Evaluating Benefit-risk Decision-making in Spinal Muscular Atrophy: A First-ever Study to Assess Risk Tolerance in the SMA Patient Community

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ABSTRACT

Purpose: Patients' perceptions of benefit–risk are essential to informing the regulatory process and the context in which potential therapies are evaluated. To bring this critical information to regulators, Cure SMA launched a first-ever Benefit-Risk Survey for spinal muscular atrophy (SMA) to characterize decision-making and benefit–risk trade-offs in SMA associated with a potential therapy. We hypothesized that risk tolerance would be correlated with SMA type/severity and disease progression. This article presents the results of a benefit–risk survey to enhance understanding of how patients with SMA and caregivers evaluate specific benefits and risks associated with potential therapies.

Methods: Affected adults, representing all SMA types (I–IV) within the Cure SMA database, and caregivers of affected individuals of all ages/types were invited via e-mail to participate. Best–worst scaling (BWS) was used to assess participants' priorities on benefit–risk trade-offs, as it provides higher discrimination and importance scaling among tested attributes. Twelve potentially clinically meaningful treatment benefits and 11 potential risks (ranging in severity and immediacy) were tested. Multiple factors were correlated with individual responses, including: SMA type/disease severity, stage of disease, respondent type, sex, and quality of life/level of independence (current and expected). Survey respondents were also evaluated for "risk-taking attitudes."

Findings: A total of 298 responses were evaluated (28% affected adults and 72% caregivers, mostly parents). Most respondents were diagnosed >5 years ago (67.3%), with 22.1% SMA type I, 45.6% SMA type II, and 27.9% SMA type III. No strong correlation was found between risk tolerance and SMA type, stage of disease progression, respondent type, sex, quality of life assessment, or rated levels of independence. Irrespective of SMA type, respondents consistently rated the following risks, associated with a potential treatment, as "least tolerable": life-threatening allergic reactions; 1 in 1000 risk of life-threatening side effects leading to possible organ failure; or worsening quality of life. Furthermore, all SMA type respondents rated these risks as "most tolerable": invasive mode of treatment administration (including need for general anesthesia); side effect of dizziness; and other common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, or fatigue.

Implications: With the approval of the first SMA treatment, these findings offer a unique opportunity to assess and characterize baseline risk-tolerance in SMA against which to evaluate future SMA treatment options. Although differences had been expected in risk tolerance among respondents based on disease baseline and certain patient attributes, this was not observed. Survey results should inform future SMA drug development and benefit–risk assessments. (*Clin Ther*. 2019;41:943–960) © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: benefit–risk assessment, drug development, patients and caregivers, rare disease, risk tolerance, spinal muscular atrophy (SMA), best-worst scaling.

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INTRODUCTION

Spinal muscular atrophy (SMA) is a genetic neuromuscular disease characterized by progressive muscle weakness and atrophy that often lead to substantial disability, including paralysis and premature death.[3,32,33] SMA, the leading genetic cause of infantile death,[3,32,33,35,39] is caused by a deletion or defect in the survival motor neuron 1 *(SMN1)* gene, which encodes the SMN protein.[1–3,27] This protein is critical to the health and survival of alpha motor neurons in the spinal cord, the nerve cells responsible for proper muscle function and strength. With a prevalence of 1 in 10,000 to 11,000 infants,[1,2,4,6,25] it is estimated that SMA affects between 8,500 and 10,300 children and adults in the United States.[8,26] Approximately 1 in 40–50 (6 million) Americans are genetic carriers.[5–7,40]

SMA has been classified into 4 primary clinical subtypes based on age of onset and the highest physical milestone achieved.[35–39,62] Each subtype represents a phenotypic continuum from the most common and severe type, with onset in infancy (type I), to the mildest form, with onset in adulthood (type IV).[35–39,63,64] SMA type I (Werdnig-Hoffmann disease), which accounts for an estimated 50%–60% of SMA diagnoses,[3,8] presents with severe generalized weakness and hypotonia. Children with this type of SMA never achieve the ability to sit, and they require intensive supportive care, including respiratory and feeding support, as they quickly lose the ability to swallow, eat, and ultimately breathe. SMA type II (also called Kugelberg-Welander disease) affects ~20%–30% of those diagnosed and usually presents between the ages of 6 and 18 months. These children can sit independently but are unable to walk without assistance.[1,3,8,35,39] Over time, they may develop difficulties chewing and swallowing, respiratory difficulties, and progressive scoliosis, often requiring surgical intervention. Recent advances in supportive care for patients with SMA type II have extended survival for this group, with life spans well into adulthood.[3,8,9,63] Juvenile SMA (type III) is diagnosed between 18 months and the teen years. These patients (~10%–15% of diagnoses)[2,3,8] can sit and walk, and have a normal life expectancy, although they develop muscle weakness over time and often eventually lose ambulation.[2,35,39] In rare cases, patients' symptoms first appear in adulthood (type IV). These patients often experience mild proximal limb weakness after the age of 30 years, but they have a normal life expectancy.[3] Until recently, no therapy was available to treat the debilitating symptoms of this disease.

The disease burden of SMA is all-encompassing and extremely challenging for patients and their families.[2,3,7,13,18] It begins with a prolonged and often traumatic diagnostic journey, followed by a lifetime of overwhelming physical, emotional, psychosocial, and financial strains associated with living with a progressive and degenerative condition.[2,3,7,13,18,66] Before the first treatment for SMA was approved by the US Food and Drug Administration (FDA), traditional management approaches for patients included supportive, rehabilitative, pulmonary, nutritional, and palliative efforts designed to reduce the impact of the disease and address the effects of severe muscle weakness.[3,41–43,65]

The SMA treatment landscape changed on December 23, 2016, when nusinersen became the first FDA-approved disease-modifying therapy for SMA.[10] The landmark approval of nusinersen ushered in an era of new hope for the SMA community with the availability of an effective treatment approved for all types of SMA.[11,12,28,60] The approval showed proof of principle that it is possible to deliver clinically meaningful benefits, affecting motor function outcomes and rates of survival for patients with SMA, particularly when treatment is introduced soon after symptom's onset, and most significantly, pre-symptomatically.[11,12,28,60,61] However, for many patients with SMA and their caregivers, the disease burden and related unmet needs remain significant, particularly when the drug is provided after significant symptom onset.[1,11–13]

