Suction to remove secretions	44 (53.0%)	17 (94.4%)	17 (34.0%)
Non-invasive ventilation (NIV), such as BiPAP	38 (45.8%)	8 (44.4%)	21 (42.0%)
Invasive ventilation / Mechanical ventilator (with tracheotomy)	14 (16.9%)	9 (50.0%)	3 (6.0%)
Other	9 (10.8%)	2 (11.1%)	6 (12.0%)

*Includes Unknown Type of SMA

18. Have you/your loved one undergone Scoliosis surgery (growing rods or spinal fusion)?	Number of participants	Type I	Type II/III
Yes	40 (41.2%)	5 (25.0%)	28 (45.9%)
No	57 (58.8%)	15 (75.0%)	33 (54.1%)

19. Have you/your loved one undergone Scoliosis surgery (growing rods or spinal fusion)?	Number of participants	Type I	Type II/III
Yes	40 (41.2%)	5 (25.0%)	28 (45.9%)
No	57 (58.8%)	15 (75.0%)	33 (54.1%)

20. Which outcome below would you rank as most important for a possible drug treatment? Select ONE option	Number of participants	Type I	Type II/III
The treatment will provide gains in function (e.g., increased strength, energy, doing something I was unable to do before)	64 (63.4%)	13 (59.1%)	39 (63.9%)
The treatment will lessen symptoms that would improve my/my loved one's current quality of life and /or allow for enhanced activities of daily living	11 (10.9%)	5 (22.7%)	3 (4.9%)
The treatment will stop or slow down disease progression (even if does not provide lessening of symptoms that would improve my/my loved one's current quality of life and /or allow for enhanced activities of daily living	24 (23.8%)	3 (13.6%)	18 (29.5%)
The treatment will prolong life span	1 (1.0%)	.	1 (1.6%)
Other	1 (1.0%)	1 (4.6%)	.

21. Which of the following factors would influence your decision to not use or stop a given treatment? Select ALL that apply	Responses / Percent of participants (n=102*)	Type I (n=22)	Type II/III (n=62)
The significant risks of serious side effects such as cardiac or kidney issues	91 (89.2%)	17 (77.3%)	56 (90.3%)
The common side effects of the treatment, such as nausea, loss of appetite, etc.	17 (16.7%)	3 (13.6%)	9 (14.5%)
The way that treatment is administered (for example, orally, intravenously, intrathecally),	16 (15.7%)	4 (18.2%)	9 (14.5%)
How long the treatment takes, whether it requires hospitalization, required doctors' visits, etc.	16 (15.7%)	5 (22.7%)	7 (11.1%)
The time that it would take away from my daily activities, job, school, etc.	20 (19.6%)	2 (9.1%)	14 (22.6%)
The burden of administration, such as the need for anesthesia, radiation exposure, surgical procedure, etc.	32 (31.4%)	10 (45.5%)	14 (22.6%)
Cost	42 (41.2%)	8 (36.4%)	26 (41.9%)
Other	7 (6.9%)	2 (9.1%)	3 (4.8%)

22. Have you /your loved one ever participated in any type of clinical trial studying experimental treatments for SMA? Select ALL that apply	Responses		Percent of participants (n=96)
	n	%	
Yes	30	23.4%	31.3%
No	39	30.5%	40.6%
Tried to enroll in a clinical trial, but did not qualify	36	28.1%	37.5%
Tried to enroll but trial enrolment was closed	11	8.9%	11.5%
Did not want to enroll due to burden of trial (travel, potential risks, time missed from work, etc.)	3	2.3%	3.1%
Did not want to enroll for other reasons	3	2.3%	3.1%
I've received access to an experimental drug through an Expanded Access / Compassionate Use Program but did not participate in a clinical trial for this drug	5	3.9%	5.2%
I'm not sure	1	0.8%	1.0%

21b. Reasons for not enrolling	Responses
Tried to enroll in a clinical trial, but did not qualify	36 (62.1%)
Tried to enroll but trial enrolment was closed	11 (19.0%)
Did not want to enroll due to burden of trial (travel, potential risks, time missed from work, etc.)	3 (5.2%)
Did not want to enroll for other reasons	3 (5.2%)
I've received access to an experimental drug through an Expanded Access / Compassionate Use Program but did not participate in a clinical trial for this drug	5 (8.6%)

22a. Which of the following factors would you rank as most important to your decision about whether to participate in a clinical trial to study an experimental treatment? Select TOP 4	Responses		Percent of participants (n=98)
	n	%	
Reputation of study site PI (Doctor)	30	9.0%	30.6%
Common side effects (headache, back-pain, skin rashes)	21	6.5%	21.4%
The risk of rare but serious side effects (life-threatening allergic reaction)	64	19.19%	65.3%
How the treatment might prevent further disease progression or improve my/my loved one's health	75	23.4%	76.5%
How the trial might affect my/my loved one's current treatment plan	21	6.5%	21.4%
Promise of receiving open label therapy at the end of the study	36	11.2%	36.7%
Proximity of the study site	18	5.6%	18.4%
Frequency of visits	13	4.1%	13.3%
Duration of visits	4	1.3%	4.1%
Availability of safety data	29	9.0%	29.6%
Availability of preclinical or animal model efficacy data	11	3.4%	11.2%

22b. Which of the following factors would you rank as most important to your decision about whether to participate in a clinical trial to study an experimental treatment? Select TOP 4	Type I Responses (19 participants)	Type II Responses (39 participants)	Type III Responses (21 participants)	Combined Type II/III responses (60 participants)
	n (%)	n (%)	n (%)	n (%)
Reputation of study site PI (Doctor)	8 (42.1%)	12 (30.8%)	3 (14.3%)	15 (25.0%)
Common side effects (headache, back-pain, skin rashes)	7 (36.8%)	7 (17.9%)	4 (19.0%)	11 (18.3%)
The risk of rare but serious side effects (life-threatening allergic reaction)	12 (63.2%)	23 (59.0%)	13 (61.9%)	36 (60.0%)
How the treatment might prevent further disease progression or improve my/my loved one's health	13 (68.4%)	32 (82.1%)	18 (85.7%)	50 (83.3%)
How the trial might affect my/my loved one's current treatment plan	5 (26.3%)	7 (17.9%)	4 (19.0%)	11 (18.3%)
Promise of receiving open label therapy at the end of the study	5 (26.3%)	17 (43.6%)	6 (28.6%)	23 (38.3%)
Proximity of the study site	2 (10.5%)	9 (23.1%)	6 (28.6%)	15 (25.0%)
Frequency of visits	1 (5.3%)	8 (20.5%)	2 (9.5%)	10 (16.7%)
Duration of visits	0	4 (10.3%)	0	4 (6.7%)
Availability of safety data	4 (21.1%)	12 (30.8%)	9 (42.9%)	21 (35.0%)
Availability of preclinical or animal model efficacy data	3 (15.8%)	5 (12.8%)	3 (14.3%)	8 (13.3%)

23a. What type of insurance do you or your loved one have? Select ALL that apply	Responses		Percent of participants (n=98)
	n	%	
Private/commercial health insurance (e.g. Aetna, Blue Cross Blue Shield, etc.)	79	53.7%	80.6%
Medicare	13	8.8%	13.3%
Medicaid	54	36.7%	55.1%
TRICARE health insurance	1	0.7%	1.0%
VA Care health insurance	.		

23b. What type of insurance do you or your loved one have? Select ALL that apply	Type I responses (19 participants)	Type II responses (36 participants)	Type III responses (22 participants)	Combined Type II/III responses (58 participants)
	n (%)	n (%)	n (%)	n (%)
Private/commercial health insurance (e.g. Aetna, Blue Cross Blue Shield, etc.)	15 (78.9%)	30 (83.3%)	20 (90.9%)	50 (86.2%)
Medicare	2 (10.5%)	6 (16.7%)	1 (4.5%)	7 (12.1%)
Medicaid	12 (63.2%)	25 (69.4%)	6 (27.3%)	31 (53.4%)
TRICARE health insurance	0	1 (2.8%)	0	1 (1.7%)
VA Care health insurance	.			

Appendix 4: Post-meeting survey - SMA Patient-Focused Drug Development Meeting

Topic Questions

1. First/Last name
2. Email:
3. I attended the meeting (2 options: In person vs Webcast)
4. What is your connection to SMA? (My child has SMA vs I have SMA)
5. What type of SMA do you have/your loved one has?

Topic 1: SMA Symptoms and Daily Impacts

1. Of all the ways SMA affects your life, which one to three symptoms have the most significant impact on you/your loved one's day-to-day life? (1000 characters)

2. Are there specific activities that are important to you/your love that you/your loved one cannot do (at all or as fully as you would like) because of SMA? (1,000 characters)

3. What specific activities (social, physical, at home, in school, etc.) that are important to you/your loved one are you not able to do due to SMA? (1,000 characters)

4. How does SMA affect you/your loved one on an average day? / Has this gotten worse over time? (1,700 characters)

5. What worries you most about your/your loved one's SMA? (1,000 characters)

Topic 2: Current and Future Approaches to Treatment

1. What are you currently doing to help treat your/your loved one SMA/SMA symptoms? *(Examples may include prescription medicines, over-the-counter products and other therapies including non-drug therapies, PT, OT, etc.) (*1,000 characters)

2. How well does your current treatment work to treat the most significant symptoms of your/your love one's SMA? (/ Which symptoms are not treated? (1000 characters)

3. What are the most significant downsides to your/your loved one's current treatments and how do they affect your/your child's daily life? (*Examples of downsides may include bothersome side effects, going to the hospital for treatment, restrictions on driving, etc.*) (1,000 characters)

4. What factors do you take into account when making decisions about using treatments? (1,000 characters)

5. Assuming there is not a complete cure for SMA, what specific things would you look for in an ideal treatment for SMA? (1,000 characters)

Summary of comments submitted to the post-meeting questionnaire on SMA symptoms

A total of 11 people with SMA (types I through IV) or their caregivers responded to the survey. The responses underscored a number of the key areas and themes touched on during the meeting, but also included some unique insights into the patient experience. Some of these comments are highlighted below.

What are your most significant symptoms?

Caregivers to those with SMA type I said that their children lacked the strength to "move their legs," sit, or "lift their head." As the child ages, swallowing and respiratory difficulties become overriding concerns that are shared by caregivers to children with SMA type II. Caregivers of children with SMA type II also stressed the symptoms of fatigue and "generalized weakness" that limit the child's ability to take care of themselves, to reach and/or hold objects and maneuver around, making them more dependent upon their caregivers, one of whom expressed frustration at how caregiving left them with little "time available for spouse or other siblings."

A number of people with SMA type III and their caregivers, as well as a caregiver to a parent with SMA IV, described similar symptoms such as fatigue and challenges as their muscles begin to fail them and they began to lose functional abilities—and independence —that they had previously had. "Lack of arm strength" made transferring more difficult, some were now "unable to walk, sit and get up..., turn in bed or go to the bathroom" by themselves. One said "recently, my arms are getting weaker, which caused me to go onto disability."

What specific activities can you or your loved not do as well or fully due to SMA?

SMA makes it difficult to take part in many valued activities of life, according to the severity of SMA type and age. For one caregiver's infant with SMA type I, tummy time was difficult, while an older SMA type I child was unable to "do the things the rest of the family wants to do." One girl with SMA type I-II "wants to walk, and imitates running when she plays with her sisters. She loves to eat but has to be watched during meal times." In order to color, someone must hold her hand. Caregivers to those with SMA type II cited the inability to hold toys, to manage basic self-care, or to travel to and see sites that are inaccessible due to their limited mobility. Responses from people with SMA type III and IV or their caregivers also stressed difficulty traveling and any activity involving transfers. One adult with SMA type III was no longer able to cook without assistance; another could only drive an adapted car.

What specific activities important to you that you cannot do at all due to SMA?

As was noted during the discussion session, fear that a child with SMA type I or II might "catch a cold" prevents many being able to go out, socialize, or attend school consistently. One caregiver said her child "must be homebound in the winter due to germs." Another caregiver said their child with SMA type I was "unable to adequately communicate needs and desires" which also "limits social relationships for her." Many physical activities with their friends are impossible for most of the children who have never reached developmental milestones such as sitting, or become impossible, as one parent said, "for my child who has lost some skills over the past year."

The loss of functional abilities was again a theme for those with SMA type III. One respondent could no longer "garden or plant flowers," and is "unable to continue working." Another could not "dish up her own food." Another felt they couldn't engage in social and physical activities. One caregiver focused on their child's lack of strength needed for fine motor skills—such as their inability to open a marker or pen.

How does SMA affect you on an average day? Has it gotten worse over time?

One insight offered by one of the respondents was that average days for caregivers of children with SMA

type I is initially spent dealing with the impact of your child having a life-threatening illness and learning how to manage it. “The first year is a huge learning curve and just when you think you have got it all figured out, there is a curveball in the form of an illness or a plug,” one said. After such an experience, each day the caregiver must be “on guard constantly for the next shoe to drop.” One mother said that the child’s treatments consume a lot of time during the average day, and that “it gets worse when [she] gets ill. I am the only one in the family who could do [her] treatment, so in this case my other two daughters miss out on a lot.”

Caregivers described the average day being spent providing full assistance to children with most activities of daily living. “She is totally dependent on her parents for care, she has a one-on-one aid to assist with everyday activities,” said one. Furthermore, as the children have gotten older and grown, they have lost physical abilities that they were previously able to do. “She used to tolerate being in a standing frame, she no longer can, she used to sit very securely without her wheelchair, she no longer can,” one parent wrote.

Those with or providing care to those with SMA type III-IV described a variety of average days depending upon their age, and how far their condition had progressed. For one girl that could still stand, the caregiver described an average day of her “feeling tired, left out with peers, and frustrated at limitations or inabilities that other peers do not have.” Another described her daughter as being “a very happy person,” but, like others with SMA type III, she has had to adjust to having lost some functional abilities (she lost the ability to walk at the age of 8) and now being more dependent upon others. As mentioned by panelists and during the discussion, a couple respondents described periods of loss, followed by relative stability. Some adults with SMA had also recently lost the ability to walk. “I would love to dance just one more time with my husband. We never danced much, but just one more time,” said one.

What worries you most about your / your loved one’s SMA?

This question had not been asked directly during the discussion session, but caregivers to children with SMA type I and type II echoed many of the same concerns that meeting participants had expressed. There were concerns about losing the ability to swallow or risks that operations might entail, or that the child might “catch a common cold or the flu and will end up hospitalized or worse.” “What scares me most is the thought of her passing away,” said one caregiver and other comments mirrored that. Others worried about specific never reaching certain developmental milestones or losing functional abilities such as head control and the ability to “lift small light objects.” One caregiver to a child with SMA type II said that they were worried about not being able to manage the economic costs of medical procedures; while another worried about the social costs for their child—that they might be bullied in school, or suffer from “feelings of not being good enough.”

Fears of the major functional losses preoccupied many of those with or caring for people with SMA type III. A couple feared losing arm strength—the time “when will I no longer be able to lift my arms to care for myself, [(e.g. to] dress [myself], [apply] make-up, [and give] hugs!” said one respondent. One caregiver worried about “the long-term consequences of being wheelchair-bound such as contractures, and weight gain.” Two caregivers worried about the prospects for their child in adulthood or parenthood, including “living independently, getting married and finding someone that will accept her and be willing to take on the extra work she requires.”

Finally, the caregiver to a father with SMA IV who has seen loss of functional abilities worried most that he might start “to have difficulty swallowing and breathing” much like caregivers to children with SMA type I or II.

Additional feedback on the symptoms of SMA

Four respondents offered further comments about the burden of SMA. Three parents of children with SMA

(types II and type III) focused on the responsibility and burden for the caregivers. One spoke about making life accessible and their child as strong as possible so that their child could "achieve goals like being a parent, doing meaningful work without lots of sick episodes, etc." Another stressed how SMA is "24 hour/seven days a week. It is difficult to watch someone lose skills and strength to become more dependent on those around them, [and] frustrating because [they] are aware of what is happening with their bodies." Another reiterated point made during the meeting was about the psychological burden: "All parents live with PTSD, being sleep deprived because we do not get nursing help, and we do not make the appointments we need for ourselves as caregivers. This disease is going to have medical implications beyond the children to be considered."

Finally, a middle-aged adult with phase III losing functional abilities worried about her own long-term care, its cost, and whether to buy long-term care insurance. "The financial burden is overwhelming," she said. "If I must be placed in a nursing home at an early age due to lack of strength, the financial cost will eliminate what we have saved."

Such concerns may become more common, as more children and young adults with SMA begin to live longer lives on treatments that may change the trajectory of SMA without putting a stop to progression.

What are you currently doing to help treat your/your loved one SMA and SMA symptoms, and how well does it work?

Many of the respondents reported using the same treatments as what participants had described using during the meeting, including medications for the symptoms of SMA, including albuterol (liquid and inhaled) and levalbuterol inhalers, minerals and supplements, antioxidants (carnitine, CQ10), anti-reflux medications (such as glycopyrronium bromide), allergy meds, medications for constipation, zoledronic acid (Zometa) infusions to improve bone density, pain medications and corticosteroid injections to treat bursitis. Similar non-pharmaceutical therapies, devices and procedures were also used including physical therapy, occupational therapy, aqua therapy (pool therapy/hydrotherapy), equine therapy, non-invasive respiratory treatment (BiPAP, Chest PT, suctioning), specialized diets, speech therapy and eye gaze for communication, and braces including the thoracolumbosacral orthosis (TLSO) back brace and ankle-foot orthotic braces (AFOs) and applying foot oils.

As for whether any of these treatments work, one caregiver thought that "pool therapy works well to maintain and improve endurance and muscle functioning," while another said that more intensive respiratory treatment during infections had stabilized their child until only BiPAP was necessary. For the most part, quite a few said that these treatments were what they thought was needed to keep their SMA stable and which might be keeping preventing further progression: One caregiver said they were "not sure it's super helpful" and that her daughter was "not gaining anything but not necessarily losing [functions] rapidly either." One person with SMA type III said that her pain and corticosteroid "treatments work for a period of time." Another said she thought her physical and occupational therapy did not work "at all."

Only two children were currently using nusinersen, but they had started it too recently for the caregiver to have formed an opinion on whether or not it was working for them.

What are the most significant downsides to your/your loved one's current treatments and how do they affect your/your child's daily life?

Respondents to the survey repeated a couple of the key themes about the downsides of treatment that had been mentioned by participants and panelists at the meeting.

One is that accessing symptomatic treatment and care, and the treatments themselves were often time-consuming, and this had consequences for the patient and their caregivers. Two focused on the "time it takes to schedule and get to appointments and therapies." One said that the "frequent trips to see doctors

and… the long drives to see necessary specialists… result in missed school days or other events." Another, who focused on the time that "it takes to perform the treatments" wrote that "there definitely is a downside—it's having a normal life, where you can plan holidays and go abroad without having to think of a thousand things to do or get sorted for your SMA kid. We can't even plan a day ahead without thinking the worst."

The investment in time would not be as much of a downside if the treatments were "doing anything to gain [functions] or strength or even slowing down the progression," said one caregiver. A few respondents reiterated the theme that these treatments were for the symptoms and not the underlying cause of the disease or its primary effect—the lack of muscle strength. "I [still] rely on my husband for 90% of all activities related to keeping our home. The treatments do not resolve these issues," said one participant with SMA type III.

One caregiver who gives her child a variety of therapies and medicinal treatments (including a laxative) wrote that their only option was to "maintain with what we do have available to us. [Yet,] there continues to be issues of constipation. She currently doesn't have much for options like Spinraza™ due to fused spine."

The two caregivers to the two children on nusinersen mentioned a couple of downsides. One said that the administration (by intrathecal infusion) was "painful" and she believed that it caused constipation. The other, whose daughter was also on a number of other treatments and therapies, said that she had developed "severe doctor/medical anxiety due to repeated doctor visits."

What factors do you take into account when making decisions about using treatment?

As in the group discussions above, most respondents to the survey also weigh the risks versus the potential benefits when making treatment decisions, and the most commonly mentioned risk was side effects—particularly serious, life-threatening side effects. "I always get opinions from other SMA parents, and weigh out the pros and cons of a certain treatment, operation or even in change of feed," said one caregiver. Caregivers to those who currently have more stable SMA were less willing to take great risks. "Even if a drug is approved by the FDA, we worry that the long-term effect has not been tested. Because she lives a fairly normal life, we are much more cautious about taking anything that could have possible side effects," one parent wrote. Another caregiver who hoped gene therapy would be an option for a child with SMA type I who had had a spinal fusion stressed considering the minor and major side effects, but said, "if it's fairly safe and effective, we go the distance!" Other factors considered included costs and the travel time required to access treatment.