With a first approved therapy now in commercial use, an evolving standard of care,[42,43] and additional therapeutic options in development,[20] there is a need to supplement the existing clinical outcome measures for SMA by further understanding, measuring, and incorporating the perspectives and priorities of patients with SMA and their caregivers within therapy development and the regulatory review processes.[24,30,48,59] The FDA has issued a series of guidance documents[44,44b] and conducted multiple workshops and public meetings to discuss its interest

in evaluating patient input, including that generated by patient-reported outcomes, patient preference studies, patient-focused drug development meetings, and advisory committee meetings.[16,29,30,55]

Patient and caregiver priorities and expectations for desired benefits from a therapeutic agent to treat the symptoms of SMA have been evaluated in several important studies.[1,2,13,18] These indicate that patient and family assessment of meaningful change varies across the continuum of SMA type and functional ability. For those dealing with SMA type I, high-priority components of meaningful change relate to immediate concerns with breathing, feeding, and swallowing, and the ability to communicate.[13] For patients with SMA types II and III, priorities include disease stabilization, independence and the ability to perform basic personal tasks, and fatigue.[1,13,18] In most cases, patients and caregivers perceive benefit in maintenance of current abilities and avoiding decline in function. They indicate that even small improvements in functional abilities would be meaningful, especially if these contribute to the ability to more independently perform activities of daily living (ADL).[1,13,18]

Although we have learned much about the burden of SMA and what patients and caregivers desire in a potential therapy,[2,3,7,13,18] little focus has been given to understanding how patients and families would weigh the possible risks associated with future therapies against any potential benefits resulting from those therapies. This is a significant gap in the evidence base for SMA, particularly given regulators' clear interest in receiving information about patient and caregiver perceptions of benefit–risk (B-R) trade-offs to augment the B-R assessment of clinical outcome measures.[19,49]

Cure SMA[14] launched a milestone study to fill this evidence gap and gather data relating to patient and family B-R assessments. The data gathered as part of this study will provide important information to inform the Benefit–Risk Framework, described in The Prescription Drug User Fee Act V and VI[44,44b] and that is critical in drug regulatory decision-making.

The objective of the B-R study was to understand and characterize, via quantitative analysis, how patients with SMA and caregivers would weigh risks (ranging in severity from mild to life-threatening) in exchange for gains (e.g., clinically meaningful benefits) associated with a potential therapy. In addition, the study sought to identify correlations, if any, between B-R trade-offs made by the surveyed population and a variety of factors that characterize subgroups within the SMA community. We hypothesized that the amount, severity, and type of risks that individuals with SMA and their caregivers would be willing to take on (or trade for certain clinically meaningful benefits) would be highly correlated with their current functional ability and present stage of disease, for all SMA and responder types. More specifically, we theorized that the more severe and advanced the disease, the more risks an individual would be willing to take on in exchange for certain clinically meaningful benefits.

Taking advantage of a particularly important time in the evolution of SMA patient management and therapy development, the present study was designed to evaluate hypothetical B-R trade-off decisions across SMA types and among patients and caregivers. This article presents the B-R survey results and discusses implications for future therapy development and regulatory decision-making.

PATIENTS AND METHODS

Participants

All who met inclusion criteria, affected adults (aged ≥18 years) with genetically confirmed SMA (of all types [I–IV]) and caregivers of affected individuals of all ages and types, were invited to participate in this study. Adults and caregivers in the Cure SMA database, who had opted to receive communications from Cure SMA (N = 3,689), were invited to participate. The institutional review board–exempt survey (WIRB #1-1037765-1) was conducted in late 2017. No personal health information was collected from survey respondents through the survey or by any other means.

Sample Size Calculation

Based on previous studies, the proportions of SMA type in the Cure SMA database represents similar prevalence values according to proportion of SMA type.[8] Therefore, the minimum sample size needed based on a 95% CI with a margin of error of ±5.68% was calculated to be 300.

SMA B-R Survey Technique: Best–Worst Scaling

Cure SMA led the development and dissemination of a quantitative survey to uncover trade-offs that

patients with SMA and caregivers would make when considering the benefits and risks associated with treating their symptoms. Best–worst scaling (BWS), case 2, also known as the maximum difference scaling technique, was selected as the survey method to obtain data on patients' B-R trade-offs. This preference method is used to systematically assess preferences, presenting profiles (attributes or treatment benefits) one at a time to elicit preferences.[50,53] In this study, survey participants were asked to make best and worst choices (most and least tolerable risk) within a profile. BWS is a branch of discrete choice modeling and a stated preference method (conjoint analysis) in random utility theory based on how people make choices of extremes from within a subset of a hypothetical choice set.[50–52] In a BWS survey instrument, a detailed set of related items (attributes)—in this case, a list of possible risks of various severity—is presented in subsets that are chosen based on a balanced incomplete block design to ensure equal probability of selection between items.[52]

The primary reason for selection of this method is that it provides higher discrimination and importance scaling between the tested attributes than simple rating and ranking questions, and it corrects for biases in individual variations in interpreting rating scales.[21,22] Because respondents are required to make forced choices rather than expressing strength of preference using some numeric scale, there is no opportunity for scale use bias. Studies trading treatment benefits and risks using this method have been used across diseases and health conditions.[21,23,24,31,51,54,68]

Instrument Development

An online survey was created, engaging key SMA stakeholders, to assess a list of patient-relevant treatment benefits versus possible risks. To inform this process, we used data from key sources, including focus groups and published reports on patient and caregiver-reported data on the experiences and needs of patients and families with SMA and their perceptions on meaningful change.[1,2,13,18] Careful consideration was given to symptoms and severity according to SMA type. In addition, learnings from engagement with the SMA community, including the SMA Patient Focused Drug Development Meeting in 2017 and the subsequent Voice of the Patient Report,[13] were used to inform this process. The initial survey draft was reviewed and refined for content validity by an internal working group that included researchers, physicians from relevant specialties (i.e., neurology, pulmonology), family support staff, and a core team from the Silicon Valley Research Group. The list of treatment benefits included various clinically meaningful and independently validated attributes. Attributes of chosen risks included severity, frequency, and predictability of the adverse events associated with each treatment benefit.[18,45,49]

After the initial development of survey items, Cure SMA interviewed 6 stakeholders (a parent and adult of each SMA type I, II, and III) to review and assess the final list of the potential benefits and risks for comprehension and content validity. No major disagreements arose, among the experts and stakeholders regarding the most important benefits or risk items to include. Benefits that were ultimately not included in the final set were "Enhancement of Activities of Daily Living," which was replaced with items that were operationalized/included quantifiable benefits (eg, 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."]). "Decreased tremors" was also eliminated; this was later encompassed as part of a broader category of items, under "Lessening of symptoms' severity … " In addition, slowing and stopping disease progression were originally listed separately but were ultimately combined.

Final B-R Item Selection

The final list of attributes (benefits vs risks) was refined and chosen based on input from the study team, expert clinicians, and family support staff at Cure SMA. A total of 12 potential clinically meaningful treatment benefits and 11 potential risks (ranging in severity and immediacy) were identified. A review of all treatment benefits and risks is given in Supplement 1, Section B (in the online version at doi:10.1016/j.clinthera.2019.03.012). For each set of B-R preferences, a specific benefit was paired against a subset of 5 randomly selected risks, presented at a given time. Of a set of 5 risks, participants were asked to choose 2 and rank them as "most" and "least" tolerable against the treatment benefit

presented. In total, 5 sets of risks were presented, per each benefit identified (Fig. 1 presents an example of BWS choice task).

Survey Design

The online survey was self-administered and included 3 main sections: a screening section, to assess inclusion criteria and responder type (affected individual vs caregiver); a section to capture information on participants' demographic characteristics, including age, SMA type, length of time since diagnosis, level of education, and marital status; and a final section including questions on disease severity, quality of life, and risk-taking attitudes. To assess disease severity, participants were shown a list of symptoms, across multiple systems, including musculoskeletal (eg, muscle weakness, contractures, scoliosis, hip weakness, bone fractures), respiratory, and gastrointestinal (including problems with feeding and swallowing) known to affect most individuals with SMA across the disease spectrum. Participants were asked to rate each symptom, if currently experienced, as mild, moderate, or severe. Details on symptoms rated are given in Supplement 1, Section C, Question D1 (in the online version at doi:10.1016/j.clinthera.2019.03.012).

To assess key aspects of clinical meaningfulness/quality of life indicators in this population, participants were asked to rank, in order of importance, a list of 2 sets of ADL: (1) those that would most enhance their quality of life; and (2) those they may want to experience due to improvements from a given therapeutic agent. These items were identified through surveys and focus groups.[2,13,15,18,34,66] They were chosen for the B-R survey due to their previously stated importance when evaluating affected individuals' feelings toward what "benefits" they would consider most important to be able to do as part of their ADL, as well as assess their attitudes toward independence, dignity, and psychosocial well-being. Supplement 1, Section C, Questions D2 and D3 (in the online version at doi:10.1016/j.clinthera.2019.03.012), provides details on ADL/quality of life indicators rated; risk-taking attitudes, as well as perceived levels of independence (including ambulatory status [Question D2]), were also assessed among survey participants (see Supplement 1, Section C, Questions D4 and D5, in the online version at doi:10.1016/j.clinthera.2019.03.012).

BWS (Case 2)

The B-R portion of the survey consisted of 5 stated preference exercises (B-R trade-offs), each associated with the same set of 11 risks, which were evaluated against a given treatment option (across 12 distinct treatments/profiles), each presented one at a time. Supplement 1, Section B (in the online version at doi:10.1016/j.clinthera.2019.03.012) presents the final list of benefits (Treatments 1−12) and risks (1−11) tested. Participants were shown one treatment option at a time (eg, Treatment 1) and were then asked to choose, from a list of 5 randomly selected risks, the "best" and "worst" risk that they would "take-on" in exchange for the specific treatment presented (eg, "Treatment 1"). Each of the 12 treatment profiles was set-up as a separate experiment and presented to all survey respondents, in multiple iterations. For each of the 11 risks, participants were asked to indicate the risk that they were most willing (best) and least willing (worst) to live with when evaluating these against the potential treatment benefit presented. Each of the 12 treatment profiles was paired against a randomized set of 5 risks and presented at a time, on 1 screen, per each treatment.

Statistical Analysis

The participants' judgment about the extremes (in this case, the "best" and "worst" risk chosen against each benefit shown) was the dependent variable in the present analysis. The analytic technique focuses on the number of times each risk was chosen as best and worst over all the choice tasks. The final score or analytic output for each chosen risk was calculated by subtracting the number of times a risk was chosen as worst from the times it was chosen as best; this number is then divided by the total number of times a risk was shown.[53] Scoring assumes equal spacing between items that were chosen as best (BW score = 1) and those chosen as worst (BW score = −1)[51] (also reviewed elsewhere[56]). A positive score means that an item/risk was selected as best/most tolerable more often than as worst or least tolerable; a negative score means that an attribute/risk was chosen as worst/least tolerable more often than as best.

We chose this simple scoring technique based on the review and findings from Gallego et al[67] and Louviere and Flynn,[50] who had shown that this method has highly correlated with more complicated regression-based techniques.[51] The higher the score (closest to 1), the more compelling the item/risk is to

Section B: Maximum Difference Questions

For the next set of questions, we will describe hypothetical treatments. For each treatment, you will be given a table listing potential side effects or risks. You will be asked to indicate the best and worst risks or side effects from that list, that is, the ones you *are most willing to live with* and the ones you are *least willing to live with*. For your convenience, the instructions will be repeated on each page.

As you answer the questions on each page, please keep the following in mind.