Assuming there is not a complete cure for SMA, what specific things would you look for in an ideal treatment for SMA?

Most of respondents to the survey are looking for an ideal treatment to deliver gains in function and strength, but many will settle for a treatment that stops progression of SMA—which was strikingly similar to the responses to the polling questions during the meeting. Survey respondents may have put a greater emphasis on the side effects and administration of treatment than in the discussions above.

Among those looking for gains in strength and function, a couple focused on gains in muscle strength. "Something that would make her strong enough to be able to use the bathroom—that would be something that would probably be worth the risk of taking drugs," said one caregiver. A caregiver of a child with SMA type II who has started nusinersen wanted a treatment with the "ability to improve function in daily life." The caregiver to the other child taking nusinersen (an infant with SMA type I) wants a treatment that will give the child the "ability to live independently—the ability to walk, breathe and eat without assistance."

While another caregiver said that improved respiratory function and "increased movement would be amazing, stopping progression is enough. Anything more than that is amazing (e.g., increased dexterity in hands, being able to move body a little more independently).

Others, notably people with SMA type III who are losing strength and functional ability would be happy with a treatment that helps them "to stay at current level," or just maintain the strength I currently have in my arms."

Those who stressed the tolerability of treatment and administration were quite explicit about what they do not want. "Unacceptable side effects for us include liver damage/failure, blindness, long term organ damage. An ideal treatment would be something which has few side effects, or side effects that are reversible if discontinued [and] would able to be given at home." A couple of other caregivers said an ideal treatment would be "easy to administer" noting factors such as the location and number of treatments and whether it required sedation or intubation. As one caregiver wrote that "the procedure [needs] to be done in a way that it is not traumatic."

Finally, a few stressed that an ideal treatment should be affordable.

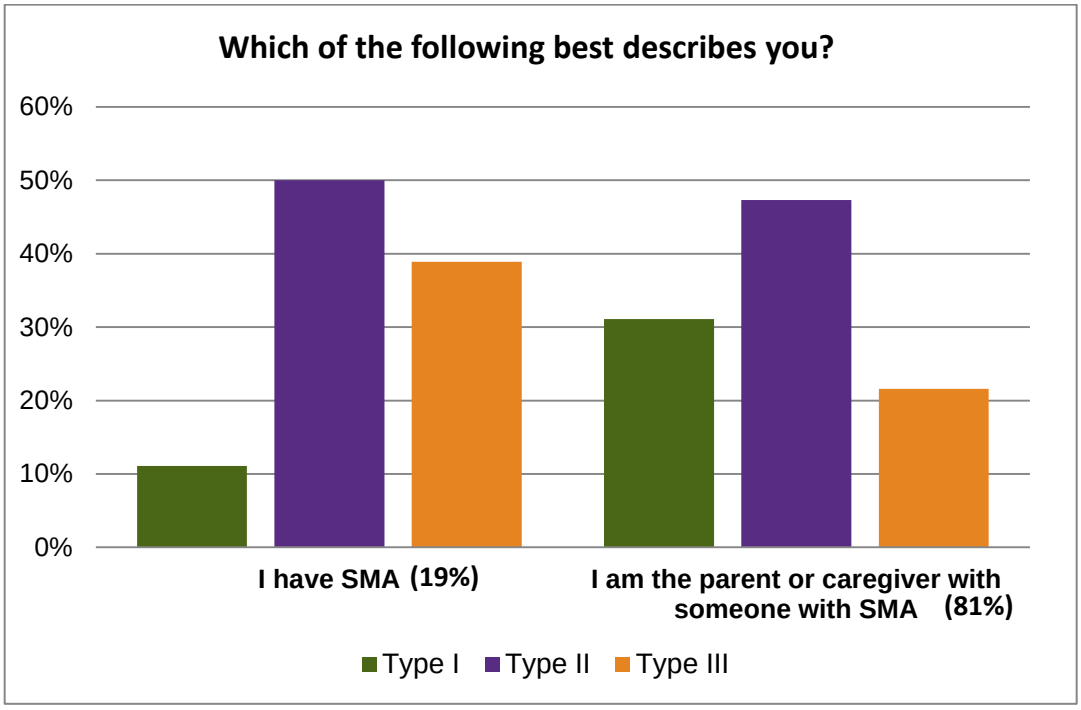
Additional feedback on the issues related to treatment

When asked for additional feedback, four sent comments about treatment—all of which regarded nusinersen. Two expressed sentiments that were aired during the VOP meeting: 1) excitement and hope for the treatment, but 2) frustrations from those who cannot access it.

"One the biggest hurdles right now are fused kids getting Spinraza™," said one caregiver. Meanwhile, one of the individuals with SMA type III, asked "why haven't people with SMA type III been able to get treatment?" and wrote that "there is a need to advise neurologists about the new treatment." The caregiver with a father with SMA type IV now suffering loss of function wrote, "I would like to see more treatment centers throughout the nation as well as more Spinraza™ being produced… to help to bring the cost down."

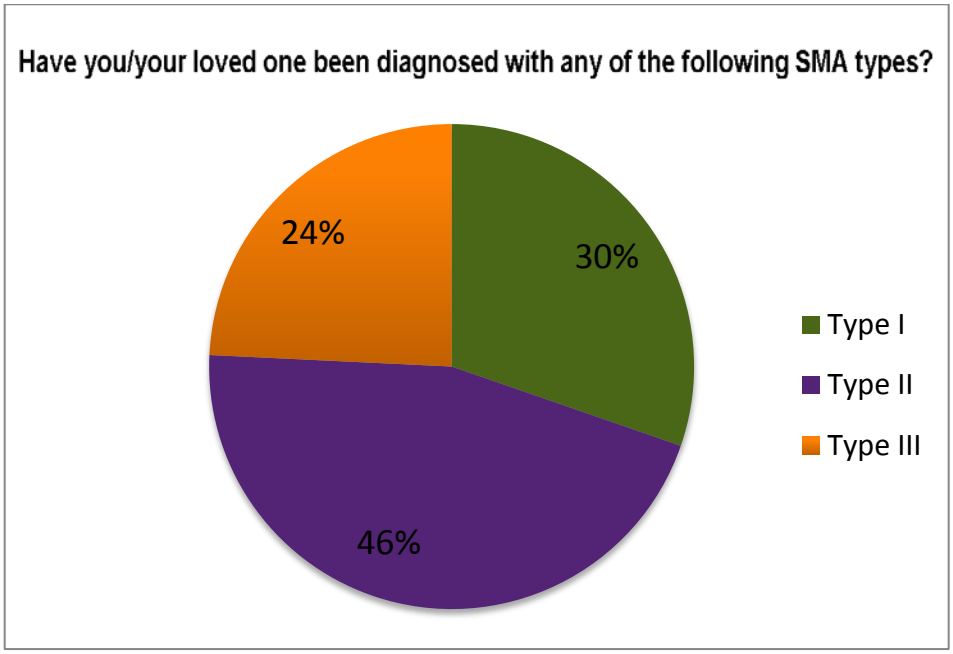
Appendix 5: Key Meeting Demographics (Polling results*)

A. Individuals Affected vs. Parents & Caregivers, by Type



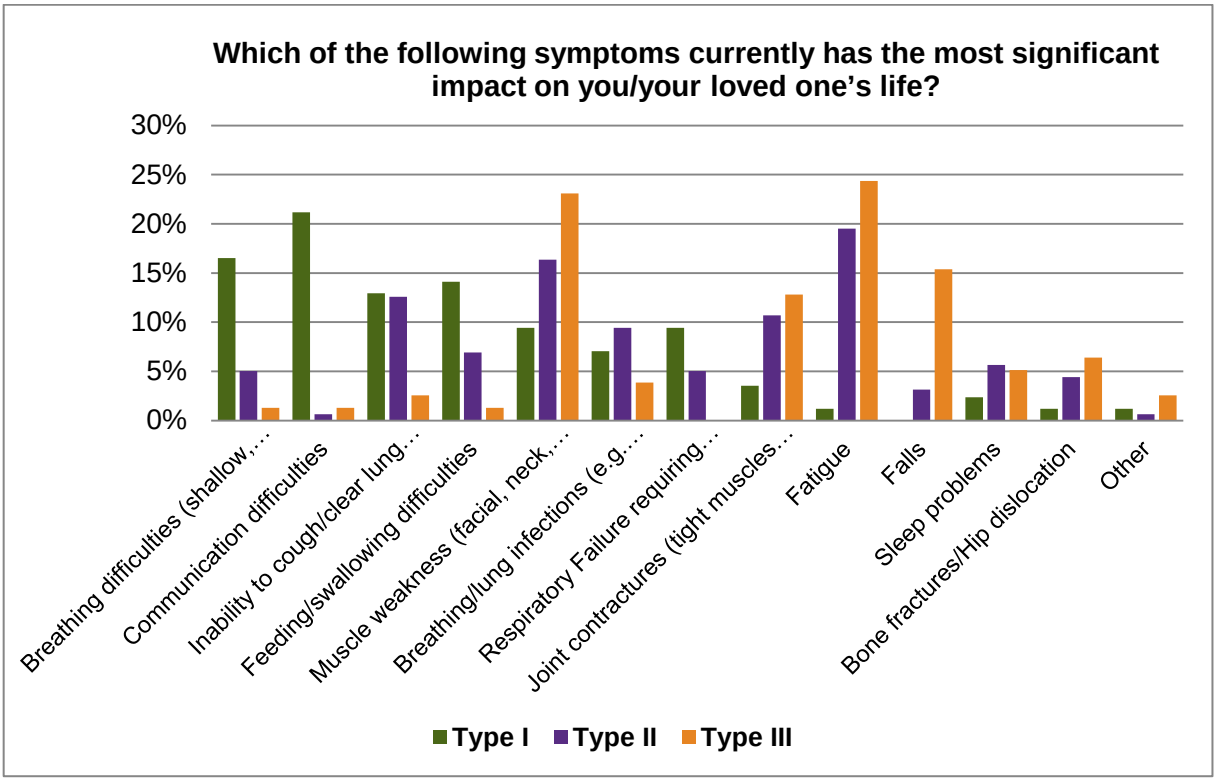
*(N = 95)

B. Breakdown by Polling Respondents



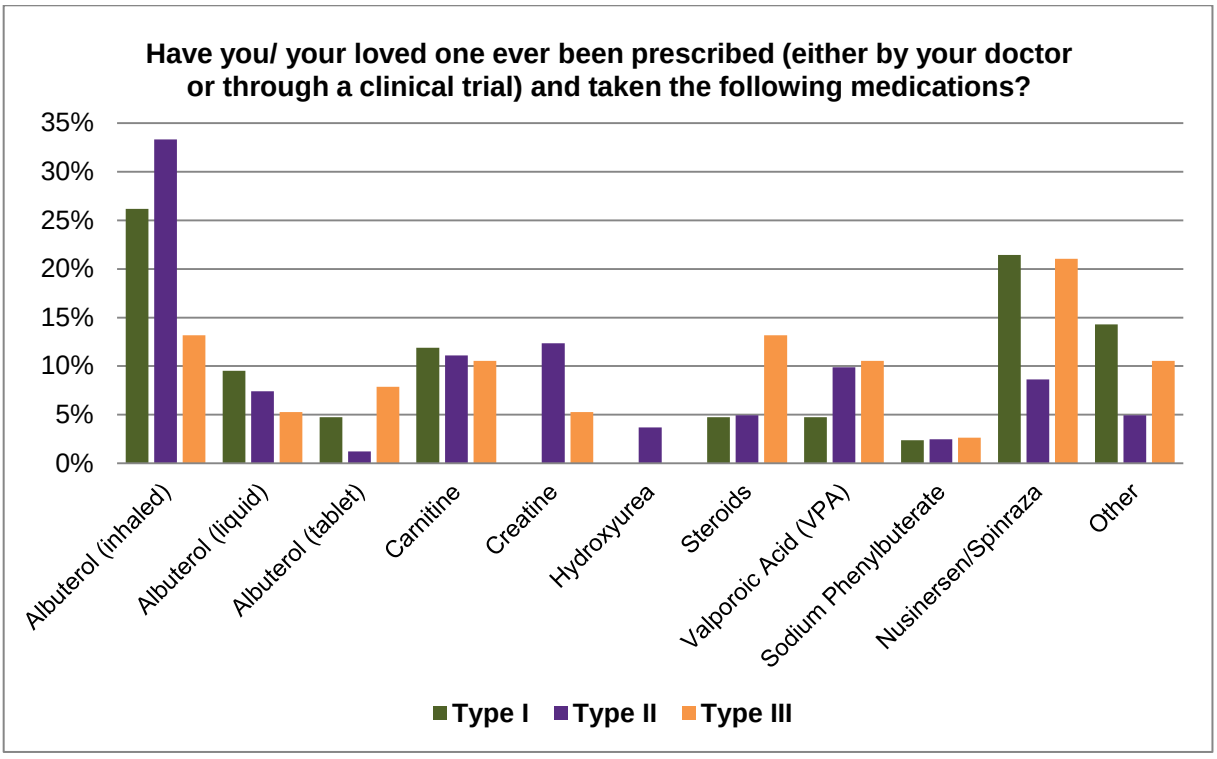
*(N = 100)

C. Symptoms that matter most, All Types



*(N= 108)

D. Drug Therapies for SMA, All Types



*(N= 98)

Appendix 6: The Benefit-Risk survey, abridged results

Cure SMA Risk/Benefit Quantification Research Final Report

December 2017

Silicon Valley RESEARCH GROUP

Presented by Alan Nazarelli

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A
Introduction & Context

B
Risk/Benefit Results-Overall

C
Risk/Benefit Results-by Subgroup

D
Classification Questions

E
Demographics

F
Major Conclusions

Section A: Introduction & Context

Project Goals & Context

- Cure SMA commissioned Silicon Valley Research Group to design and conduct a quantitative survey of SMA patients to uncover tradeoffs they make when considering the benefits and risks associated with treating their symptoms.
- The results will inform the foundation on priorities for supporting the community and will also be presented to the FDA to guide support for drug development and ultimately, a treatment and a cure for SMA.

Together, we can cure SMA

Methodology-Selection

- Best/Worst Scaling, also known as Maximum Differential Scaling (Max-Diff), a subset of conjoint and discrete choice modeling, was selected as the survey methodology to obtain data on patients risk/benefit tradeoffs.
- The main reason for the selection of this methodology is that it provides higher discrimination and importance scaling between the tested attributes than simple rating and ranking questions and corrects for biases in individual variations in interpreting rating scales.
- Research has shown that Best/Worst Scaling scores provide greater discrimination among items and between respondents on the items than survey questions using standard scales. Since respondents make choices rather than expressing strength of preference using some numeric scale, there is no opportunity for scale use bias.
- Lastly, several similar studies trading treatment benefits and risks have used this methodology. The FDA is familiar with this research design and in addition, several “research on research” studies have validated both the benefits and validity of the data obtained using this methodology design for medical patient studies.

Methodology-Execution

- An online survey was created and hosted during the months of October & November 2017 by Silicon Valley Research Group.
- Respondents were invited by Cure SMA to participate in the survey via email containing a link to the survey.
- Responses were collected, tallied and analyzed by Silicon Valley Research Group.
- No PHI was collected from survey respondents through the survey or by any other means.
- The survey was submitted to the IRB for approval prior to data collection and is IRB approved and compliant .
- The total sample size for the study was 298 completed responses, yielding a margin of error of 5.68%.

Section B: Risk/Benefit Results-Overall

Treatments (benefits) tested

- TREATMENT 1 – Increased overall muscle strength (may include hips, neck, arms, legs, face, etc.) such that one is able to do something one was unable to do before
- TREATMENT 2 – Consistent muscle performance/strength (i.e., muscles work relatively the same throughout the day; muscle strength does not vary greatly from day to day).
- TREATMENT 3 – Improvement in ability to swallow
- TREATMENT 4 – Improvement in ability to speak/communicate
- TREATMENT 5 – Improvement in breathing function (may include, less infections, less time on BiPAP or vent; stronger cough, decrease in belly breathing)
- TREATMENT 6 – Improved proximal mobility/ functionality (getting up, balancing when sitting or standing, walking, jumping, running, climbing stairs, fewer falls)
- TREATMENT 7 – Increased core strength (to allow for greater and longer stability when sitting, better rolling while sleeping, etc.)
- TREATMENT 8 – Increased upper limb (arm) strength allowing the ability to perform basic personal tasks (such as brushing teeth, washing face, writing with a pen, putting on glasses, scratching head, using the keyboard, opening doors, self-feeding, etc.)
- TREATMENT 9 – Decreased fatigue, increased energy and ability to do more in a day.
- TREATMENT 10 – Lessening of symptoms' severity (decrease in, tremors, muscle weakness, etc.) or experiencing less symptoms than before treatment was introduced
- TREATMENT 11 – Prolonging lifespan (Increasing length of life)
- TREATMENT 12 – Slowing or stopping of disease progression

Risks tested

- 1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention
- 1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention
- 1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure
- 1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure
- Increased risks of respiratory or other infections as a result of treatment
- Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.
- Side effect of dizziness (may increase risk of falls)
- Possible need for general anesthesia to administer treatment
- Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).
- Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.)
- Life-threatening allergic reactions

Primer on Interpreting Max-Diff Scores

Maximum-Differential Scaling - A Primer

A survey question design and analysis technique that:

1. Provides higher granularity in responses
2. Enables us to test a large set of attributes without overwhelming the respondent
3. Removes respondent biases such as order bias, leniency/strictness polarity
4. Enables testing of attribute “levels”, e.g. 3 months free or 6 months free (without 6 month free always being preferred)
5. More precision in data collected due to high number of iterations for each attribute tested
6. Difficult for respondent to guess what we are trying to uncover (& therefore tell us what they think we want to hear)
7. Higher statistical precision in results

1. Which of these services are most important to you when considering a wedding planner?

	Least Important	Somewhat Important	Neutral	Important	Very Important
Wedding Timeline coordination	○	○	○	○	○
Reception Coordination	○	○	○	○	○
Email and Phone availability	○	○	○	○	○
Music Selection	○	○	○	○	○
Venue Location Services	○	○	○	○	○
Design Coordination	○	○	○	○	○
Vendor Coordination	○	○	○	○	○

1. Please pick the most important and least important service that a wedding planner can provide t

You will be evaluating 3 sets of features, click next to evaluate the next set.

Least Important	Service	Most Important
○	Music Selection	○
○	Wedding Timeline coordination	○
○	Email and Phone availability	○

1 of 3 sets

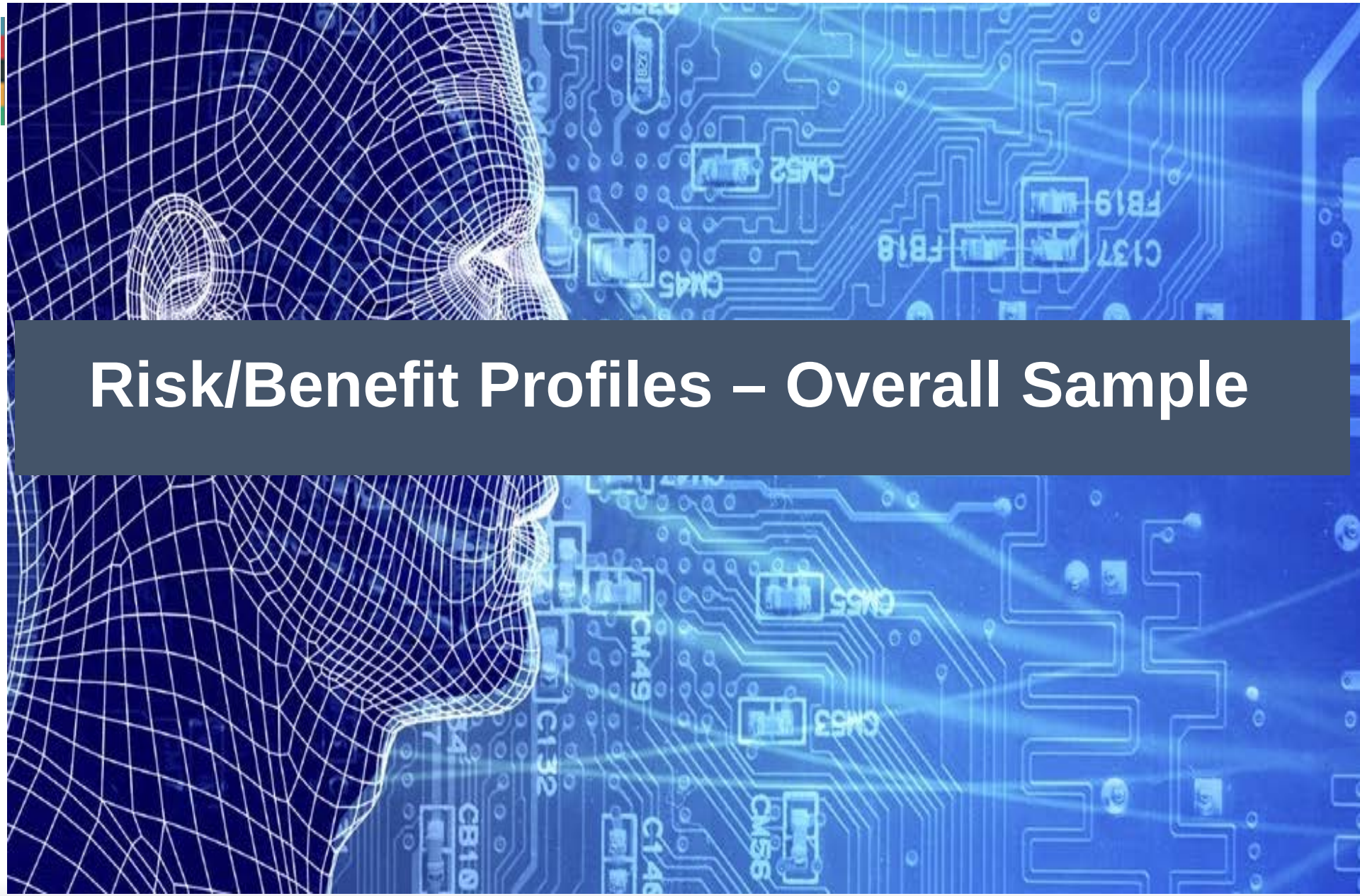
Interpretation of Max Diff Scores

The attributes will be ranked based on the score which is computed using the below formula:

 # times attribute was selected as best
 # times attribute was selected as worst
 # times the item appeared

From the score we can determine a couple of things:

- The higher the score, the more the feature is compelling to respondents.
- A positive score means that that attribute was selected as BEST more often than Worst.
- A negative score means that that attribute was chosen as WORST more often than Best.
- A score of zero means that that attribute was chosen as BEST and WORST an equal number of times OR it has never been chosen as Best and Worst.
- If a score of an item is two times bigger than another item, it can be interpreted that it is twice as compelling.



Risk/Benefit Profiles – Overall Sample

Treatment 1 - Increased overall muscle strength (may include hips, neck, arms, legs, face, etc.) such that one is able to do something one was unable to do before.

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for general anesthesia to administer treatment	1	49.84	3.79	46.37	0.46
Side effect of dizziness (may increase risk of falls).	2	44.26	1.07	54.67	0.43
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	3	46.12	4.19	49.69	0.42
Possible need for invasive means to administer treatment	4	34.4	3.67	61.93	0.31
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may interfere with normal organ functioning and therefore require immediate medical attention	5	18.27	7.28	74.45	0.11
1 in 100,000 risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure.	6	9.59	15.25	75.16	-0.06
Increased risks of respiratory or other infections as a result of medication.	7	8.91	15.31	75.78	-0.06
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may interfere with normal organ functioning and therefore require immediate medical attention	8	2.83	22.76	74.41	-0.2
Life threatening allergic reactions.	9	1.74	36.12	62.14	-0.34
1 in 1,000 risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.94	44.18	54.88	-0.43
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	0.94	66.82	32.24	-0.66

N=298

Treatment 2 - Consistent muscle performance/strength (i.e., muscles work relatively the same throughout the day; muscle strength does not vary greatly from day to day)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	46.42	2.7	50.88	0.44
Possible need for general anesthesia to administer treatment.	2	46.14	3.05	50.81	0.43
Side effect of dizziness (may increase risk of falls).	3	43.83	1.11	55.06	0.43
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	43.35	2.35	54.3	0.41
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	16.21	6.65	77.14	0.1
Increased risks of respiratory or other infections as a result of medication.	6	10.95	14.76	74.29	-0.04
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	7	7.68	15.36	76.96	-0.08
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.1	24.03	73.87	-0.22
Life-threatening allergic reactions.	9	1.55	35.14	63.31	-0.34
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.32	48.7	50.98	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	0.94	65.62	33.44	-0.65

N=298

Treatment 3 - Improvement in ability to swallow

Attribute	Rank	Best	Worst	Not Chosen	Score
Side effect of dizziness (may increase risk of falls).	1	45.67	1.28	53.05	0.44
Possible need for general anesthesia to administer treatment.	2	47.36	4.16	48.48	0.43
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	3	45.38	2.71	51.91	0.43
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	39.97	2.82	57.21	0.37
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	17.44	7.84	74.72	0.1
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	7.05	12.98	79.97	-0.06
Increased risks of respiratory or other infections as a result of medication.	7	9.13	18.75	72.12	-0.1
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.91	24.27	72.82	-0.21
Life-threatening allergic reactions.	9	1.47	36.87	61.66	-0.35
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.96	49.36	49.68	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.74	59.31	38.95	-0.58

n=298

Treatment 4 - Improvement in ability to communicate

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	47.43	2.41	50.16	0.45
Possible need for general anesthesia to administer treatment.	2	47.31	3.59	49.1	0.44
Side effect of dizziness (may increase risk of falls).	3	44.17	2.43	53.4	0.42
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	43.65	2.06	54.29	0.42
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	14.17	5.15	80.68	0.09
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	7.8	13.17	79.03	-0.05
Increased risks of respiratory or other infections as a result of medication.	7	9.03	16.64	74.33	-0.08
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.68	23.03	74.29	-0.2
Life-threatening allergic reactions.	9	1.96	38.4	59.64	-0.36
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.79	49.21	50	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.6	63.46	34.94	-0.62

n=298

Treatment 5 - Improvement in respiratory function (may include, less infections, less time on BiPAP or vent; stronger cough, decrease in belly breathing)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	47.8	2.28	49.92	0.46
Possible need for general anesthesia to administer treatment.	2	47.07	4.44	48.49	0.43
Side effect of dizziness (may increase risk of falls).	3	44.75	2.58	52.67	0.42
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	43.07	2.12	54.81	0.41
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	15.46	4.11	80.43	0.11
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	8.59	11.51	79.9	-0.03
Increased risks of respiratory or other infections as a result of medication.	7	8.12	18.63	73.25	-0.11
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.51	26.84	70.65	-0.24
Life-threatening allergic reactions.	9	1.15	36.08	62.77	-0.35
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.65	47.65	51.7	-0.47
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.26	62.72	36.02	-0.61

n=298

Treatment 6 - Improved proximal mobility/ functionality (getting up, balancing when sitting or standing, walking, jumping, running, climbing stairs, fewer falls)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	48.75	3.33	47.92	0.45
Possible need for general anesthesia to administer treatment.	2	46.92	3.41	49.67	0.44
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	3	43.04	1.28	55.68	0.42
Side effect of dizziness (may increase risk of falls).	4	40.13	3.88	55.99	0.36
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	16.5	5.45	78.05	0.11
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	8.37	12.32	79.31	-0.04
Increased risks of respiratory or other infections as a result of medication.	7	8.78	17.07	74.15	-0.08
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.98	23.84	73.18	-0.21
Life-threatening allergic reactions.	9	0.82	35.9	63.28	-0.35
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	1.49	49.25	49.26	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.46	64.56	33.98	-0.63

n=298

Treatment 7 - Increased core strength (to allow for greater and longer stability when sitting, better rolling while sleeping, etc.)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	48.2	2.45	49.35	0.46
Side effect of dizziness (may increase risk of falls).	2	43.92	1.94	54.14	0.42
Possible need for general anesthesia to administer treatment.	3	45.62	4.71	49.67	0.41
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	40.1	2.92	56.98	0.37
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	16.14	6.59	77.27	0.1
Increased risks of respiratory or other infections as a result of medication.	6	9.18	15.25	75.57	-0.06
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	7	8.03	14.92	77.05	-0.07
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	4.3	23.51	72.19	-0.19
Life-threatening allergic reactions.	9	0.82	36.62	62.56	-0.36
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	1.62	49.51	48.87	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.16	62.05	36.79	-0.61

n=298

Treatment 8 - Increased upper limb (arm) strength allowing the ability to perform basic personal tasks (such as brushing teeth, washing face, writing with a pen, putting on glasses, scratching head, using the keyboard, opening doors, self-feeding, etc.)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	47.42	3.06	49.52	0.44
Possible need for general anesthesia to administer treatment.	2	47.97	3.74	48.29	0.44
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	3	45.14	2.31	52.55	0.43
Side effect of dizziness (may increase risk of falls).	4	41.64	2.13	56.23	0.4
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	14.83	6.75	78.42	0.08
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	7	12.54	80.46	-0.06
Increased risks of respiratory or other infections as a result of medication.	7	9.11	15.28	75.61	-0.06
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	3.86	24.28	71.86	-0.2
Life-threatening allergic reactions.	9	1.01	38.85	60.14	-0.38
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.66	47.95	51.39	-0.47
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	0.81	63.68	35.51	-0.63

n=298

Treatment 9 - Decreased fatigue, increased energy and ability to do more in a day

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	48.7	2.92	48.38	0.46
Possible need for general anesthesia to administer treatment.	2	47.13	3.45	49.42	0.44
Side effect of dizziness (may increase risk of falls).	3	42.56	2.59	54.85	0.4
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	41.21	4.4	54.39	0.37
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	15.07	5.83	79.1	0.09
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	7.18	11.58	81.24	-0.04
Increased risks of respiratory or other infections as a result of medication.	7	9.42	17.21	73.37	-0.08
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	4.75	23.28	71.97	-0.19
Life-threatening allergic reactions.	9	0.66	39.53	59.81	-0.39
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	1.31	49.59	49.1	-0.48
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1.01	61.31	37.68	-0.6

n=298

Treatment 10 - Lessening of symptoms' severity (decrease in, tremors, muscle weakness, etc.) or experiencing less symptoms than before treatment was introduced

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	52.33	3.54	44.13	0.49
Side effect of dizziness (may increase risk of falls).	2	41.89	1.49	56.62	0.4
Possible need for general anesthesia to administer treatment.	3	43.89	4.13	51.98	0.4
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	41.71	2.85	55.44	0.39
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	18.4	5.7	75.9	0.13
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	6.97	10.86	82.17	-0.04
Increased risks of respiratory or other infections as a result of medication.	7	8.06	16.45	75.49	-0.08
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.8	24.38	72.82	-0.22
Life-threatening allergic reactions.	9	1.13	36.45	62.42	-0.35
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	1.15	49.75	49.1	-0.49
Worsening in "quality of life" (possibly due to drug's side effects, worsening condition, etc.).	11	1.63	63.24	35.13	-0.62

n=298

Treatment 11 - Prolonging lifespan (Increasing length of life)

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	49.51	2.46	48.03	0.47
Possible need for general anesthesia to administer treatment.	2	45.38	3.14	51.48	0.42
Side effect of dizziness (may increase risk of falls).	3	42.9	2.67	54.43	0.4
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	4	41.63	2.6	55.77	0.39
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	18.68	5.45	75.87	0.13
Increased risks of respiratory or other infections as a result of medication.	6	9.76	14.31	75.93	-0.05
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	7	6.27	13.2	80.53	-0.07
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.45	25.2	72.35	-0.23
Life-threatening allergic reactions.	9	0.67	37.83	61.5	-0.37
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.66	49.18	50.16	-0.49
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	1	63.83	35.17	-0.63

n=298

Treatment 12 - Slowdown or stopping of disease progression

Attribute	Rank	Best	Worst	Not Chosen	Score
Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.).	1	51.51	1.84	46.65	0.5
Possible need for general anesthesia to administer treatment.	2	45.99	3.76	50.25	0.42
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.	3	43.63	2.45	53.92	0.41
Side effect of dizziness (may increase risk of falls).	4	40.94	1.34	57.72	0.4
1 in 100,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	5	16.12	7	76.88	0.09
1 in 100,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	6	6.49	11.53	81.98	-0.05
Increased risks of respiratory or other infections as a result of medication.	7	9.68	15.36	74.96	-0.06
1 in 1,000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	8	2.83	23.5	73.67	-0.21
Life-threatening allergic reactions.	9	0.84	38.19	60.97	-0.37
1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.	10	0.83	49.92	49.25	-0.49
Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).	11	0.99	65.73	33.28	-0.65

n=298

Top Takeaways

Survey respondents consistently rated the following as the most tolerable risks regardless of the benefit of the treatment:

- Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.)
- Possible need for general anesthesia to administer treatment
- Side effect of dizziness (may increase risk of falls)
- Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.

Top Takeaways (continued)

Conversely, respondents consistently rated the following as the least tolerable risks regardless of the benefit of the treatment:

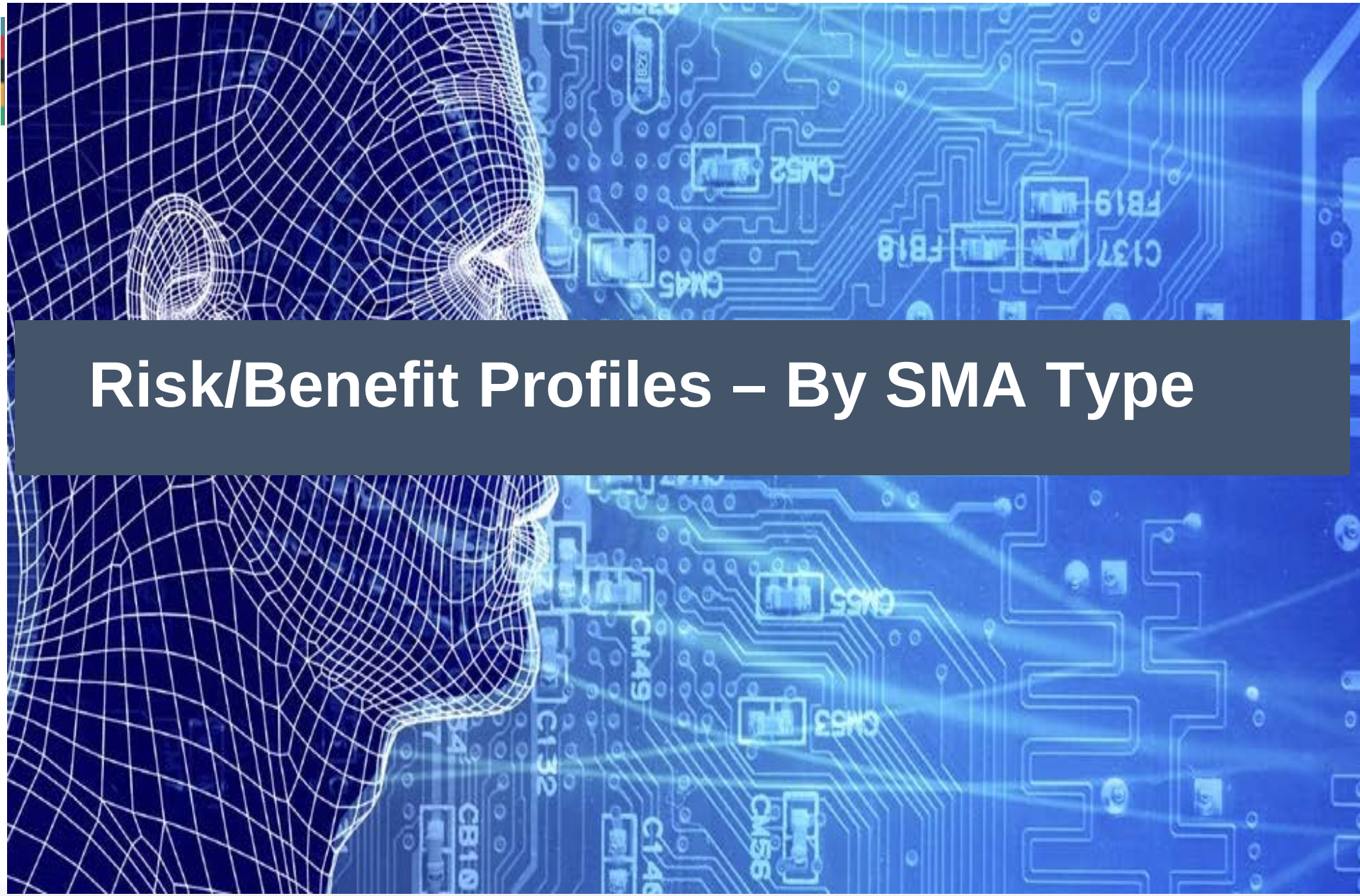
- Life-threatening allergic reactions.
- 1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.
- Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).

Analysis & Interpretation

- A possible explanation for the consistency in most tolerable and least tolerable risks across all treatments is that SMA sufferers and their caregivers consider any of the benefits of treatments presented as equally important, i.e. they are not trading off risks for different treatments.

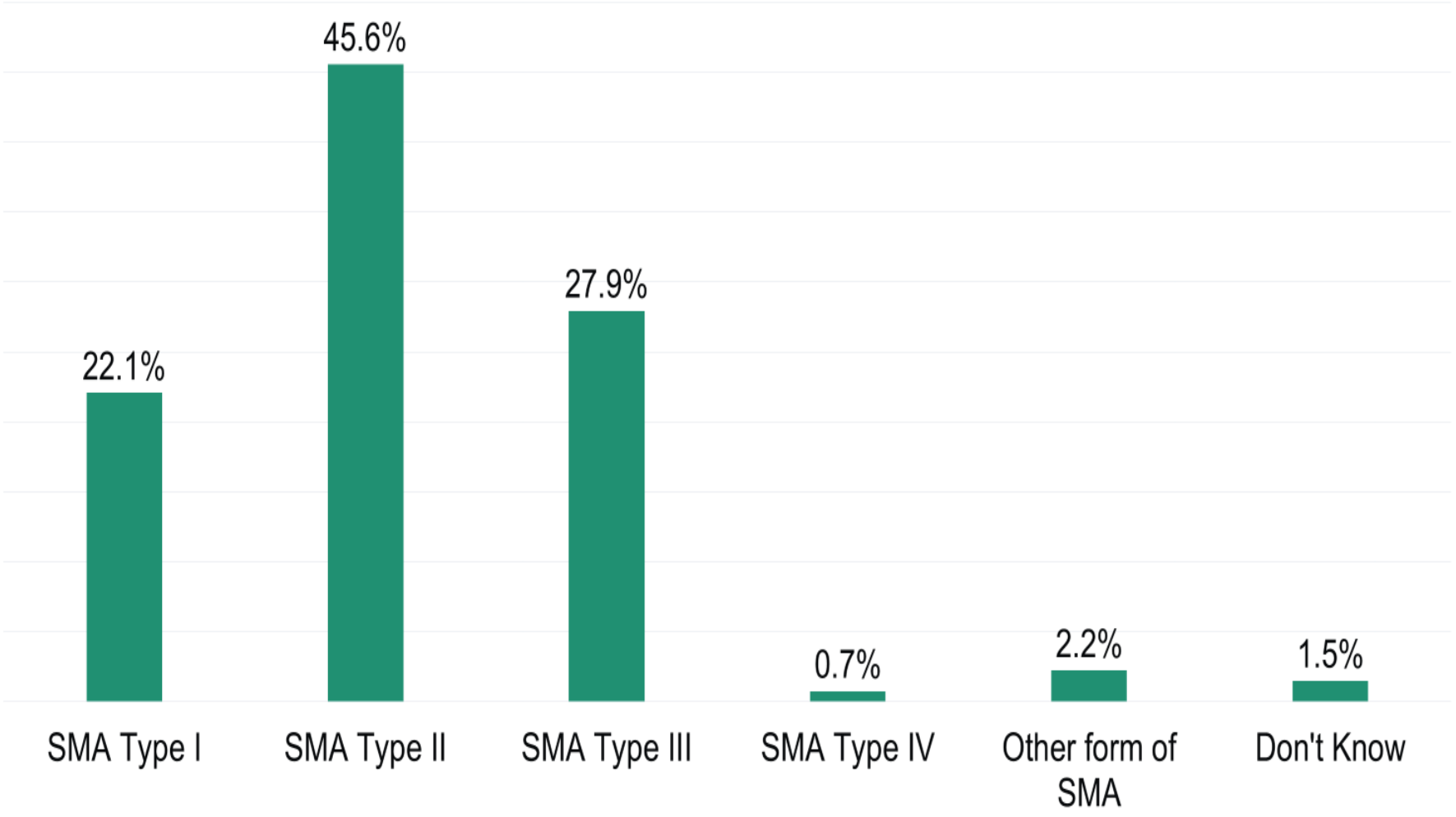
- Survey respondents also appeared to weigh risks against their probabilities of occurrence. Consistently, high probabilities of occurrence made a risk less tolerable. While this may seem obvious, it indicates respondents seriously evaluated the probability associated with a particular risk into account when evaluating it-the same risk with a low probability of 1 in 100,000 was consistently rated more tolerable than the same risk with a higher probability of 1 on 1,000