1. Please pick only one Best Risk and one Worst Risk on each page. You will not be able to move to the next page until you pick one of each.
2. Sometimes it may be difficult make a choice or to pick just one. Please do your best to make a choice. This is not a test. There are no right or wrong answers.
3. Please read the description of each treatment on top of the page carefully before you answer. You may find that some of the treatments sound very similar to each other. Likewise, please read each risk or side effect in the table carefully as some of these may also sound very similar to each other.
4. For each treatment, you will be asked to choose between different sets of risks or side effects several times before moving on to the next treatment. Please read the entire page to make sure you keep track of which treatment you are being asked about.
5. Please also note that the treatments that we describe in this survey have not been developed yet. We are interested in getting your opinions on what risks or sideseffects you would be willing to live with if they were developed.

Hypothetical Treatment

"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."

Best ("Most willing to live with")	Risks/Attributes	**Worst** ("Least willing to live with")
○	Risk 1: 1 in 1000 risk of serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention.	○
○	Risk 3: 1 in 1000 risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure.	○
○	Risk 7: Side effect of dizziness (may increase risk of falls).	○
○	Risk 10: Worsening in "quality of life"(eg, possibly due to drug's side effects, worsening condition, etc.).	○
○	Risk 11: Life-threatening allergic reactions.	○

Figure 1. Sample choice task for best–worst scaling.

respondents. Cross-tabulations on the overall dataset were used to examine differences between demographic and psychographic subgroups (including SMA type, responder type, age, sex, and risk-taking attitudes). The statistical analyses were conducted by using choice modeling in R statistical software (R Foundation for Statistical Computing, Vienna, Austria) and SPSS version number 25 (IBM SPSS Statistics, IBM Corporation, Armonk, New York).

RESULTS

Respondents' Characteristics

A total of 3,689 individuals, parents, and caregivers with SMA were invited to participate in the survey via e-mail; 2,031 opened the initial survey outreach e-mail (55.1% view rate). Of these, 298 affected individuals, parents, and caregivers completed the B-R portion of the survey (20 of these participants did not complete all demographic questions in the survey). Of all respondents, 28% were affected adults and 72% were caregivers, mostly parents (94%), with 4% of parents caring for >1 affected individual with SMA. Most respondents indicated a length of diagnosis of >5 years (67.3%), with 22.1% indicating SMA type I, 45.6% SMA type II, and 27.9% SMA type III. The age of all affected individuals ranged from <1 year (5.5%) to ≥50 years (7.3%), with most individuals falling between the ages of 3–17 years (42.6%) and 18–49 years (34.2%). Most respondents (79.8%) were nonambulatory, with ~11% being able to walk with an assistive device. Supplemental Table IA (in the online version at doi:10.1016/j.clinthera.2019.03.012) presents a summary of all respondent characteristics, including a breakdown of SMA type according to responder type (parents/caregivers vs affected adults).

Table I presents a summary of the characteristics of the survey sample across SMA types, compared with population estimates and the overall Cure SMA membership database.[1–3,8] The Cure SMA database is generally collected from a newly diagnosed population[15] and is anticipated to represent an incidence population, whereas the survey respondents represent a prevalence population that reflects long-term survival rates among SMA subtypes.

Table I. Incidence estimates of participants with spinal muscular atrophy (SMA) types 1 through IV versus benefit–risk survey cohort breakdown (N = 298).

Type	SMA Population Estimates[1–3,8]	Cure SMA Database Estimates[8]	SMA Benefit–Risk Survey Respondents
Type I	50%–60%	51.90%	22.10%
Type II	20–30%	32.30%	45.60%
Type III	10–15%	15.80%	27.90%
Type IV	<1%	–	0.70%

B-R Preferences in SMA

The SMA B-R survey found no significant difference in B-R trade-off according to sex, caregiver versus patient, or risk-taking profile. The survey underscored the expectation that all types of patients with SMA and their caregivers will generally be intolerant of a future therapy that significantly worsens their quality of life either because of the potential side effects of the therapy or the likelihood that the patient's condition could worsen. An example of B-R trade-off scores from all respondents (N = 298), per Treatment 1 presented, is given in Table II and Fig. 2 (see also Supplemental Table II and the Supplemental Figure 1 in the online version at doi:10.1016/j.clinthera.2019.03.012).

There was consistency observed in the rankings of "most willing to live with" and "least willing to live with" risks across the various potential treatment benefits presented. Participants were asked to choose between 1/1000 chances (very likely to occur in the context of a rare disease) or 1/100,000 chances (very rare and unlikely to occur even in the context of a rare disease such as SMA) risk of "serious side effects to the heart, liver, or kidney that may affect normal organ functioning and therefore require immediate medical attention." The second set of risks attached to these probabilities was "risk of life-threatening side effects to the heart, liver, or kidney that may result in possible organ failure." Respondents consistently rated these risks associated with a potential treatment as least tolerable: life-threatening allergic reactions; 1/1000 risk of serious or life-threatening side effects involving organs; or worsening quality of life. Risks described as life-threatening and with a high probability of occurrence or that would worsen quality of life were viewed as least tolerable across all participants.

Furthermore, respondents consistently rated these risks as most tolerable: invasive mode of treatment

Table II. Benefit–risk trade-off scores for Treatment 1 for all respondents (N = 298).