Section C: Risk/Benefit Results-by Sub-Group



Risk/Benefit Profiles – By SMA Type

SMA type



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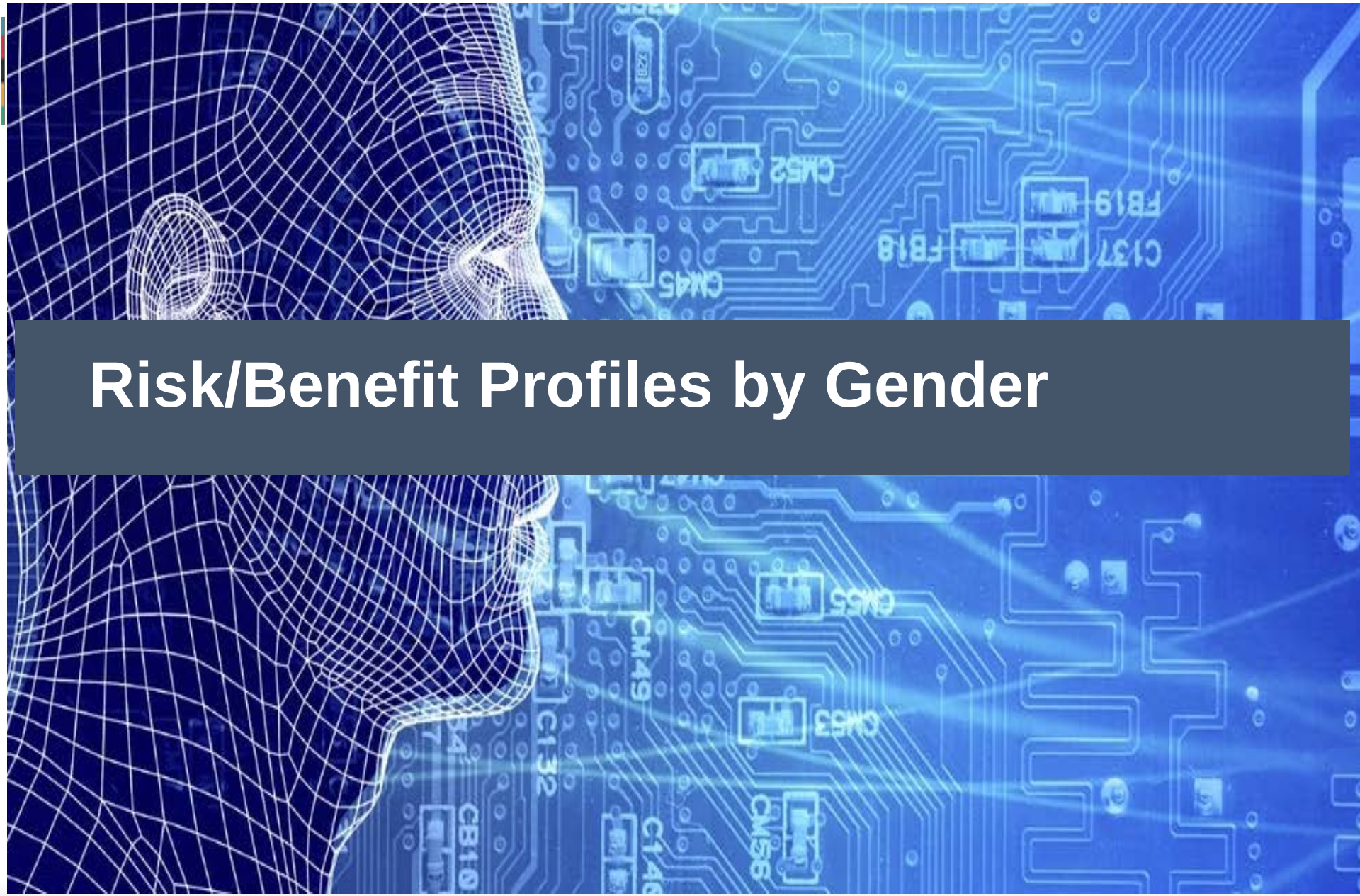
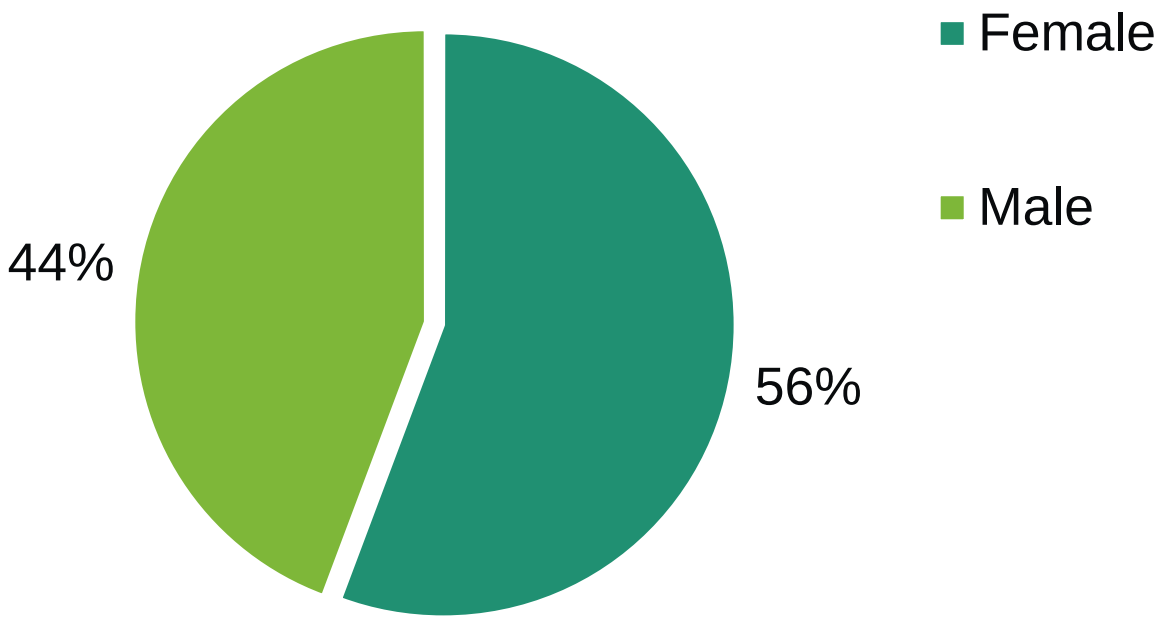


Risk/Benefit Profiles by Gender

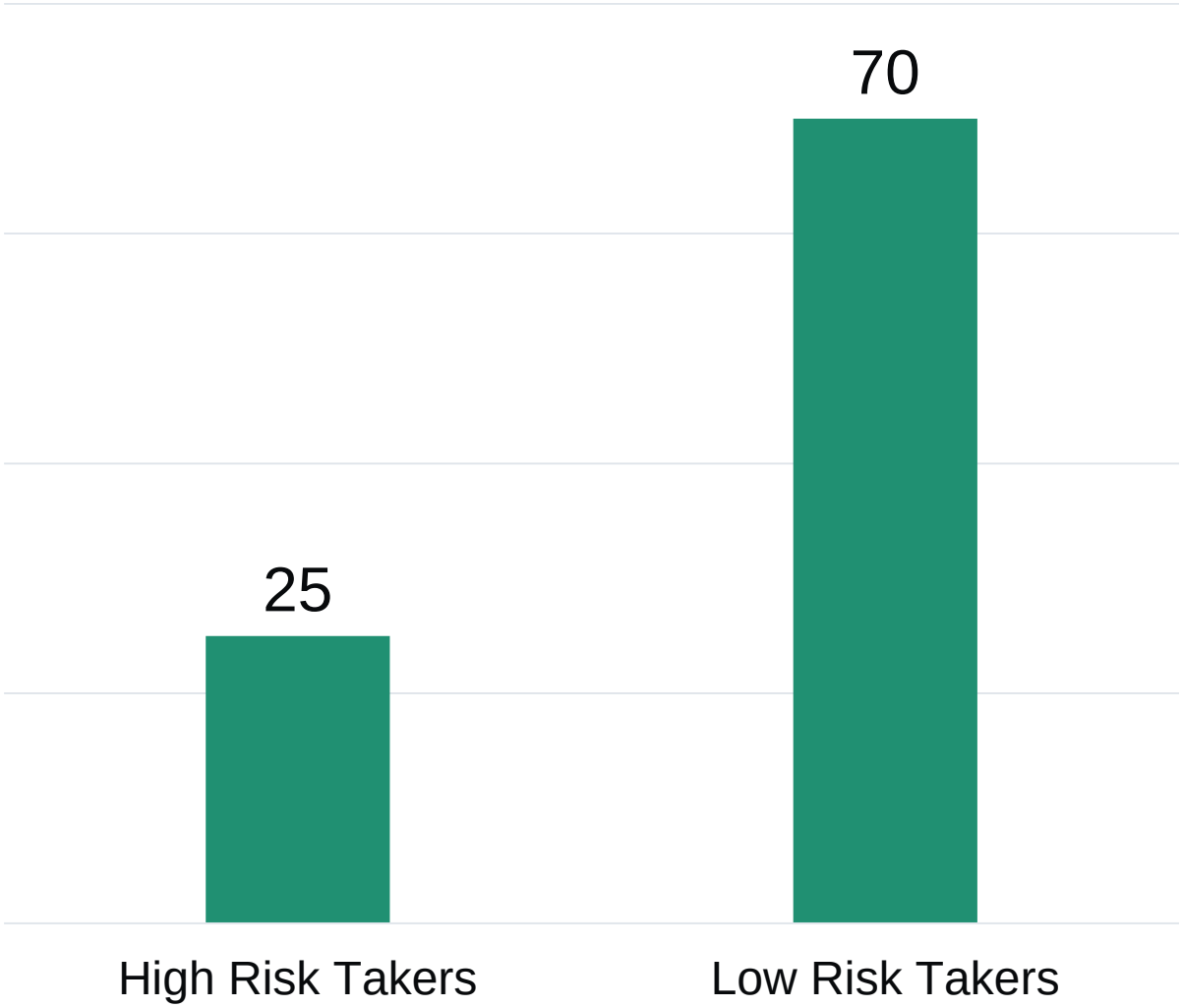
Gender



n=298

Risk/Benefit Profiles by Risk Tolerance

Risk Taking & Risk Averse (Percent)



n=95

Risk/Benefit Profile-High Risk Takers

Context

- The section examines the impact of risk taking attitudes on survey respondents' risk/benefit tradeoff patterns. The hypothesis being tested here is: Do attitudes towards risk influence how SMA caregivers and affected individuals assess risks against benefits of treatments.
- A standards risk taking question was added to the survey. Those who scored as high risk takers (4 and 5 on a 5 point scale) were then compared to those who scored as low risk takers (1 and 2 on the same scale).
- This section analyzes results comparing the two subgroups to each other and to all survey respondents.

Top Takeaways – Risk Profile

- Risk taking attitudes did not appear to influence their risk/benefit tradeoffs. Both high risk takers and low risk takers exhibit risk/benefit profiles consistent with all respondents.

- There was very little deviation in the risk/benefit tradeoffs of high and low risk takers with the exception of high risk takers selecting the 1 in 100,000 risk of serious side effects as a more tolerable option more often than not compared to low risk takers.

Section D: Classification Questions

B-R Survey – Participation Criteria

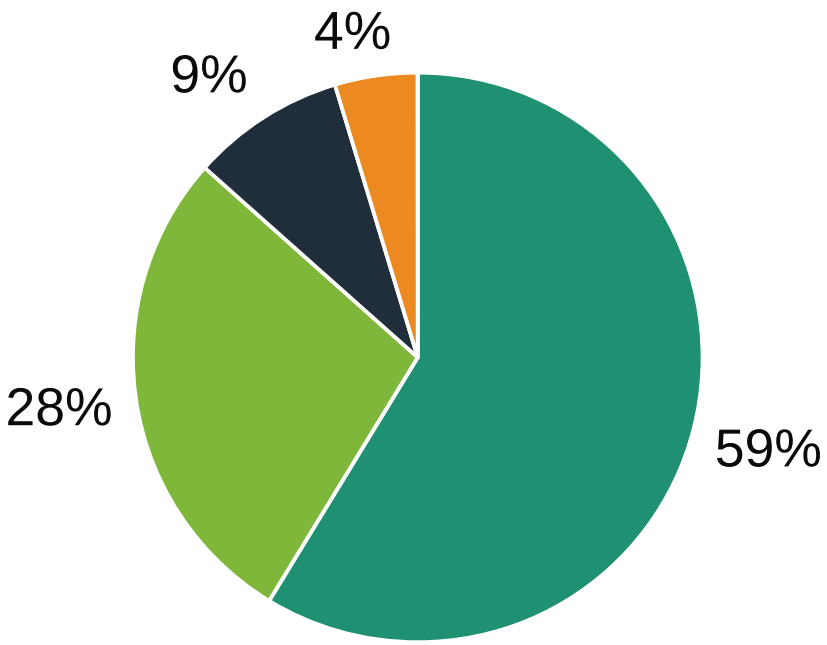
Affected Individuals

- Individuals with SMA who have reached the majority of age (18-21 depending on the State)
- Have a confirmed diagnosis of SMA Type I, II, III or IV

Caregivers

- Parents of infants with SMA Type I aged 0-18 years
- Parents of children with SMA Type II-IV ages 2-18
- Parents of adults with SMA Types I-III who may be too limited in mobility to respond independently

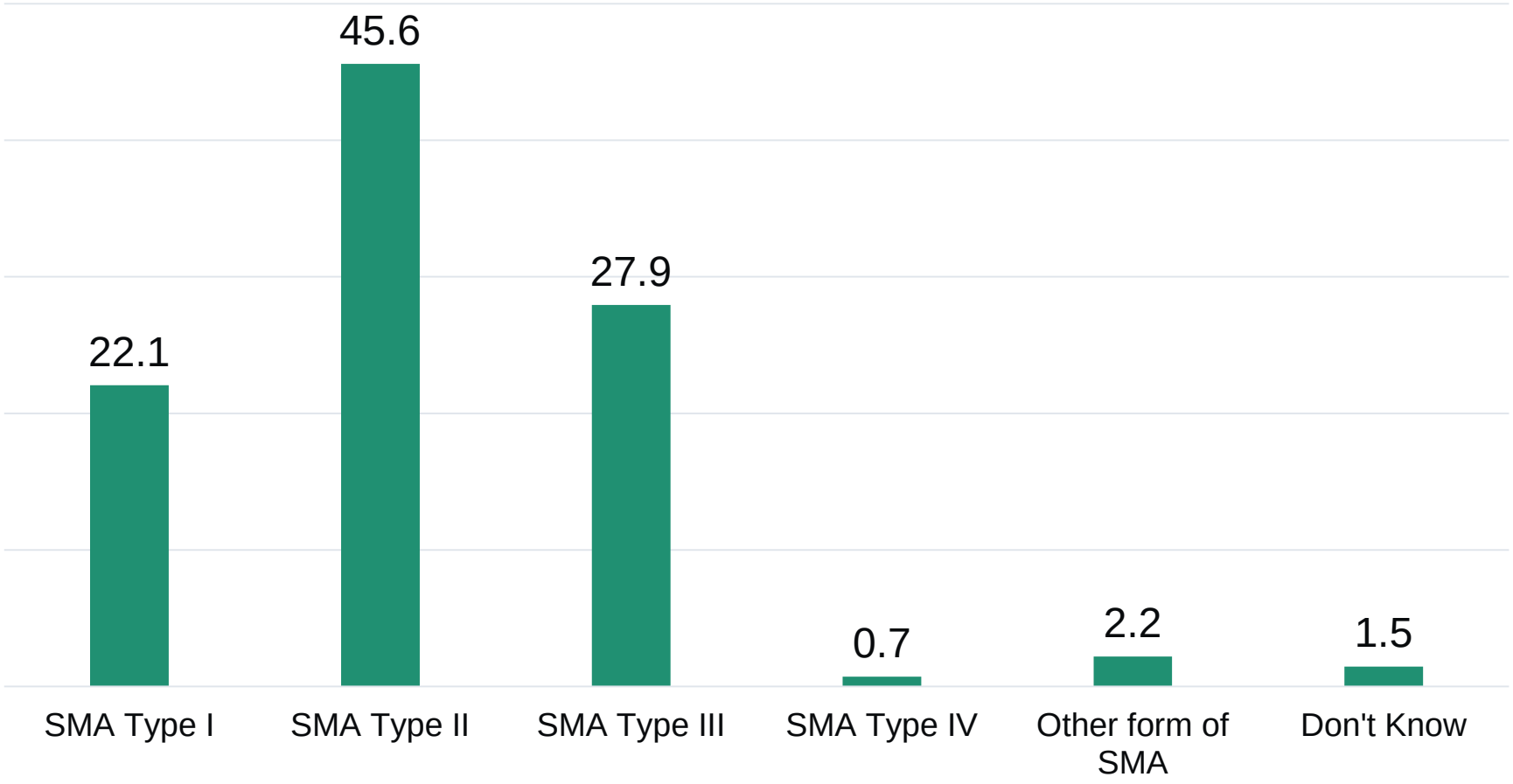
Which of the following best describes your situation?



- I am the caregiver for an affected individual with SMA
- I have SMA
- I was a caregiver for an individual affected by SMA, now deceased
- I am the caregiver for more than one affected individual with SMA

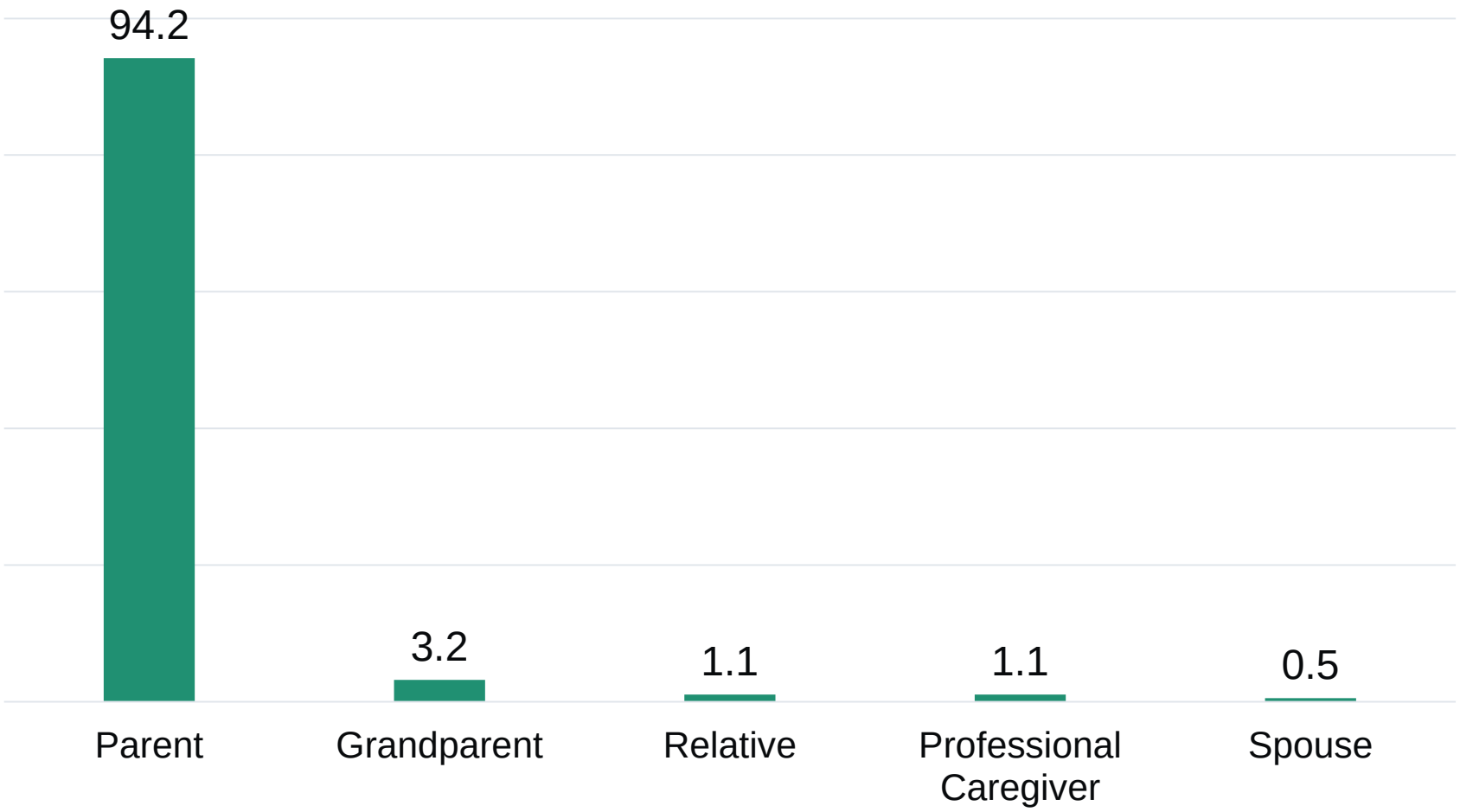
n=298

SMA type (Percent)



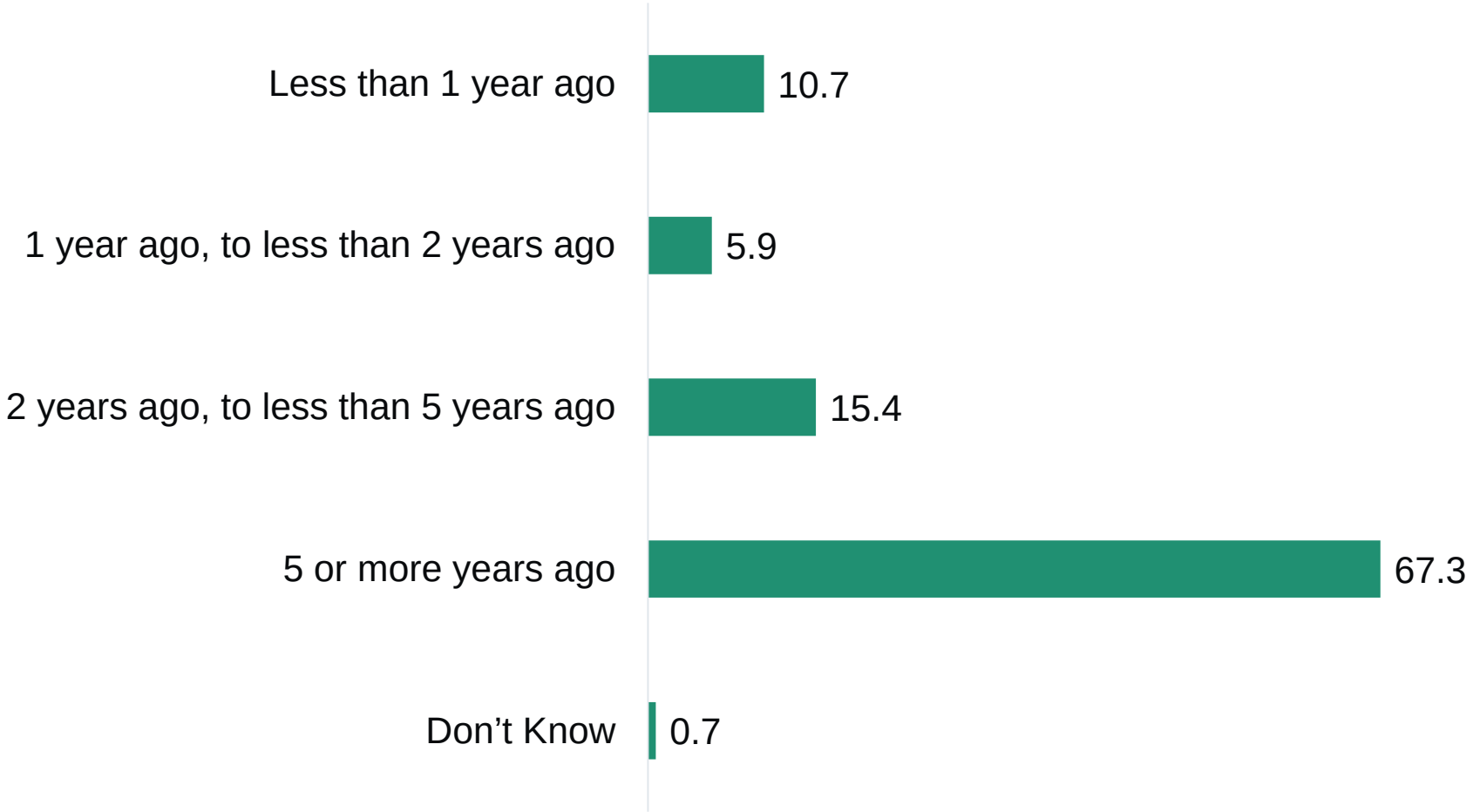
n=272

Relationship to the affected individual (Percent)



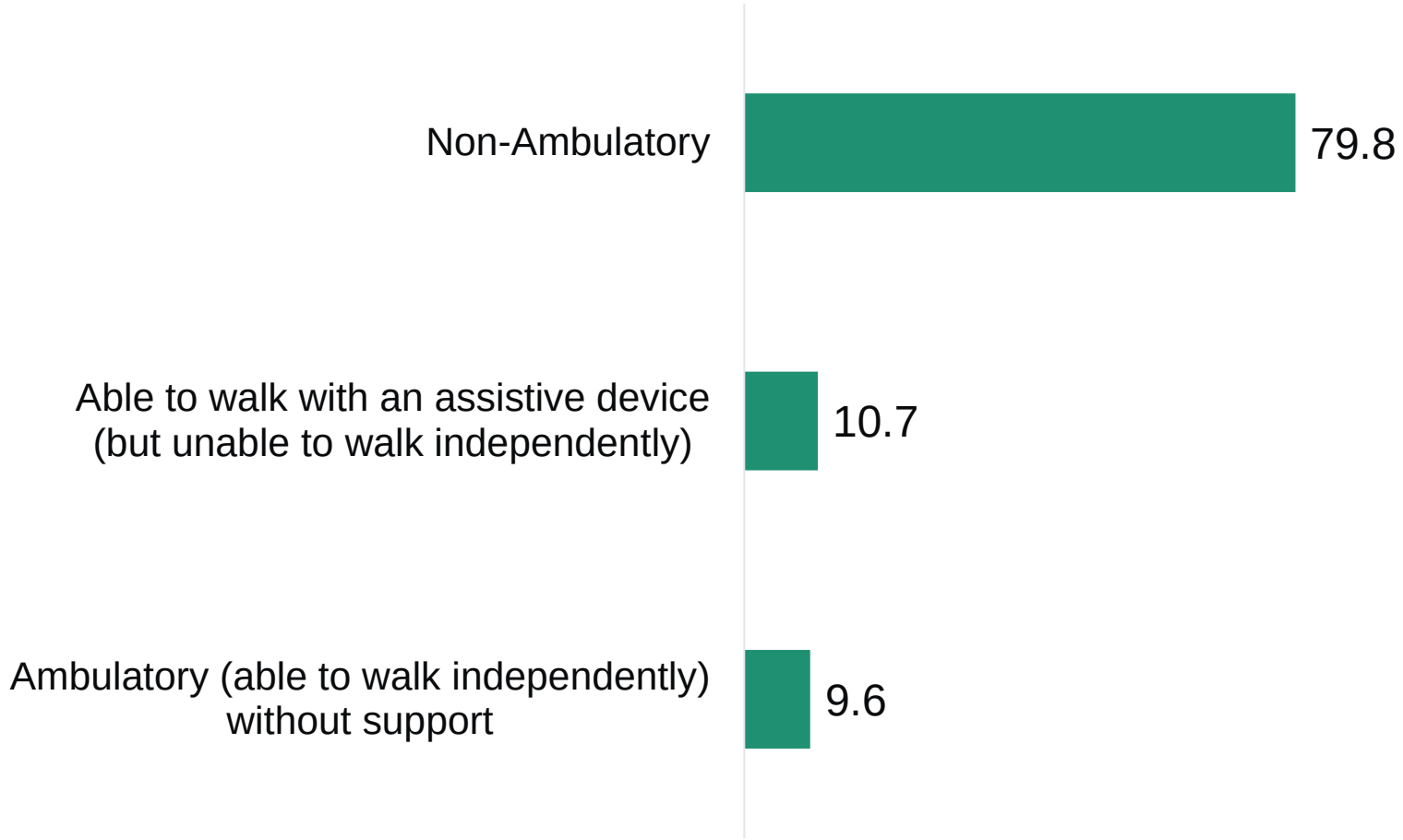
n=189

Length of time since diagnosis (Percent)



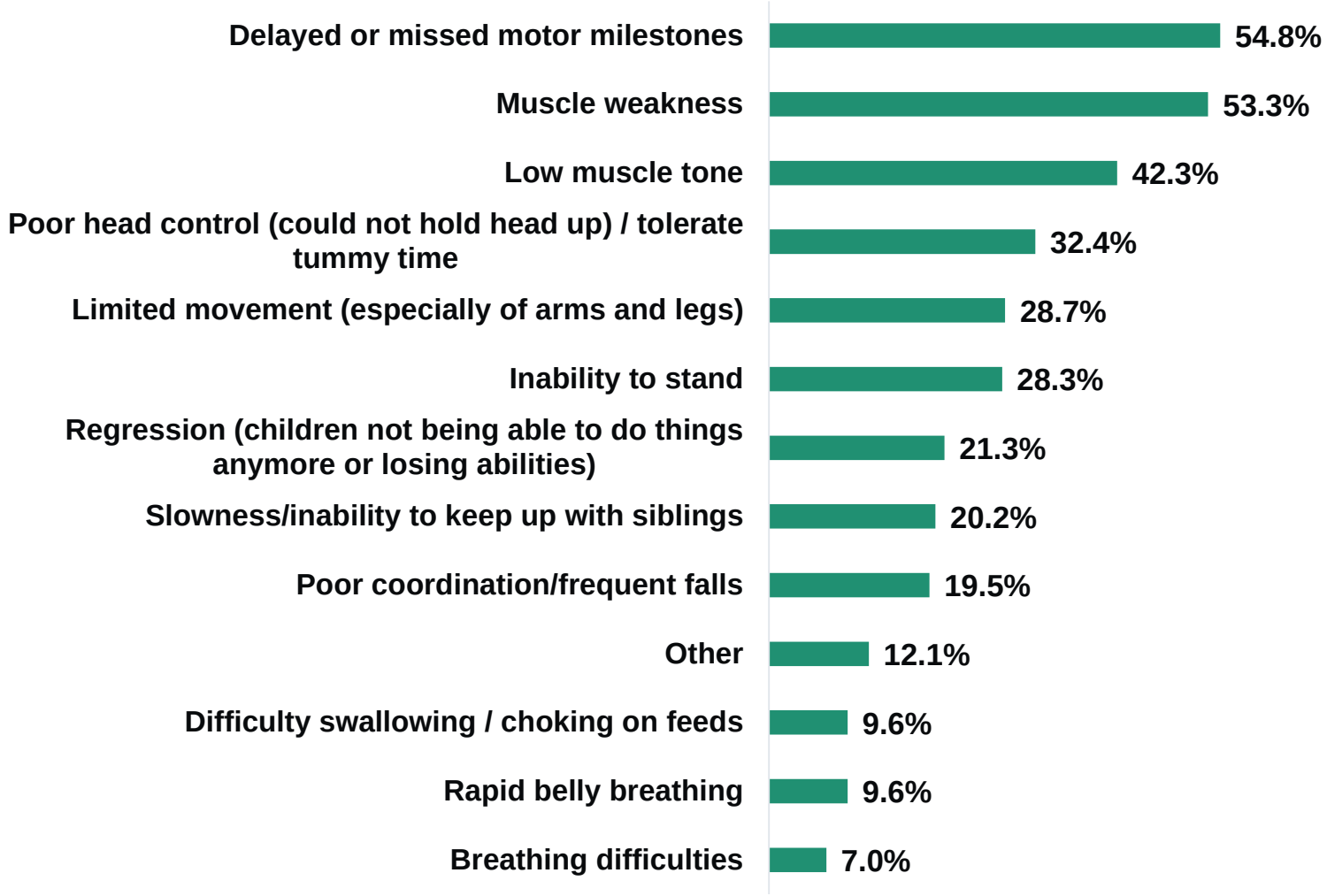
n=272

Ambulatory status (Percent)



n=272

Symptoms leading to diagnosis of SMA



n=272

Ranking Questions Scoring Guide (for next two slides)

- The score is a weighted calculation.
- Items ranked first are given a higher value or "weight."
- The score, computed for each answer option/row header, is the sum of all the weighted values.
- The weighted values are determined by the number of columns, which is usually the same as the number of rows.
- For example, because there are 11 options, the weighted sum for an option that was placed in the first position (1) would be worth 11. The table below shows the formula for computing the total rank for each answer option/row header:

Total Responses		Weight		Score
Rank 1 Count	x	11	=	
Rank 2 Count	x	10	=	
Rank 3 Count	x	9	=	
Rank 4 Count	x	8	=	
Rank 5 Count	x	7	=	
Rank 6 Count	x	6	=	
Rank 7 Count	x	5	=	
Rank 8 Count	x	4	=	
Rank 9 Count	x	3	=	
Rank 10 Count	x	2	=	
Rank 11 Count	x	1	=	

Disease Severity was Evaluated as a Potential Factor of Risk Tolerance

Factors analyzed were as follows:

- Length of time since diagnosis (from less than 1 year to > 5 years)
- Current symptoms of disease
  - Including early/late symptoms experienced by SMA type I-III
  - Same questions as in PFDD polling were used for comparison
- Ranking of activities of daily living (ADLs) -- from most to least important to enhance quality of life
  - Included: turning in bed, brushing hair/teeth, toileting self, writing with pen, using keyboard, etc.
- Ranking of ADLs -- from most to least important that you wish to experience as improvement(s) from a treatment
  - From increased independence to tangible improvements in function

Please rank the options below **in order of importance from most important to least important for the enhancement of activities of daily living** for you or the affected individual.

Overall Rank	Item	Score
1	Increased independence in mobility	1,994
2	Going to the restroom by self/ Toileting self	1,830
3	Feeding self	1,783
4	Ability to spend time alone / be independent	1,747
5	Turning in bed	1,622
6	Dressing self	1,369
7	Transferring from wheelchair to bed unaided	1,289
8	Using a keyboard	1,237
9	Writing with pen	1,021
10	Brushing teeth	999
11	Brushing hair	880

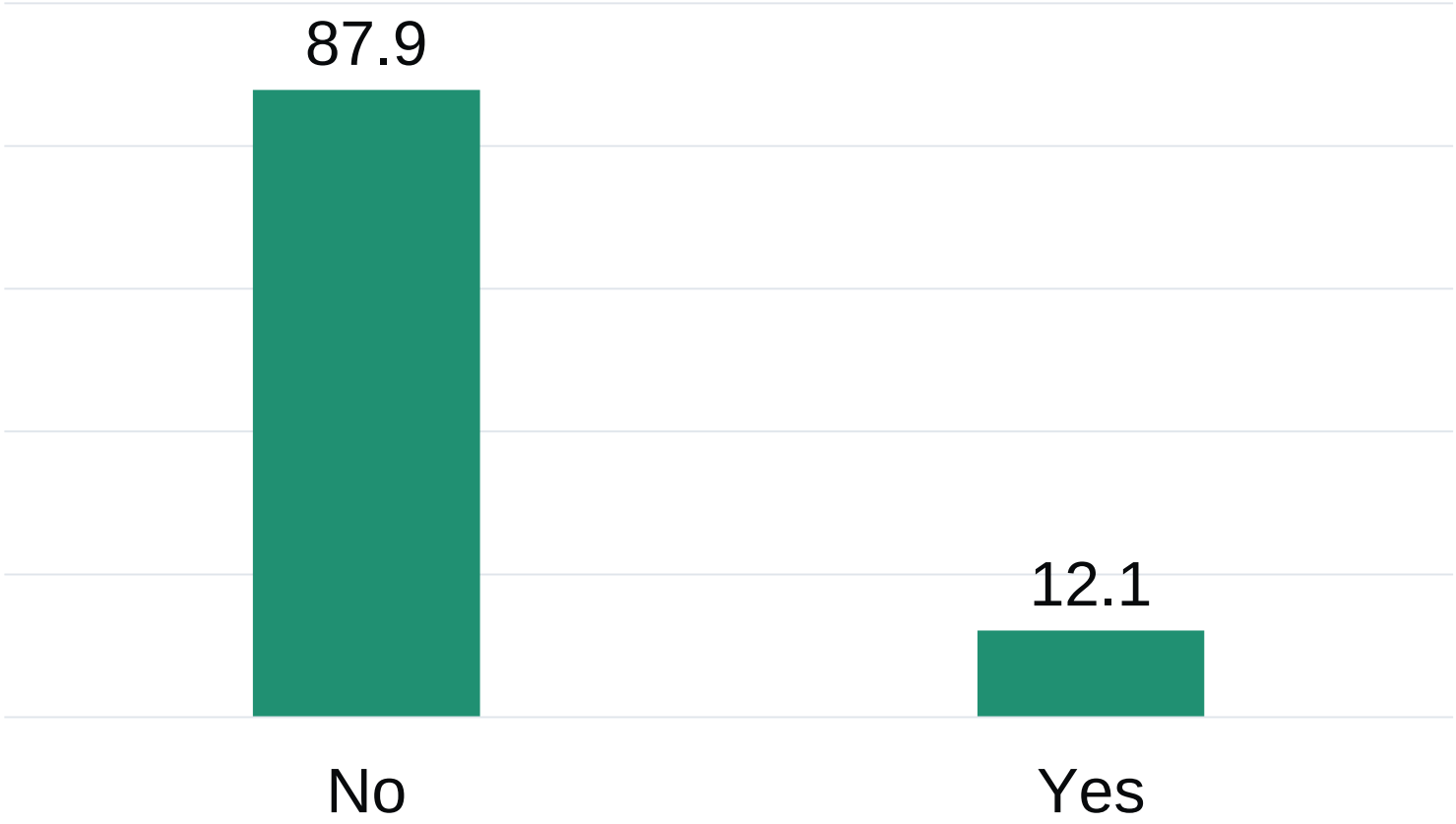
n=272

Please rank the options **below in order of importance from most important to least important for enhancements in quality of life you might experience as a result of improvements from a given drug/therapy** for you or the affected individual.

Overall Rank	Item	Score
1	Going to restroom by oneself	1,667
2	Spend time alone / be independent	1,625
3	Engage in social activities and build relationships (playdates, dining out, dating, hugging my partner)	1,621
4	Attend to personal hygiene independently	1,566
5	Chew & swallow food	1,517
6	Sit up (assisted or independently) without the need for frequent suctioning	1,508
7	Attend work or school	1,423
8	Dress oneself	1,314
9	Hug my loved ones or for my loved one to hug me	1,297
10	Engage in physical activities (playing sports, going to the gym)	1,243
11	Sleep by myself (in my own room)	993

n=272

Have you ever lost a loved one to SMA? (Percent)



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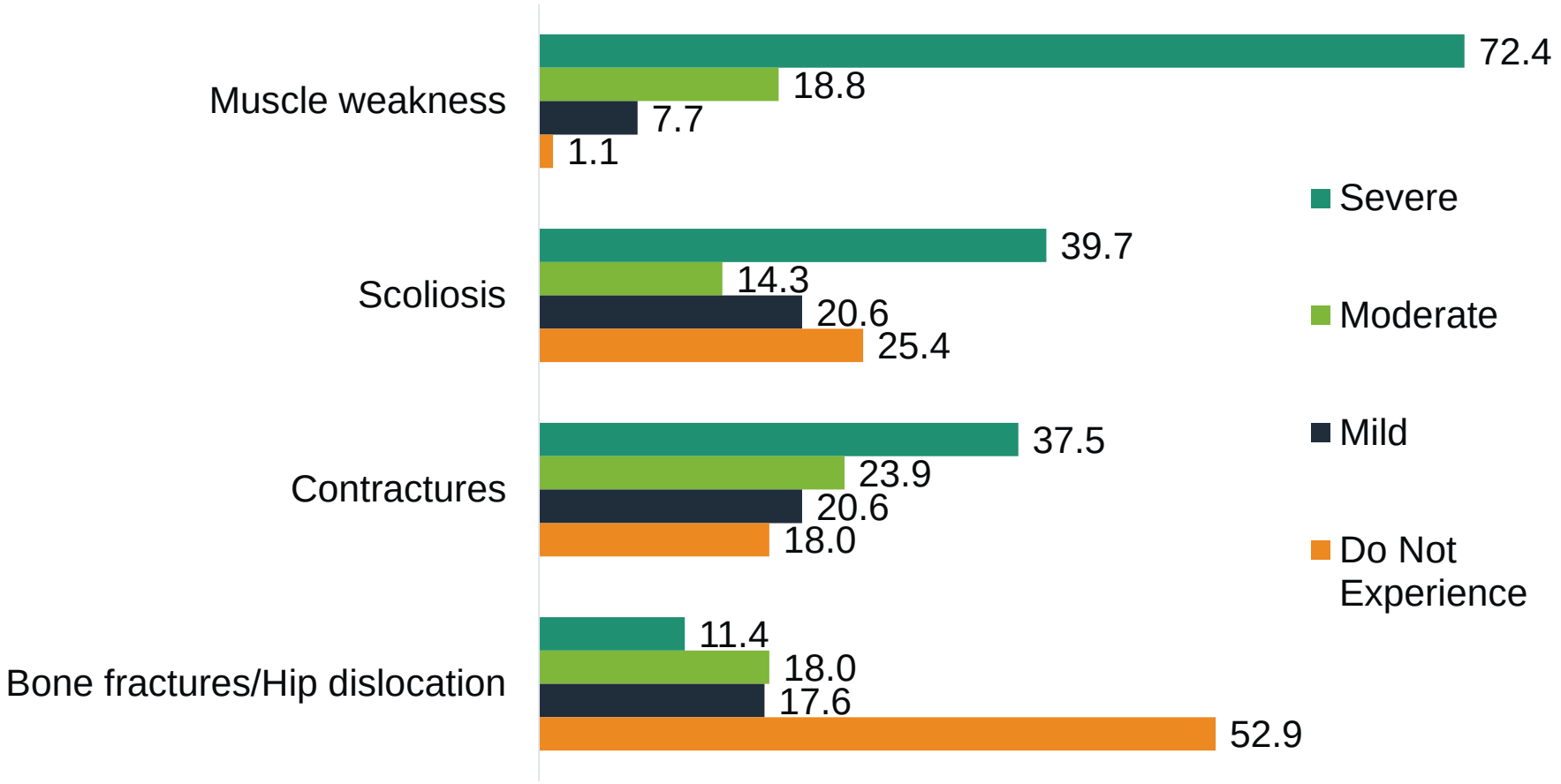
Degree of Symptoms (Percent)



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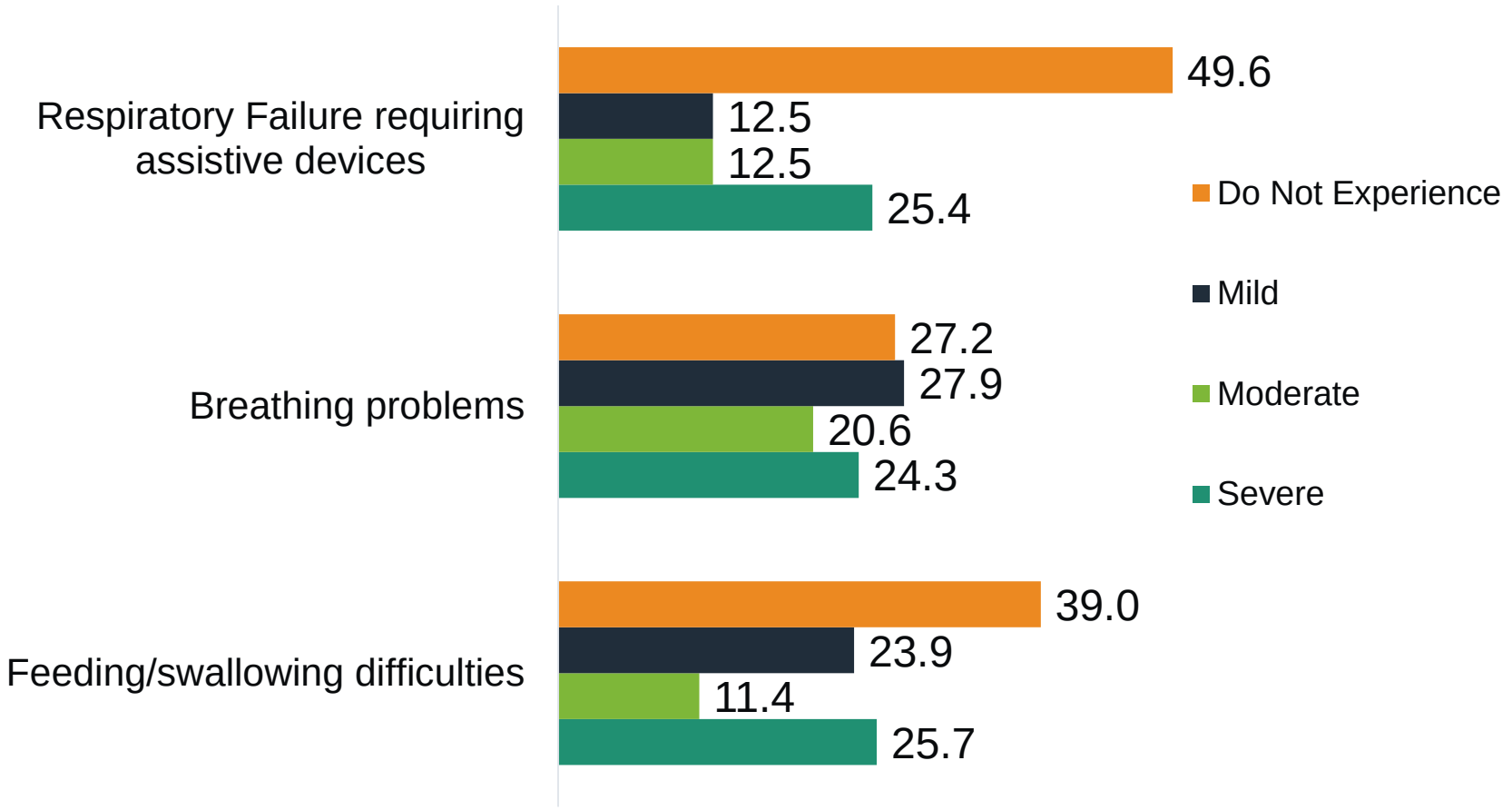
Degree of Symptoms (Percent), continued



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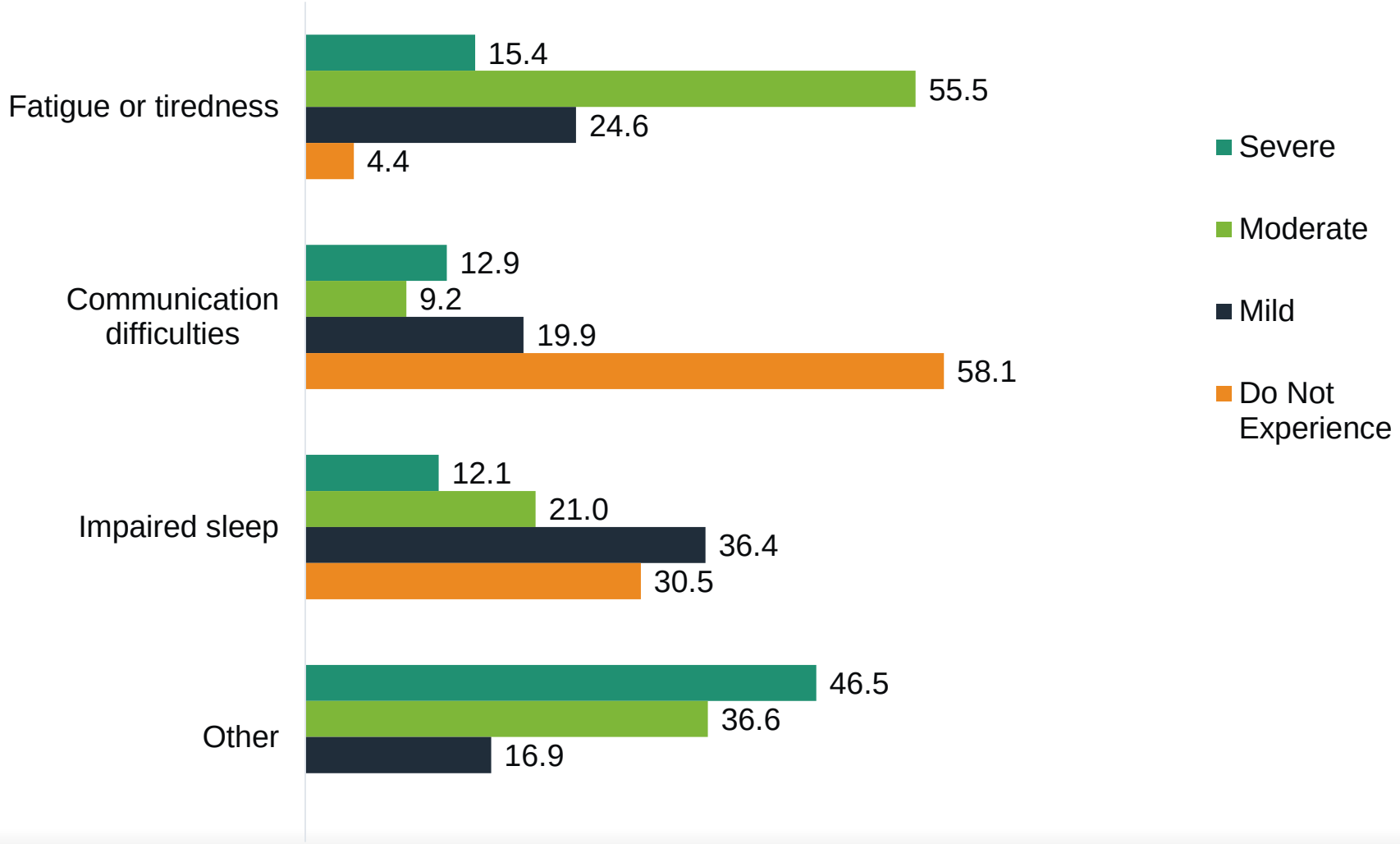
Degree of Symptoms (Percent), continued



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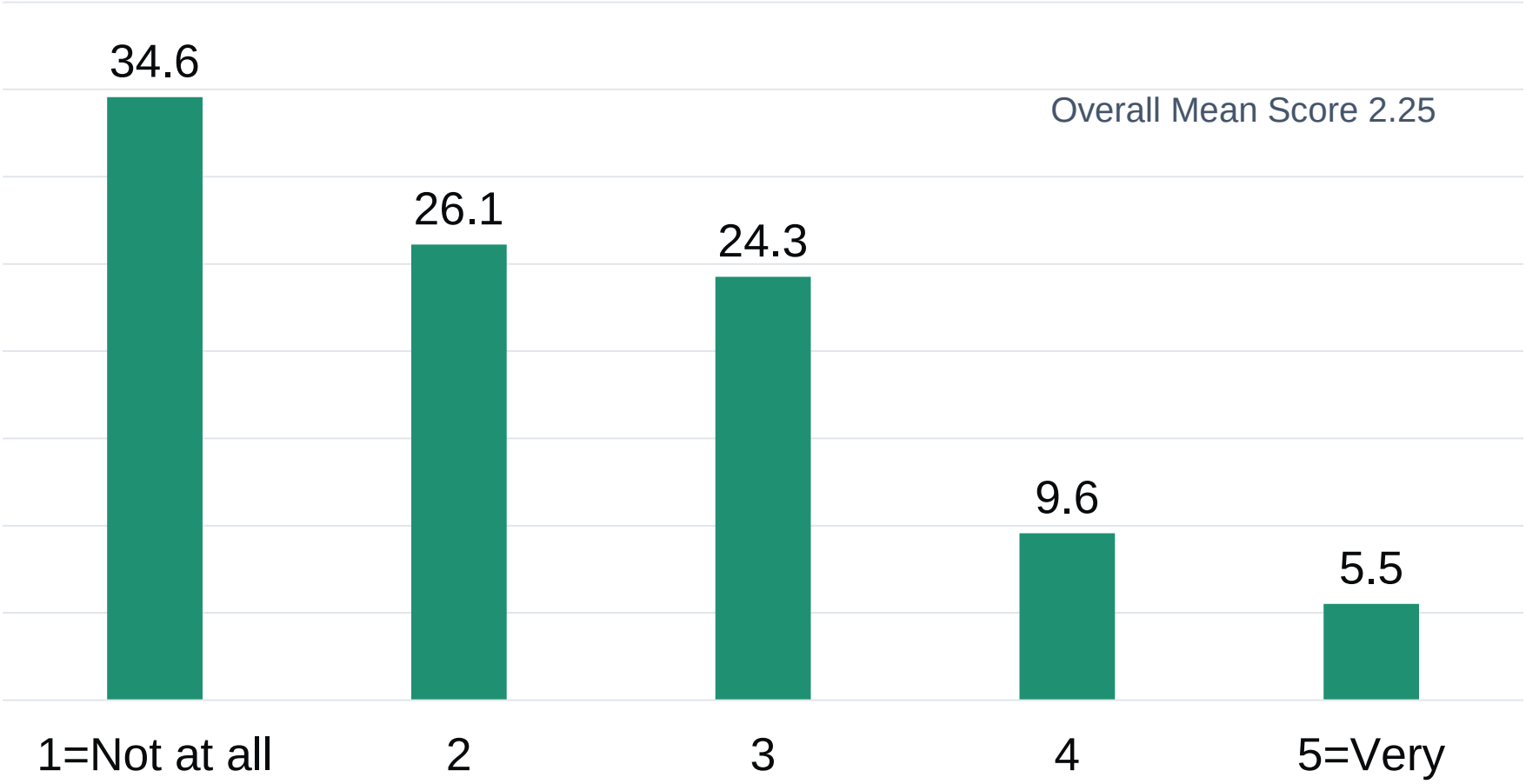
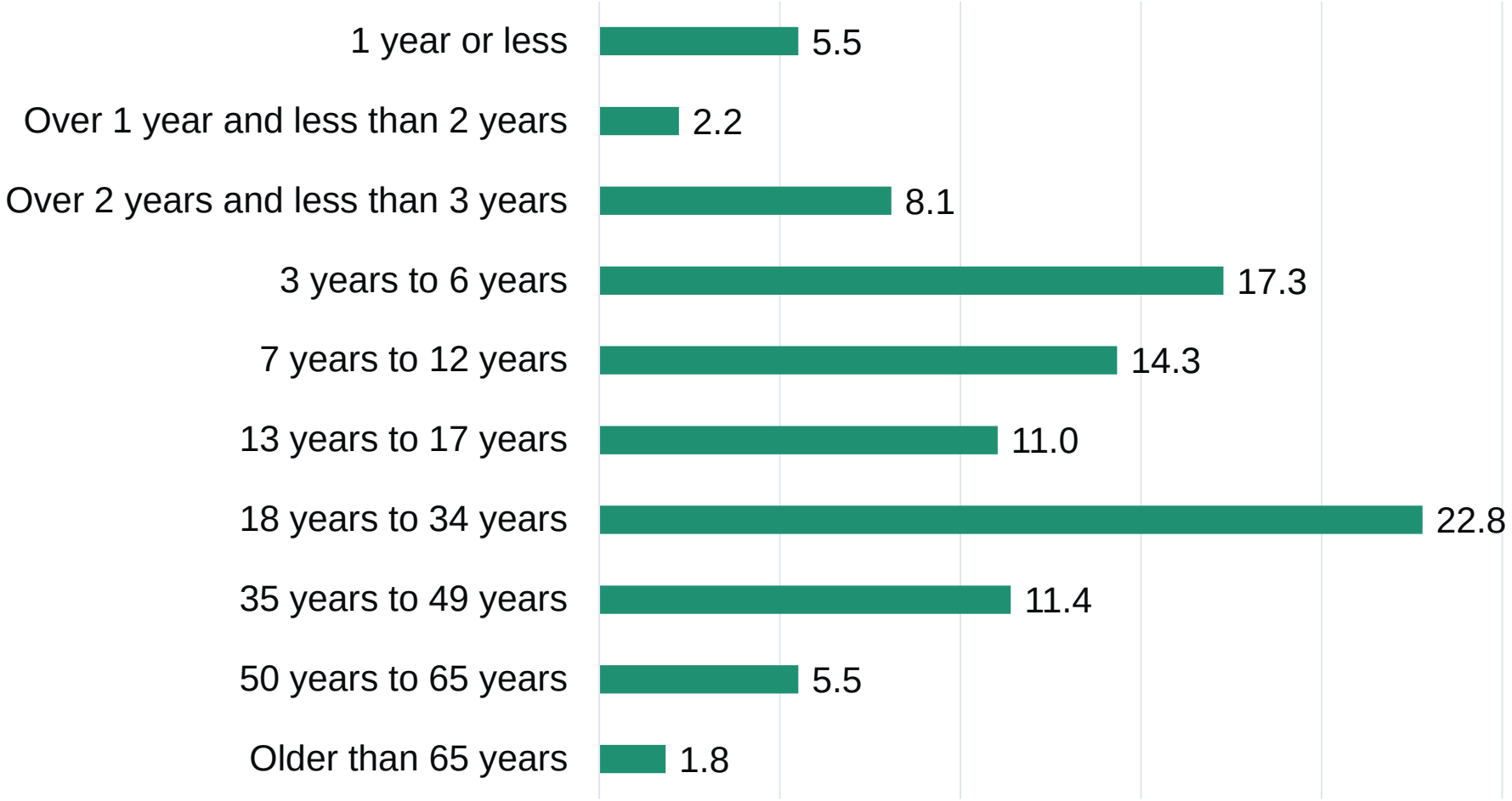
On a scale from 1 to 5 how would you describe your or the affected individual's level of independence?



n=272

Section D: Demographics

Age – Affected Individual (Percent)

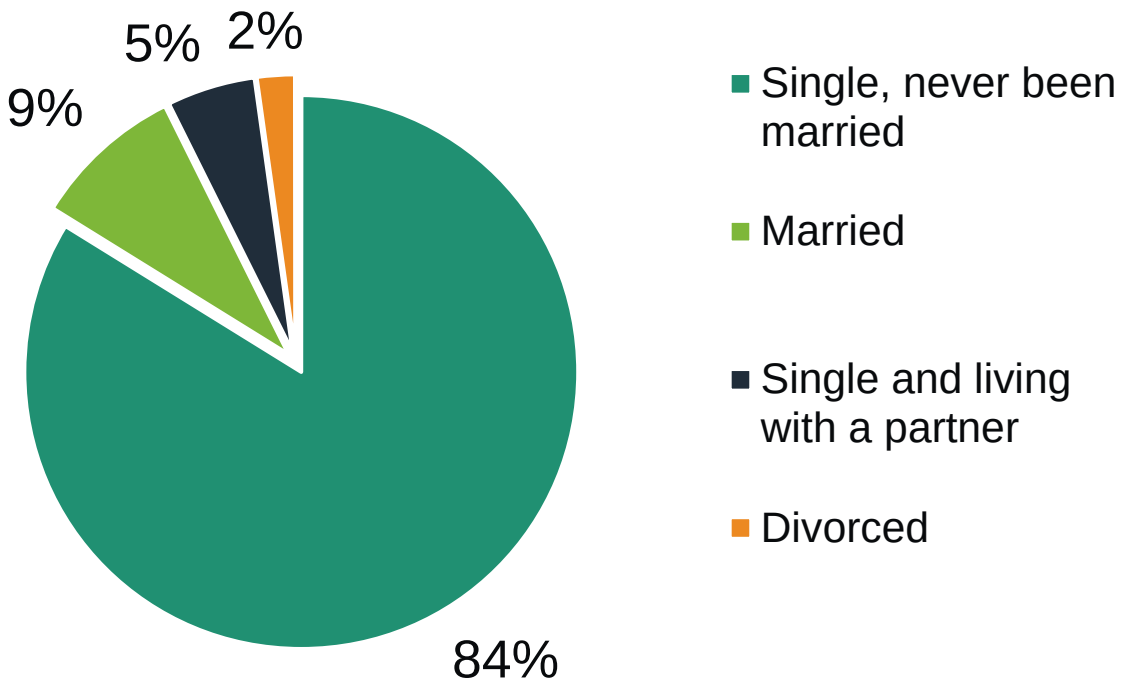


n=272

Characteristics of Respondents

- By patient/caregiver (n=298)
  - 28% were individuals affected by SMA
  - 72% were caregivers
    - Vast majority of caregivers were parents (94.2%)
- SMA Type (n=272)
  - SMA Type I – 22.1%
  - SMA Type II – 46.5%
  - SMA Type III – 29.1%
- Diagnosis timeframe (n=272)
  - Most (67.3%) diagnosed more than 5 years ago
- Ambulatory status (n=272)
  - Non-ambulatory (79.8%)
  - Able to walk with assistive device (10.7%)
  - Ambulatory without support (9.6%)