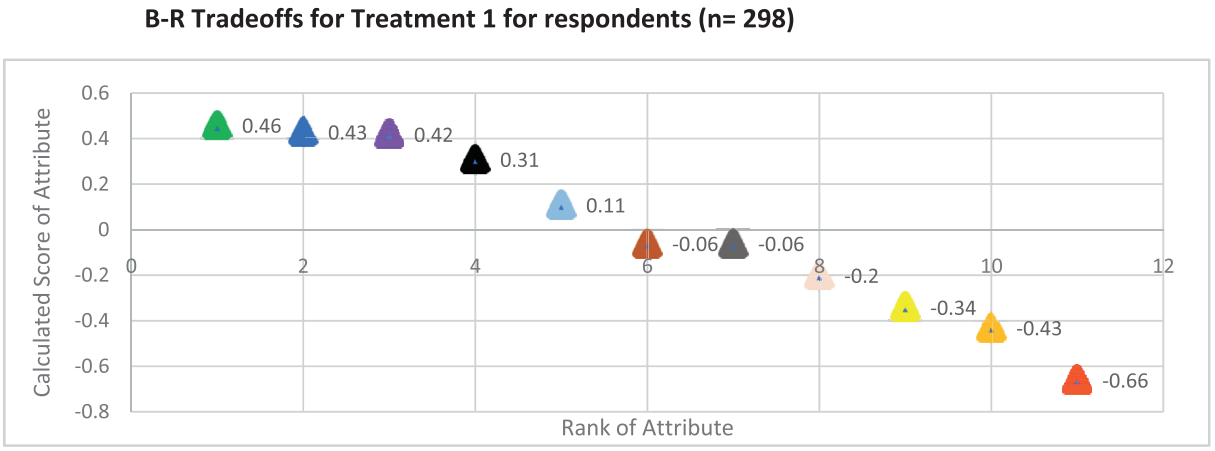
Attribute (Risks)	Rank	Best	Worst	Not Chosen	Score	*P-value*	Std. Error
Possible need for general anesthesia to administer treatment	1	49.84	3.79	46.37	0.46		
Side effect of dizziness (may increase risk of falls)	2	44.46	1.07	54.67	0.43	0.0210	0.0150
Common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, and fatigue	3	46.16	4.19	49.69	0.42	0.0070	0.0050
Possible need for invasive means to administer treatment	4	34.4	3.67	61.93	0.31	0.095	0.055
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	0.283	0.1
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	0.818	0.085
Increased risks of respiratory or other infections as a result of medication	7	8.91	15.31	75.78	−0.06	NA	NA
1 in 1000 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	0.314	0.099
Life-threatening allergic reactions	9	1.74	36.12	62.14	−0.34	0.074	0.045
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	0.074	0.045
Worsening in "quality of life" (eg, possibly due to drug's side effects, worsening condition)	11	0.94	66.82	32.24	−0.66	0.132	0.115

List of all risk preferences per 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"). Ranked from "most" to "least tolerable" by patients and caregivers with spinal muscular atrophy (types I–IV).

administration (including need for general anesthesia); side effect of dizziness (with potential for falls); and other common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, or fatigue. Even as the risks were presented in varying order throughout the survey, respondents consistently placed them in similar order throughout (Fig. 3A and B; see also Supplemental Table II and the Supplemental Figure 1 in the online version at doi:10.1016/j.clinthera.2019.03.012).

There were some nuanced variations observed with respect to a willingness to accept certain risks in exchange for specific benefit, but overall the differences were minor. Survey respondents did seem to weigh risks against their probabilities of occurrence (eg, when provided with probabilities of 1 in 1000 vs 1 in 100,000 for certain risks), judging as more tolerable those serious risks whose likelihood of occurring was exponentially lower.

Although a context for the likelihood of a specific risk occurrence in everyday life was not provided,



Regardless of the treatment benefit of a potential drug, independent of SMA type, or responder type, *all* respondents consistently rated as "Worst"/*Least willing to live* with the following: life-threatening allergic reactions; 1 in 1,000 risk of life-threatening side effects leading to possible organ failure; or worsening quality of life. In contrast, all participants, rated these risks as "Best"/*Most willing to live with*: invasive mode of treatment administration (including need for general anesthesia); side effect of dizziness; and other common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, or fatigue.

Legend: List of all risks presented

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.	
Possible need for invasive means to administer treatment	
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	
1 in 100,000 risk of life-threatening 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 medication.	
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	
Life threatening allergic reactions.	
1 in 1,000 risk of life-threatening 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.).	

Figure 2. Benefit–risk trade-off scores for Treatment 1 for all respondents. SMA = spinal muscular atrophy.

consistently, high probabilities of occurrence made a significant risk less tolerable.

Analysis of Factors That May Affect Risk Tolerance in SMA: Disease Severity/Current Quality of Life/Perceived Levels of Independence/Risk-Taking Profile

To minimize potential confounding factors in the analysis of the survey results, the B-R survey cohort was evaluated across a series of demographic characteristics such as age, sex, responder type, and SMA type and other key factors. These other key factors included length of time since diagnosis, disease severity/progression, perceived levels of independence (current and expected), and ranking of ADL that would most influence quality of life (eg, turning in bed, brushing hair/teeth, toileting self). Survey respondents were also evaluated for risk-taking attitudes.

Given the heterogeneity of SMA, we had hypothesized that disease stage (and associated functional limitations) at baseline could be important contributing factors to how patients and families approach B-R decisions.

Ratings on Disease Severity/Progression

To assess symptom severity among participants, we asked subjects to rate the severity of their disease/symptoms across multiple systems and other disease comorbidities, including fatigue, sleep, and communication difficulties (due to muscle weakness), often experienced in individuals with SMA type I. Most survey participants rated the following symptoms as most severe: muscle weakness (72%), scoliosis (40%), contractures (38%), and respiratory failure (25%). These results strongly reflect the prevalence of the surveyed population of ~75% of SMA type II and III adults and caregivers of adults, managing the complex, advanced symptoms of SMA. Table III presents the complete results of ratings on disease severity.

Rankings on ADL/Quality of Life That Matter Most

To arrive at a better understanding of what participants would consider to be most clinically meaningful in terms of their ability to independently perform certain ADL, we asked respondents to rank which items would matter most to them across a selection of ADL and quality of life

A

Type I (22.1%)	Type II (45.2%)	Type III (27.9%)
(1) Possible need for invasive means of administration	(1) Side effect of dizziness	(1) Possible need for invasive means of administration
(2) Common side effects	(2) Possible need for invasive means of administration	(2) Need for general anesthesia for administration
(3) Need for general anesthesia for administration	(3) Common side effects	(3) Common side effects

B

Type I (22.1%)	Type II (45.2%)	Type III (27.9%)
(1) 1 in 1000 risk of serious side effects affecting key organs requiring immediate medical attention	(1) Life-threatening allergic reactions	(1) Life-threatening allergic reactions
(2) 1 in 1000 risk of life-threatening side effects leading to organ failure	(2) 1 in 1000 risk of life-threatening side effects leading to organ failure	(2) Worsening quality of life
(3) Worsening quality of life	(3) Worsening quality of life	(3) 1 in 1000 risk of life-threatening side effects leading to organ failure

Figure 3. (A) Most and (B) least tolerable risk rankings according to type (I–III) of spinal muscular atrophy (SMA).