Marital Status – Affected Individual



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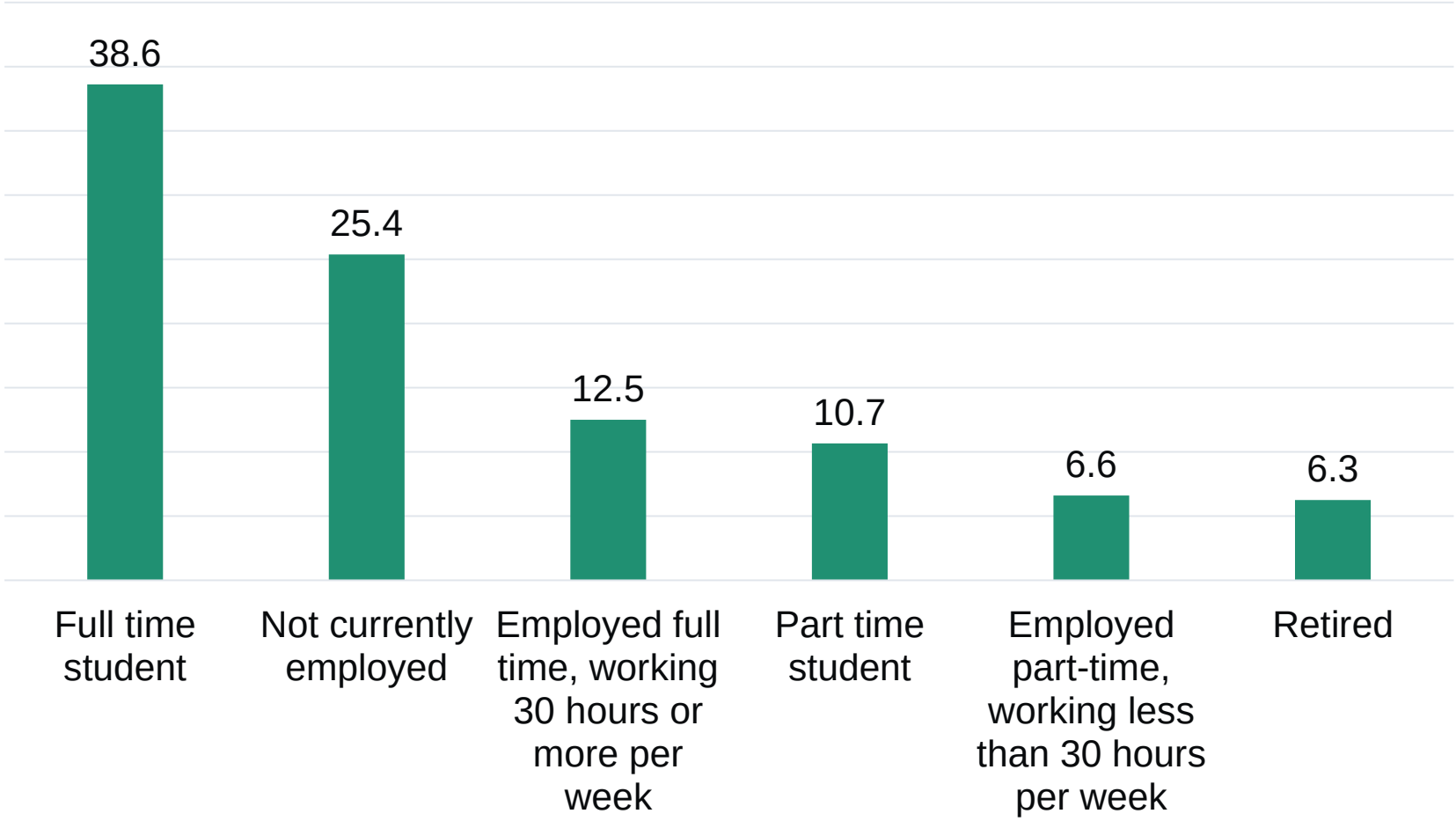
Employment Status – Affected Individual (Percent)



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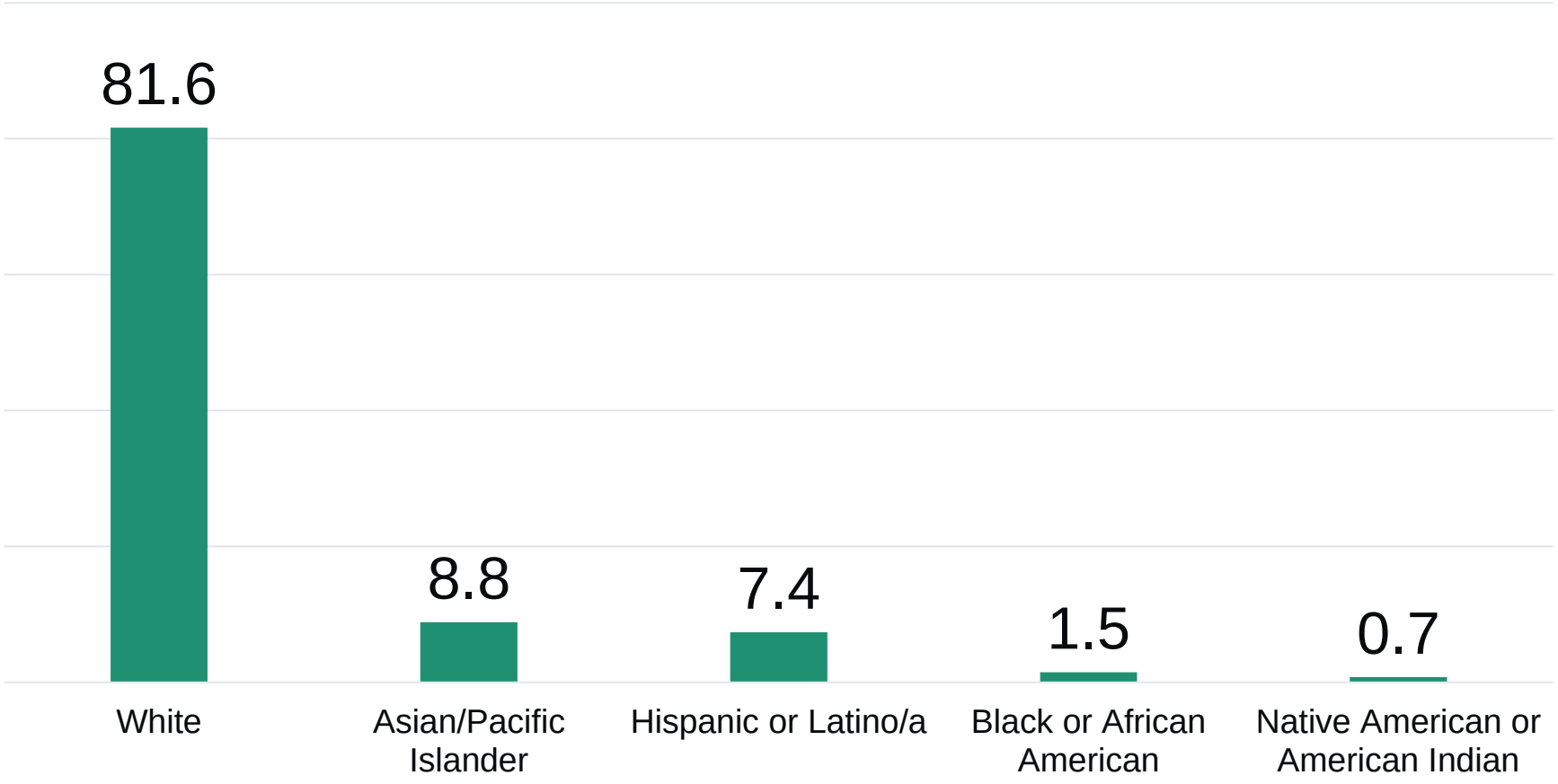
Race – Affected Individual (Percent)



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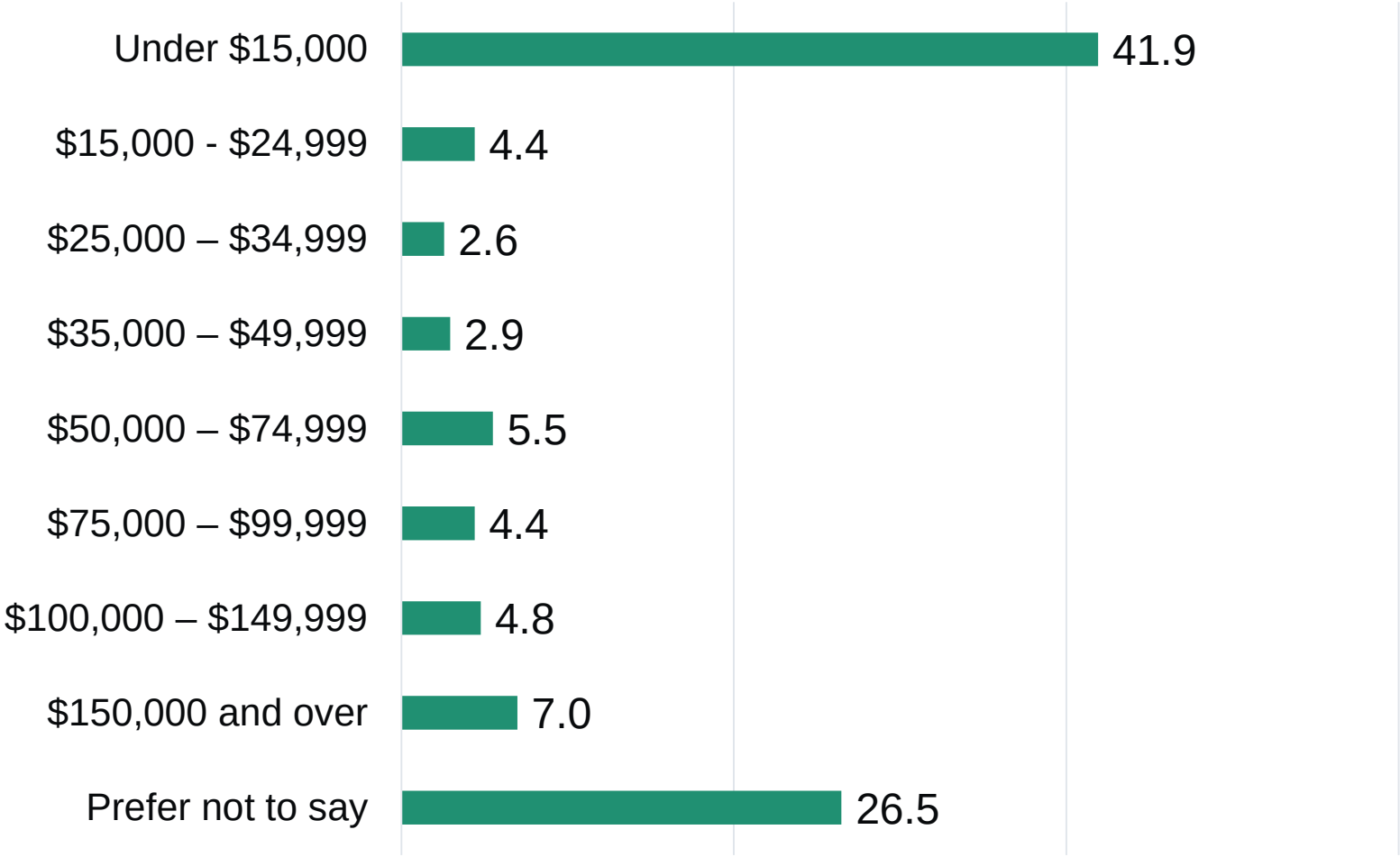
Income – Affected Individual (Percent)



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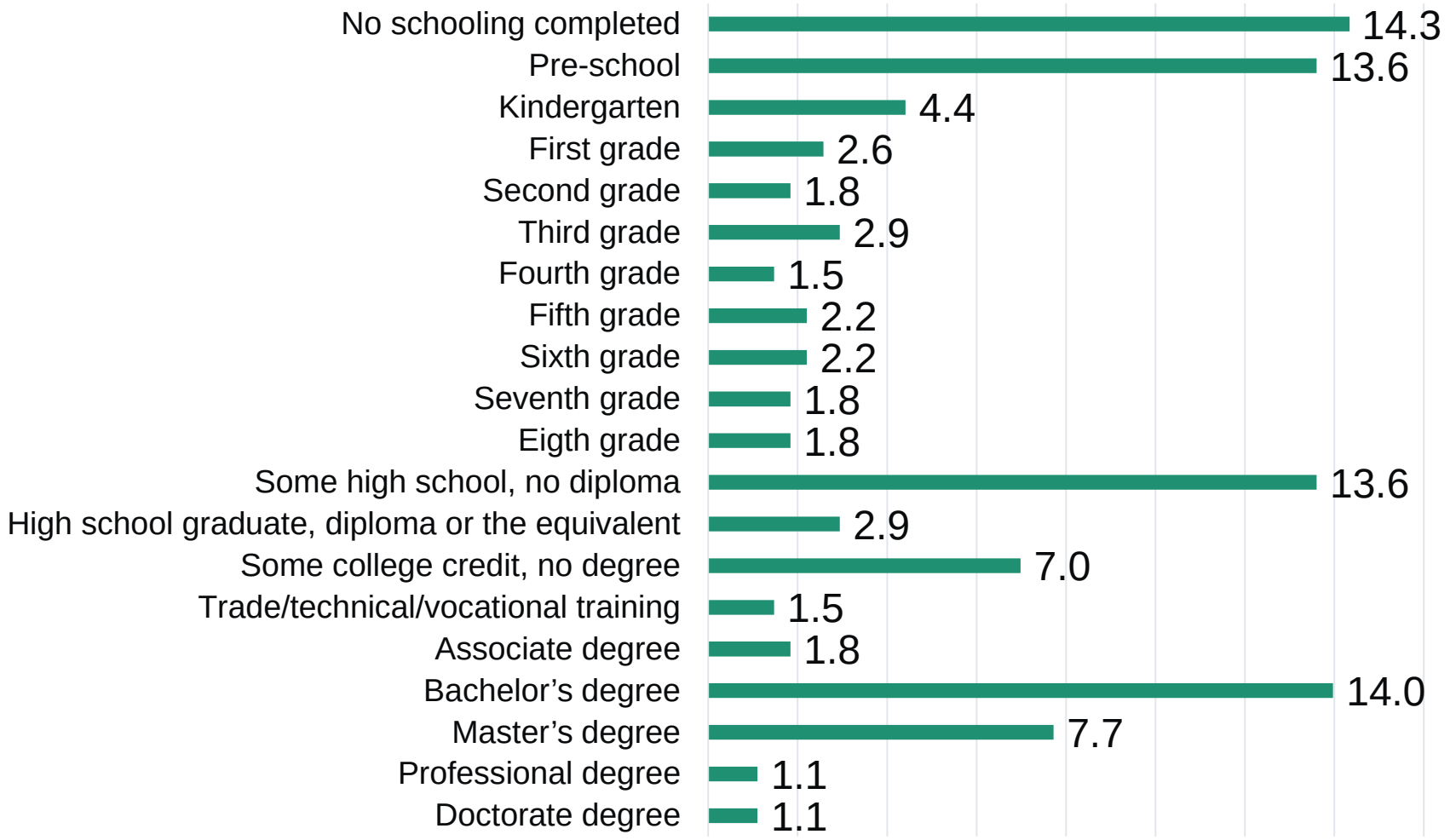
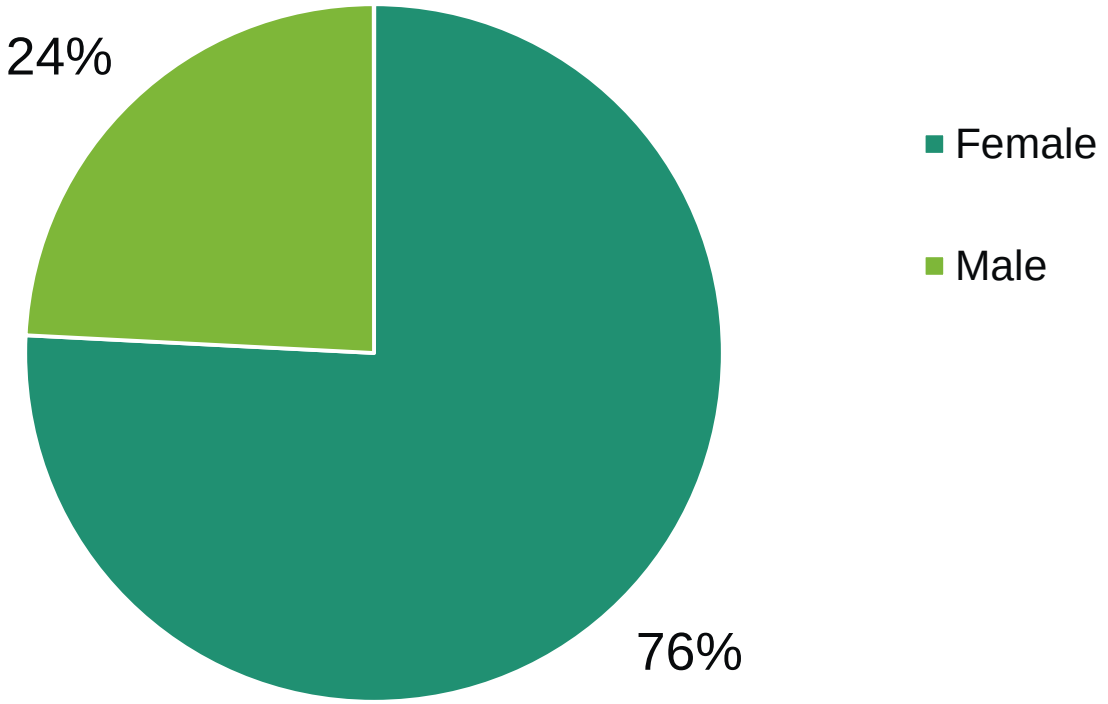
Education – Affected Individual (Percent)