Table III. Benefit—risk survey of affected individual: degree of symptoms.

Affected Individual Characteristic	Breakdown of Characteristics
Nonambulatory/ambulatory	80%/20%
Muscle weakness	72% severe 19% moderate 8% mild
Scoliosis	40% severe 14% moderate 21% mild
Contractures	37.5% severe 24% moderate 21% mild
Bone fractures	11% severe 18% moderate 18% mild
Respiratory failure	25% severe 12.5% moderate 12.5% mild
Breathing problems	24% severe 21% moderate 28% mild
Feeding/swallowing difficulties	26% severe 11% moderate 24% mild
Degree of symptoms: fatigue	15% severe 55.5% moderate 25% mild
Communication difficulties	13% severe 9% moderate 20% mild
Impaired sleep	12% severe 21% moderate 36% mild

In some cases, percentages do not total 100% because of missing values or question was not answered by the entire cohort..

indicators.[2,13,15,18,34,66] It is important to note that 94% of respondents in this survey were parents of affected individuals (with caregivers representing 72% of the entire sample).

Patients and caregivers who completed this survey ranked increased mobility, toileting self, feeding oneself, spending time alone/being independent, and being engaged in social activities/building relationships to be of utmost importance among the possible treatment benefits of a potential therapy (rated as top 3 among the 11 benefits listed). This finding is consistent with previous research regarding the activities that matter most to patients or would be most desired from a therapy.[2,13,15,18,66] Attending to personal hygiene independently was also rated highly among all critical factors affecting quality of life. Undoubtedly, increased levels of perceived independence are clinically meaningful to adults and caregivers of individuals with SMA. Table IV presents results on the B-R survey ranking of ADL and importance of quality of life indicators (affected individuals and caregivers).

Perceived Levels of Independence

The importance placed on independence by patients with SMA and their families has been well documented.[1,2,13,18] Interestingly, a significant difference was found in the way that parents and caregivers versus affected adults rated "levels of independence." Parents/caregivers rated their loved one as much more dependent ("not at all independent," 44% [parents] vs 19% [affected adults]; $P < 0.001$). Conversely, only 2.5% of the parents/caregivers rated their child as "very independent" compared with 14% of affected adults (Fig. 4). This finding may be partially explained by the fact that 30% of caregivers who participated had a child with SMA type I (the most severe and life-threatening of SMA types), whereas ~49% of all affected adults reported a diagnosis of SMA type III (most of the participants were nonambulant), closely followed by 41% diagnosed with SMA type II (see Supplemental Table IB in the online version at doi:10.1016/j.clinthera.2019.03.012). This finding, however, does reflect previous literature findings that parents/caregivers tend to rate their child's quality of life as much worse than their children do.[57,58] The relationship between caregivers' responders and that of the affected adults was not assessed.

Risk-taking Profile

The B-R survey respondents were also asked to self-define as "high" or "low" risk takers to evaluate whether their inherent risk-taking profile would affect their responses about benefits and risks for possible SMA treatments.

Table IV. Results of benefit–risk survey ranking of activities of daily living (ADL) and importance ranking of quality of life (QoL) indicators (affected individuals and caregivers).

Overall Rank (Importance)	Enhancement of ADLs ("Most Important to You")	Enhancement of QoL Indicators (Most Important From Treatment)
1	Increased mobility independence	Toileting self
2	Toileting self	Spending time alone/being independent
3	Feeding oneself	Engage in social activities/build relationships
4	Spending time alone/being independent	Attend to personal hygiene independently /be independent
5	Turning in bed	Chew and swallow food
6	Dressing oneself	Sit up without frequent suctioning
7	Transferring from wheelchair to bed unaided	Attend work or school
8	Using a keyboard	Dress oneself
9	Writing with a pen	Hug loved ones
10	Brushing teeth	Engage in physical activities
11	Brushing hair	Sleep by oneself

The middle column displays the importance ranking on ADL (from most to least important), that would most impact the QoL of individuals and caregivers with spinal muscular atrophy (types I–IV). Column to the far right depicts the importance ranking of activities that patients and caregivers would wish to experience from a given therapy to enhance quality of life.

A standard risk-taking attitude survey instrument was administered to elicit each respondent's risk-taking profile. Of the respondents, 25% ranked themselves as "high" risk takers while 70% ranked themselves as "low" risk takers. The hypothesis we wanted to test is: Do those who view themselves as high risk takers (4 and 5 on a 5-point scale) tolerate the risks of treatments we tested better than those who rated themselves as low risk takers (1 and 2 on the same scale)? If the hypothesis holds, then based on our sample, we potentially have a bifurcated population with respect to treatment risk tolerance.

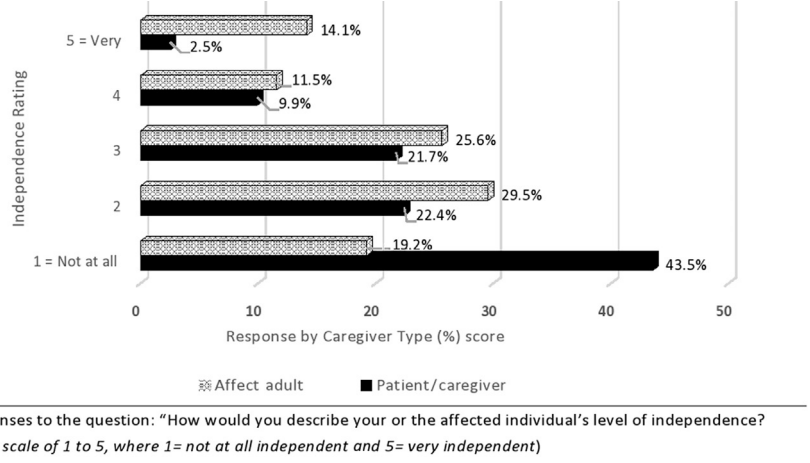


Figure 4. Benefit–risk survey perceived levels of independence by caregivers and adults with spinal muscular atrophy (N = 239).

In this case, the hypothesis did not hold: regardless of how they view themselves on the risk-taking dimension, when it comes to assessing and taking risks related to their SMA condition, survey respondents exhibit very similar B-R profiles.