Gender – Caregiver



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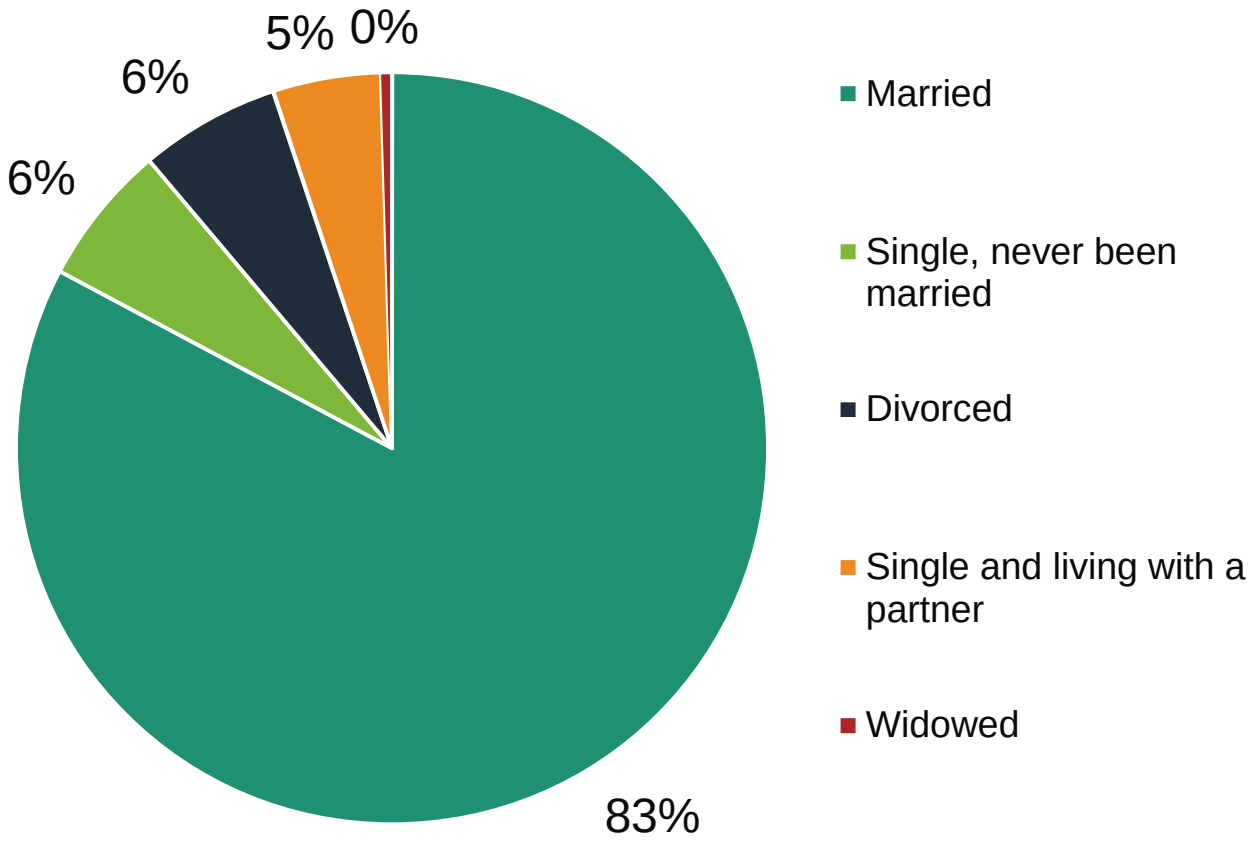
Marital Status - Caregiver



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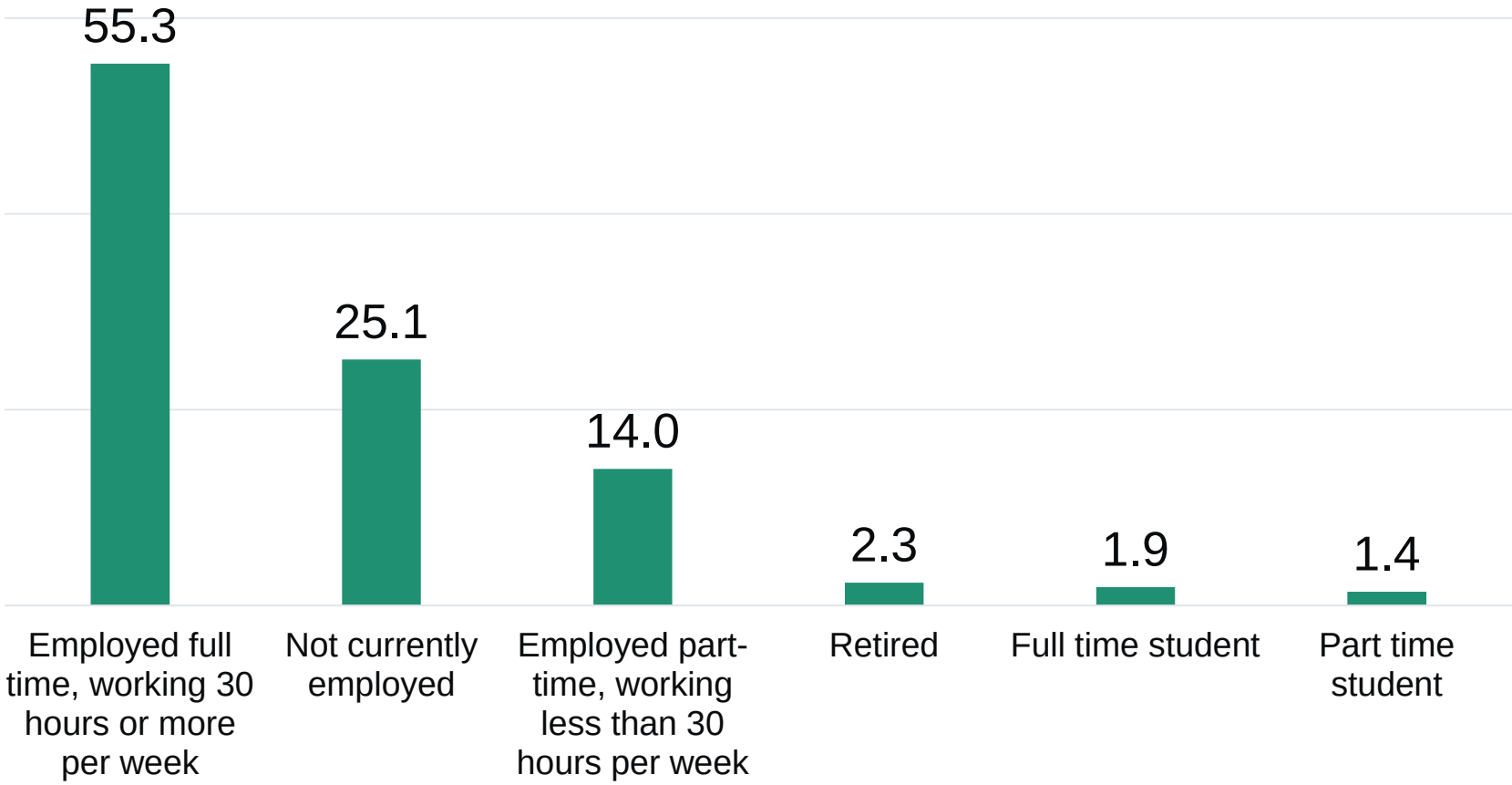
Employment Status - Caregiver



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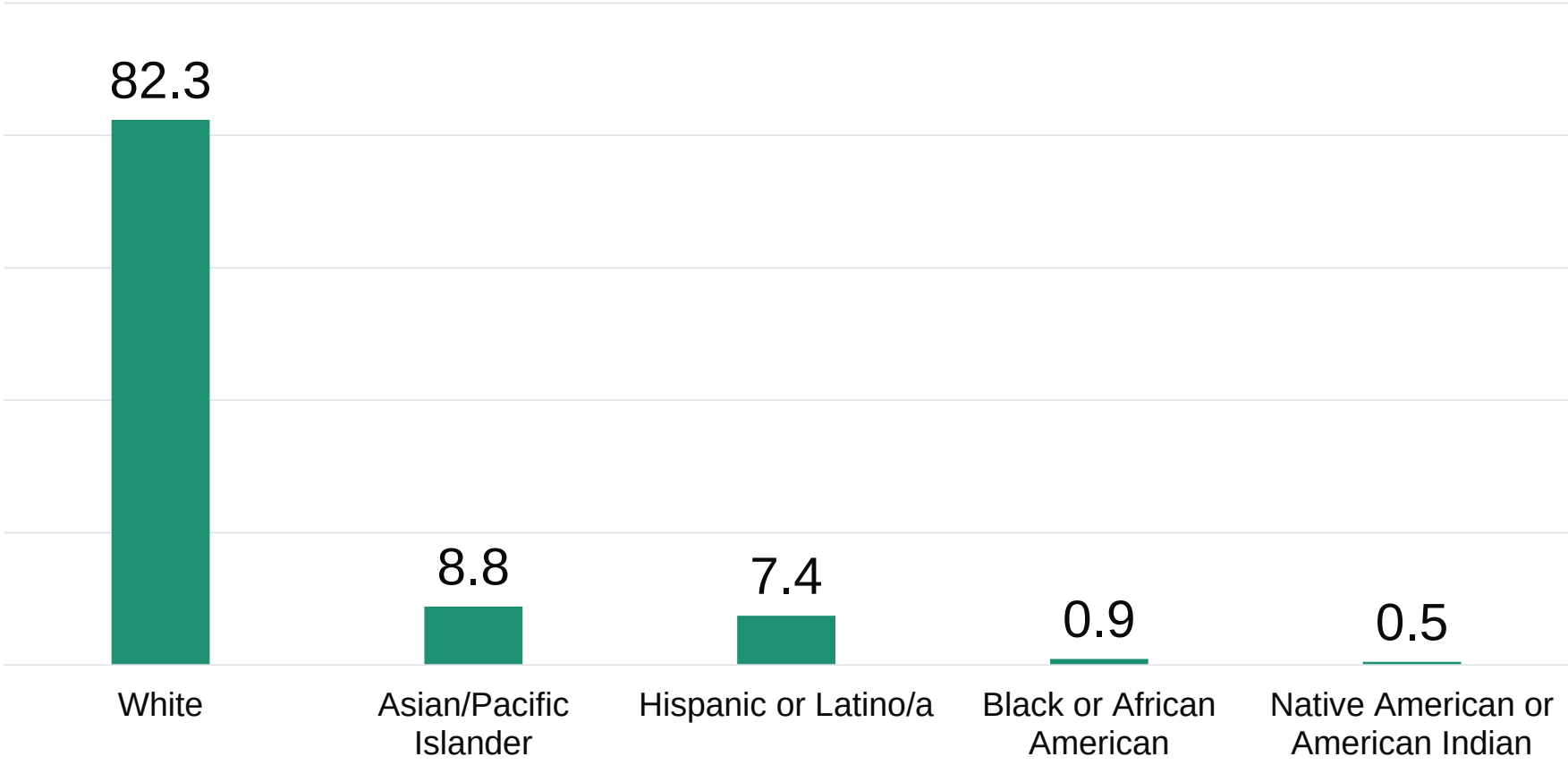
Race - Caregiver



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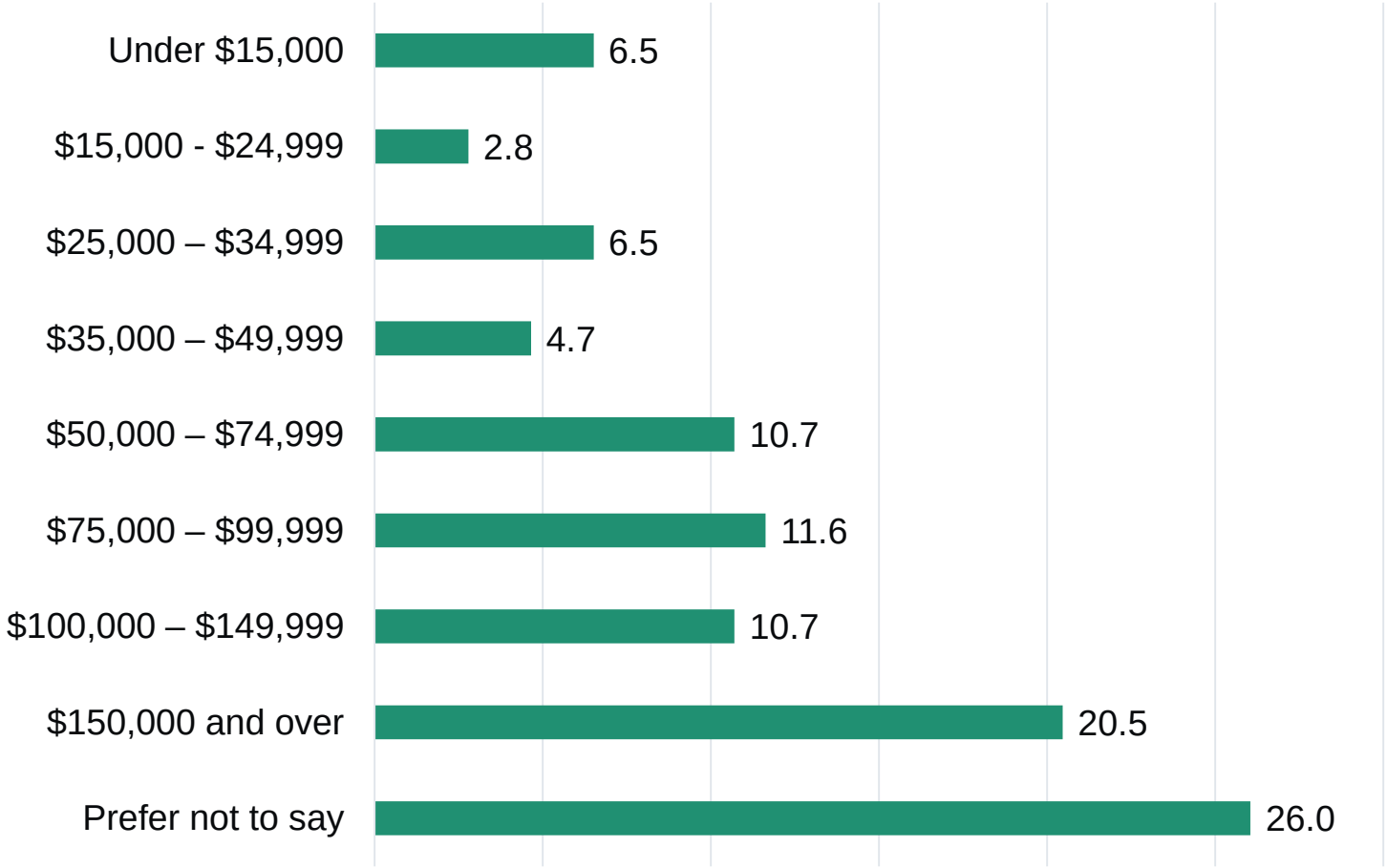
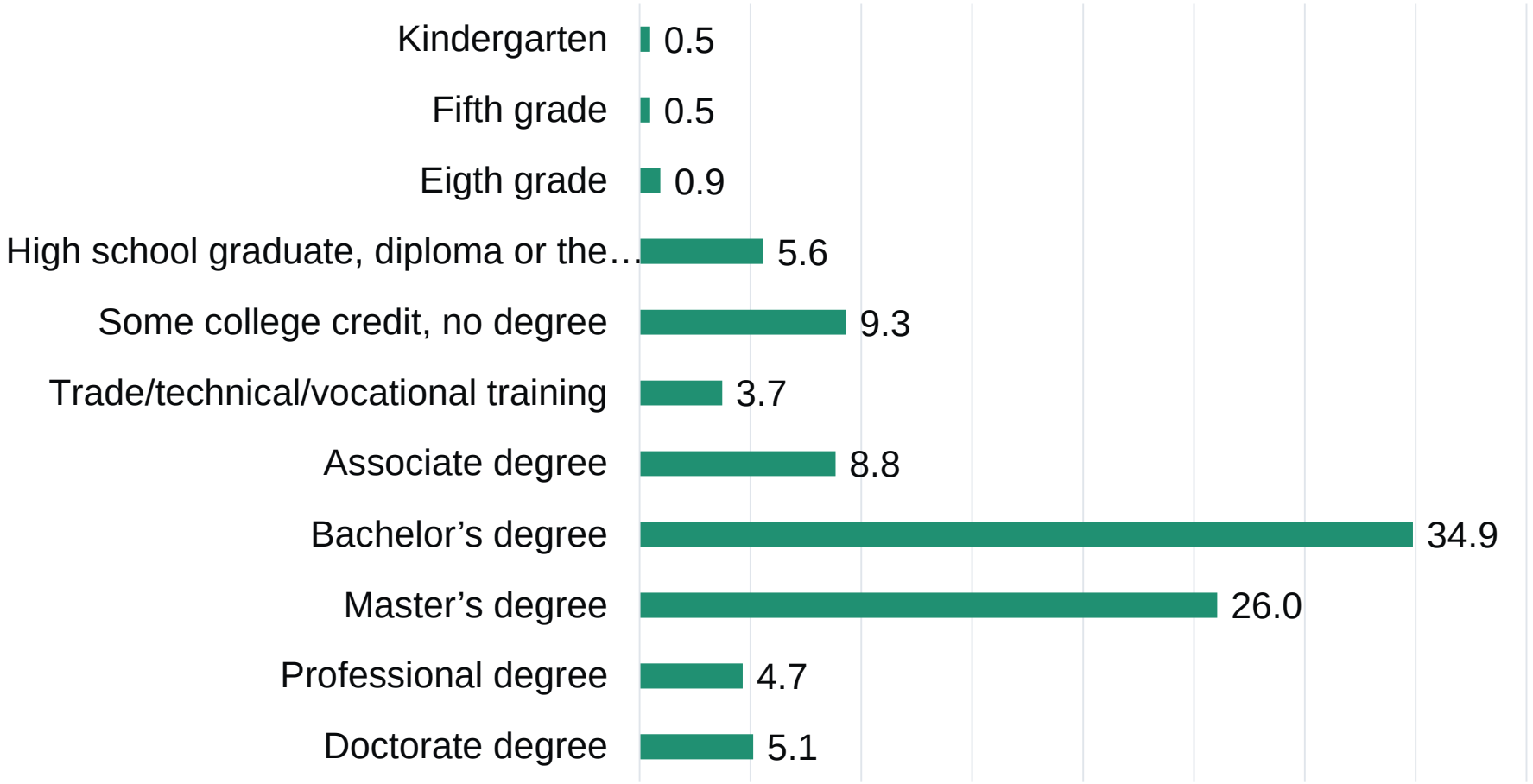
Income – Caregiver (Percent)



n=215

Education – Caregiver (Percent)



n=215

Section F: Major Conclusions

Major Conclusions

1. Survey respondents consistently rated the following as the most tolerable risks regardless of the benefit of the treatment:

- Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.)
- Possible need for general anesthesia to administer treatment
- Side effect of dizziness (may increase risk of falls)
- Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.

Conversely, respondents consistently rated the following as the least tolerable risks regardless of the benefit of the treatment:

- Life-threatening allergic reactions.
- 1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.
- Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).

Major Conclusions

2. Type I caregivers and affected individuals surveyed were less tolerant than the total sample of the side effect of dizziness, with its potential to increase risk of falls for all of the treatments except for:

- Consistent muscle strength
- Improved ability to communicate
- Improved respiratory function
- Lessening of symptoms

SMA Type 1 caregivers and affected individuals consistently rated the following as the least tolerable risks regardless of the benefit of the treatment:

- 1 in 1,000 risk of serious side effects to the heart, liver or kidney that may affect normal organ functioning and therefore require immediate medical attention.
- 1 in 1,000 risk of life-threating side effects to the heart, liver, or kidney that may result in possible organ failure.
- Worsening in “quality of life” (possibly due to drug’s side effects, worsening condition, etc.).
- Serious allergic reactions, appear less of a concern for these respondents, when compared to all respondents.

Major Conclusions

3. Type II caregivers and affected individuals surveyed consistently rated the following as the most tolerable risks regardless of the benefit of the treatment:

- Side effect of dizziness (may increase risk of falls)
- Possible need for invasive means to administer treatment (e.g., infusion, injections (using a needle) into veins, spinal canal, etc.)
- Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, fatigue, etc.

Type II survey respondents also found the possible need for general anesthesia to be less tolerable than all respondents, with the exception of the following benefits:

- Increased upper limb (arm strength)
- Slowdown of progression of symptoms
- Type II caregivers and affected individuals were also willing to tolerate 1 in 100,000 risk of serious side effects to heart, liver and kidney requiring immediate medical attention for a prolonged lifespan more readily than all respondents.

Major Conclusions

4. Both male and female respondents were consistent with all respondents for risks they considered most and least tolerable, regardless of treatment. Female respondents, however, were generally more tolerant of the side effects of dizziness with its potential to increase risk of falls than males respondents.

5. Risk taking attitudes did not appear to influence their risk/benefit tradeoffs. Both high risk takers and low risk takers exhibit risk/benefit profiles consistent with all respondents. There was very little deviation in the risk/benefit tradeoffs of high and low risk respondents with the exception of high risk takers selecting the 1 in 100,000 risk of serious side effects as a more tolerable option more often than not compared to low risk takers.

6. Likewise, risk profiles for caregivers taking the survey on behalf of affected individuals versus those affected individuals answering the survey questions on their own behalf did not exhibit significant variation from those of all survey respondents, with the minor exception that caregivers were slightly more likely to rate possible need for general anesthesia as the most tolerable risk compared to affected individuals responding for themselves

Cure SMA Risk/Benefit Quantification Research Final Report

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