DISCUSSION

Overall, SMA type and participants' age and sex did not generally affect respondents' risk tolerance, regardless of potential treatment and risk being considered, except for the side effect of dizziness, which was more tolerable for female respondents than male respondents. There was also no significant variation observed between the risk profiles of caregivers completing the survey and patients who completed the survey for themselves. Furthermore, no strong correlation was found between risk tolerance and SMA type, stage of disease progression, quality of life assessment, or rated levels of independence. However, perceived levels of independence varied between caregivers and affected adults, although this finding did not ultimately affect their B-R choices (Fig. 4).

In evaluating the results of this study, consideration should be given to the fact that the B-R study was completed in the context of regulatory approval of the first therapy ever for all SMA types that is both effective and safe.[11,12,28,60] It is reasonable that this milestone in the history of such a devastating disease would serve as a benchmark and thus influence the views of the SMA community about risks and benefits associated with future therapies. Patients and caregivers are likely considering nusinersen as the new baseline for treatment risks and benefits, expecting any new therapeutic options to be at least as safe and effective and offering some other drug benefit (eg, making utilization of the drug more convenient). In addition, patients and caregivers will also assess therapies based on mode of administration. At this point in time, as seen in the survey results, invasiveness of treatment (mode of administration) was repeatedly selected as one of the "most willing to live with"/least offensive risks or trade-offs. With that said, 5 additional promising therapeutic agents are presently in clinical development for SMA. Given the heterogeneity of this population and breadth of clinical presentation, our goal is to develop maximally effective treatments that target the underlying genetics of SMA and other systems and/or disease processes. Therapeutic agents that may be used alone or in combination and that may be administered through various routes to treat all ages, types, and stages of SMA are necessary.

Interestingly, we did not observe substantially increased risk tolerance in SMA type I, which might have been expected due to the life-threatening nature of this form of SMA. During the recent SMA Patient Focused Drug Development Meeting, several parents of children with SMA type I, especially those who had lost a child to SMA, stated that they would essentially "try anything as long as it could help … as we knew what could easily happen if we didn't try something."[13] It is noteworthy that 12% of respondents in the survey had lost a loved one to SMA.

It is also important to note, however, that the SMA type I population participating in this survey represented a subpopulation of SMA type I that had been living longer (chronically) with the disease, rather than a newly diagnosed population, who would typically be facing a less stable, and often life-threatening, situation. Overall, the survey cohort did not include many patients newly diagnosed with SMA type I, which may have influenced the lack of substantial observed differences in B-R assessment according to SMA type.

Moreover, we speculate that if this study had been completed 5 years ago, before approval of an effective SMA treatment (nusinersen), observed risk tolerance would likely have been higher and more differentiated according to SMA type. We further speculate that caregivers of children with SMA type I, facing an imminently life-threatening situation for their child with SMA and with no approved therapy available, would have had the biggest difference in risk tolerance compared with our dataset.

Another interesting nuance in risk tolerance was observed among SMA type II respondents; both parents and affected individuals were less tolerant than the total study sample of a potential treatment that required general anesthesia for administration, unless the treatment offered potential benefits of increased arm strength or a slowdown in progression of symptoms. This finding can be explained based on a fear of complication from extubation with individuals who have compromised respiratory systems (typical in patients with type II SMA).[46] These respondents were also more willing to tolerate a 1 in 100,000 risk of serious treatment side effect

leading to organ failure and requiring immediate medical attention in exchange for the potential of prolonged life span.

Again, neither disease progression or severity nor perceived levels of quality life (including levels of independence) had a significant correlation with risk tolerance in SMA, as rated by parents or affected adults. However, a difference was noted in how patients and caregivers perceived the overall independence of the patients.

Another important finding from this study are the results of patients' and parents'/caregivers' assessments of aspects of quality of life that matter most to them as possible treatment benefits: increased mobility, toileting self, feeding oneself, spending time alone, independence, and being engaged in social activities/building relationships. These findings continue to support and corroborate important learnings on clinical meaningfulness and what this population considers to be the most important benefits from a therapy.[1,2,13,18,66] We believe that this information would be invaluable to regulators and sponsors alike as new therapeutic agents for SMA emerge and are evaluated by key leaders at the FDA, the Center for Biologics Evaluation and Research/ Center for Drug Evaluation and Research, who are determining risk and benefits (how fit or disease altering/clinically meaningful these therapies may be for our heterogeneous patient population).

Study Limitations

It is possible that the results of the B-R survey may not be fully representative of the overall SMA community in the United States and that they reflect some response bias.[8] For example, those who responded to the invitation and participated in the B-R survey may represent a more "engaged" and "healthier" cohort and may be more likely to take on treatment risks. Given the heterogeneity of SMA, however, we consider that the potential limitations in representativeness/generalizability and the potential for some response bias within the study are small and unlikely to suggest significant flaws in our overall findings. As discussed previously, it is also important to note that the age of the patients with SMA type I in the survey cohort is older and represents a living longer (chronically) subpopulation of SMA type I.[33,35,47] As stated previously, it seems possible that the newly diagnosed population, facing an imminent life-threatening situation, would exhibit a different risk tolerance profile than reported here.

In addition, the education level of the participants could also have played a role in the understanding and interpretation of survey questions, as were intended by investigators, and may have influenced the type of responses received. Of note, ~71% of parents/caregivers who participated in this survey reported having a bachelors' degree or higher (see Supplemental Table IA in the online version at doi:10.1016/j.clinthera.2019.03.012).

Finally, we point out a potential limitation in this survey whereby some of the treatment benefits presented to participants may not have been applicable or pertinent to all survey respondents (eg, ability to communicate is not a clinically meaningful benefit to an SMA type II/III patient or caregiver). As such, and given the heterogeneity of the disease, some respondents may have found it difficult to gauge risk preferences when considering theoretical possibilities. For example, a patient who is not experiencing respiratory problems is less likely to put more weight on whether a potential treatment could improve such problems.

Opportunities for Future Exploration

In addition to providing an important baseline for understanding risk tolerance among patients with SMA and caregivers, this study suggests several opportunities for future exploration. As additional information (including real-world evidence) becomes available (ie, physician-collected or patient-reported data from registries, surveys, medical records) relating to patients' clinical experience with the treatment/administration of nusinersen and its impact among different patient subpopulations and as new treatment options emerge, it will be important to periodically re-survey the SMA community to evaluate any changes in risk tolerance over time. In addition, it would be valuable to further assess the data from this baseline survey, including comparing results across subpopulations versus data from existing quality of life instruments.

CONCLUSIONS

We believe that the findings from this study provide an important new baseline assessment of risk tolerance among patients with SMA and families against which to evaluate future SMA treatment options. As the benefits and limits of treatment across the spectrum

of SMA are more clearly characterized, it is anticipated that subpopulations of patients who may not benefit from nusinersen may emerge, and B-R perceptions will continue to evolve. B-R perceptions/preferences in SMA will be further affected as new therapeutic options become available, used alone or in combination, and administered via various routes, in turn presenting ever-evolving B-R profiles for the treatment of SMA.

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Ms. Cruz participated in conceptualization; funding acquisition; investigation; validation; project administration and supervision; writing of the original draft; and review and editing of the manuscript. Ms. Belter participated in conceptualization and review and editing of the manuscript. Mr. Wasnock participated in data curation, and formal analysis. Mr. Nazarelli participated in project administration; data curation; methodology; formal analysis; and review and editing of the manuscript. Dr. Jarecki participated in conceptualization; validation; funding acquisition; supervision; and review and editing of the manuscript. Silicon Valley Research Group provided the survey platform and statistical software for the data analysis.

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CONFLICTS OF INTEREST

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clinthera.2019.03.012.

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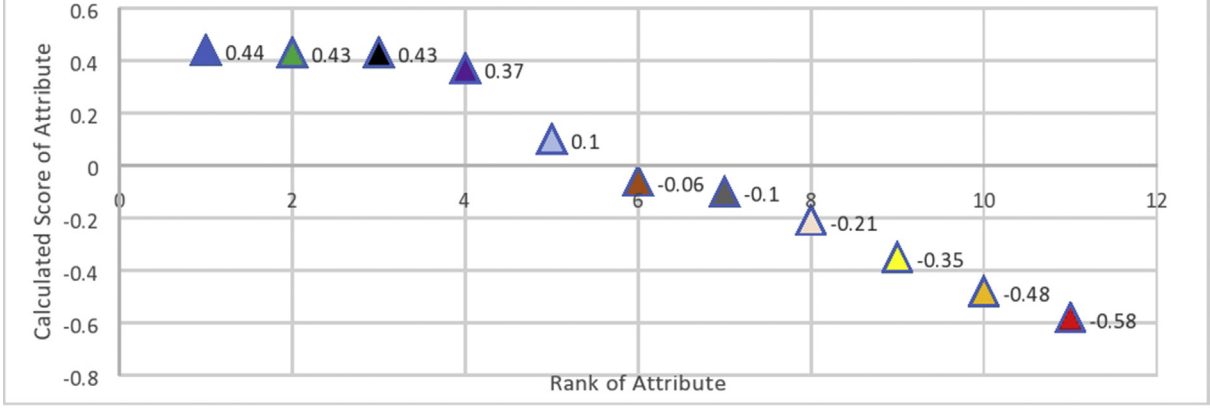
APPENDIX A. SUPPLEMENTARY DATA

Figure 1.B-R Tradeoffs for Treatment 3 for respondents (n= 298). Regardless of the treatment benefit of a potential drug, independent of SMA type, or responder type, *all* respondents consistently rated as "Worst"/*Least willing to live* with the following: life-threatening allergic reactions; 1 in 1,000 risk of life-threatening side effects leading to possible organ failure; or worsening quality of life. In contrast, all participants, rated these risks as "Best"/*Most willing to live with*: invasive mode of treatment administration (including need for general anesthesia); side effect of dizziness; and other common side effects such as nausea, vomiting, loss of appetite, headaches, back pain, or fatigue.



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.	
Possible need for invasive means to administer treatment	
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	
1 in 100,000 risk of life-threatening 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 medication.	
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	
Life threatening allergic reactions.	
1 in 1,000 risk of life-threatening 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.).	

Table 1A. B-R Survey Respondent Characteristics (n=298)

Survey Respondent Characteristics	Characteristics Breakdown (%)
Status	72% (94.2%) Caregiver (Parent) 28% Affected Individual (Patient)
Race (affected individual)	82% White 9% Asian Pacific Islander 1.5% African American
Gender (all respondents)	56% Female 44% Male
Education Level (caregivers*) (n =215)	7.5% HS/GED 13% Technical/Some College 8.8% Associate 34.9% Bachelors 35.8% Masters/Doctorate
Time Since Diagnosis	67% >5 years 32% <5 years
Age (affected individual)	8% 1-2 years 40% 3-12 years 11% 13-17 years 23% 18-34 years 19% >35
Risk Taking (all respondents)	25% High 70% Low
Overall Assessment of Patient Independence (rated by caregiver or affected individual) (Level 1= not at all; Level 5= very)	61% rating of 1-2 24% rating of 3 15.1% rating of 4-5

In some cases, percentages do not add up to 100% because of missing values or question was not answered by entire cohort.

* Education levels of affected adults not shown. 78% of adults (n=83) had a Bachelor's degree or higher.

Table 1B. B-R Survey Respondent Type Breakdown (n= 298).

Caregivers n=215	Affected Individual n=83
Type I	Type I
n=58	n=2
(30.7%)	(2.4%)
Type II	Type II
n=90	n=34
(47.6%)	(41%)
Type III	Type III
n=35	n=41
(18.5%)	(49.4%)

Table 2. B-R Tradeoffs for Treatment 3 for all respondents (n= 298)

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	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 100,00 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	17.44	7.84	74.72	0.1
1 in 100,00 risk of life-threatening 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	-0.21
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	2.91	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-threatening 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	39.95	-0.58

List of all risk preferences per treatment (#1), ranked from “most” to “least tolerable” by patients and caregivers with SMA (types I-IVThe following are the supplementary data related to this article: