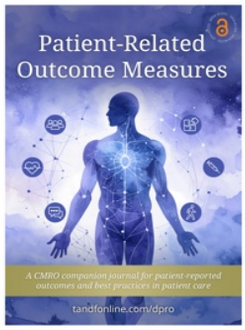


Taylor & Francis
Taylor & Francis Group

Patient Related Outcome Measures

ISSN: 1179-271X (Online) Journal homepage: www.tandfonline.com/journals/dpro20

# Agreement Between Child Self- and Parent Proxy-Reports of Health-Related Quality of Life in Spinal Muscular Atrophy: Preliminary Insights from a Nationwide Patient Registry in Germany

**Erik Landfeldt, Berenike Leibrock, Justine Hussong, Simone Thiele, Maggie C Walter, Eva Moehler, Michael Zemlin, Ulrich Dillmann & Marina Flotats-Bastardas**

**To cite this article:** Erik Landfeldt, Berenike Leibrock, Justine Hussong, Simone Thiele, Maggie C Walter, Eva Moehler, Michael Zemlin, Ulrich Dillmann & Marina Flotats-Bastardas (2025) Agreement Between Child Self- and Parent Proxy-Reports of Health-Related Quality of Life in Spinal Muscular Atrophy: Preliminary Insights from a Nationwide Patient Registry in Germany, Patient Related Outcome Measures, , 93-103, DOI: 10.2147/PROM.S517362

**To link to this article:** https://doi.org/10.2147/PROM.S517362



Published online: 26 Jun 2025.

Patient Related Outcome Measures

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

# Agreement Between Child Self- and Parent Proxy-Reports of Health-Related Quality of Life in Spinal Muscular Atrophy: Preliminary Insights from a Nationwide Patient Registry in Germany

Erik Landfeldt[1], Berenike Leibrock[2], Justine Hussong[3], Simone Thiele[4], Maggie C Walter[4], Eva Moehler[3], Michael Zemlin[5], Ulrich Dillmann[6], Marina Flotats-Bastardas[7]

[1]IQVIA, Stockholm, Sweden; [2]Department of Medicine, University of Saarland, Saarbruecken, Germany; [3]Department of Child and Adolescent Psychiatry, Saarland University Hospital, Homburg, Germany; [4]Friedrich Baur Institute at the Department of Neurology, LMU University Hospital, LMU Munich, Munich, Germany; [5]Department of General Pediatrics and Neonatology, Saarland University Hospital, Homburg, Germany; [6]Department of Neurology, Saarland University, Homburg, Germany; [7]Department of General Pediatrics and Neonatology, Division of Neuropediatrics, Saarland University, Homburg, Germany

Correspondence: Marina Flotats-Bastardas, Department of General Pediatrics and Neonatology, Division of Neuropediatrics, Saarland University, Kirrbergerst 100, Homburg, 66421, Germany, Tel +49 68411628352, Email Marina.flotats-bastardas@uks.eu

**Objective:** The objective of this pilot study was to examine the agreement between child self- and parent proxy-assessment of health-related quality of life (HRQoL) in spinal muscular atrophy (SMA) in the era of disease-modifying therapy.

**Methods:** Children with SMA and one of their parents were recruited via the German national TREAT-NMD SMA patient registry. HRQoL was measured using the Pediatric Quality of Life Inventory 3.0 Neuromuscular Module (PedsQL 3.0 NMM), KIDSCREEN-27, and the Health Utilities Index (HUI). Agreement between child self- and parent proxy-ratings of ordinal measures was estimated using Cohen's κ, and for continuous measures using intraclass correlation coefficients (ICCs) from one-way random-effects models.

**Results:** The final sample comprised 17 children with SMA (mean age: 9.88 years, SD: 4.33 years, range: 5–16 years; 59% female) and one of their parents. All but two patients (88%) were receiving disease-modifying therapy (nusinersen or risdiplam). The ICC for the total PedsQL 3.0 NMM score was estimated at 0.85 (95% CI: 0.64–0.94, $p < 0.001$) (indicative of excellent agreement). The corresponding estimate for the KIDSCREEN total score was 0.27 (95% CI: 0.00–0.75, $p = 0.197$) (poor/fair agreement) and the global HUI utility 0.98 (95% CI: 0.93 to 0.9952, $p < 0.001$) (excellent agreement). The lowest levels of concordance were found for school and family life, as well as mental well-being, as opposed to physical functioning and disability.

**Conclusion:** We show that the agreement between child self- and parent proxy-reports of HRQoL in SMA varies markedly across HRQoL measures and examined domains, ranging from poor/fair to excellent. Compared with previous research, agreement for the PedsQL 3.0 NMM was markedly higher in our contemporary cohort of patients treated with novel therapies. These preliminary findings will be helpful in informing the design of future research of HRQoL in SMA.

**Keywords:** HRQoL, PROMs, well-being, proxy, disability, SMA, neuromuscular, utilities

## Introduction

Spinal muscular atrophy (SMA) is a neurodegenerative disease of the spinal motor neuron that causes progressive muscle weakness, loss of motor abilities and respiratory functioning, and in severe cases death. Depending on the underlying genetic mutation, there are different subtypes of SMA according to age at onset of clinical symptoms and highest motor function milestone achieved.[1,2] However, in recent years, the introduction of novel therapies (ie, nusinersen, onasemnogene abeparvovec, and risdiplam) has dramatically transformed the prognosis of the disease, allowing patients to achieve new motor milestones (eg, sitting or walking) and thereby modify the natural history of SMA.[3,4] These medications differ



Received: 24 January 2025
Accepted: 9 May 2025
Published: 27 June 2025

in mode of action and application: intrathecally every 4 months via painful lumbar punction, single application intravenously, or orally every day.

Health-related quality of life (HRQoL) – defined as the individual's perception of the impact of health and illness on physical, mental, and social aspects of life[5,6] – has emerged as an increasingly important outcome to clinicians, researchers, and decision-makers to help understand the overall disease burden, guide treatment strategies, and inform analyses of cost-effectiveness. Numerous generic and disease-specific patient-reported outcome measures of HRQoL exist, including instruments designed specifically for administration to children and adolescents, such as the Pediatric Quality of Life Inventory (PedsQL)[7] and KIDSCREEN[8] However, measuring HRQoL in paediatric populations, including children with SMA, poses unique challenges because of limitations in cognitive and linguistic abilities. Indeed, younger children may have limited vocabulary and comprehension skills, making it difficult for them to effectively appreciate and articulate their feelings, symptoms, and functional limitations.[5,6,9,10]

In response, as a complement to and/or substitute for self-reports, researchers and clinicians have employed proxy-reports of HRQoL. Such measures involve recording information from parents or other individuals who can provide insight into the child's experiences and functioning. Yet, although proxy-reports offer valuable perspectives, parents may have difficulty accurately representing the child's experiences, particularly in domains such as pain or emotional well-being, where subjective experiences can vary greatly. It is therefore important to evaluate the agreement between child self-reports and parent proxy-reports to help assess to what extent the latter could substitute the former.[5,9]

Previous research of other rare neuromuscular diseases, for example, Duchenne muscular dystrophy, has demonstrated variable concordance between self and proxy assessments (ranging from poor to good);[11–15] yet, there is currently a paucity of evidence of this topic in populations with SMA. Moreover, in SMA, little is known about the agreement between self- and proxy-reports in the era of disease modifying therapy. To that end, the objective of this pilot study was to measure the agreement between child self- and parent proxy-assessment of HRQoL in a contemporary cohort of patients with SMA receiving novel therapies.

## Materials and Methods

The data reported as part of this work was collected in a cross-sectional, observational cohort study comprising German children with SMA and one of their caregivers. Results for some objectives (ie, clinical characteristics, treatments, and self-assessed HRQoL among paediatric participants and adults) have been previously reported.[16–18]

### Study Population

On June 14, 2021, we invited patients with SMA (and one of their parents or legal guardians) enrolled in the German national TREAT-NMD SMA patient registry (www.sma-register.de). To be eligible to participate, patients had to meet all of the following inclusion criteria: (1) genetically confirmed diagnosis of SMA, (2) ≥5 and <18 years of age, and (3) currently residing in Germany.

### Study Procedures

Children with SMA and their parents were invited to complete a questionnaire administered via a dedicated study website online. The questionnaire contained information about the study and age-specific informed consent forms, as well as questions capturing patients' demographic and clinical characteristics. Additionally, the children with SMA were asked to self-complete a set of age-specific measures of HRQoL, and parents were asked to proxy-complete the same instruments. The tools considered included the Pediatric Quality of Life Inventory (PedsQL) 3.0 Neuromuscular Module (PedsQL 3.0 NMM),[7] KIDSCREEN-27,[8] and the Health Utilities Index (HUI).[19] The PedsQL 3.0 NMM, a module to the PedsQL measurement model, is a measure of HRQoL specific to children and adolescents with neuromuscular diseases aged 5 to 18 years encompassing 25 questions, each described in five levels, covering three domains: About my neuromuscular disorder, Communication, About my family resources (Young Child Report [ages 5–7] only consists of the 17-item About My Neuromuscular Disease Scale). Domain and total scale scores range from 0 to 100 (higher score = better HRQoL).[7] The PedsQL is one of the most commonly employed measures of HRQoL in paediatric populations, including patients with rare, neuromuscular diseases, such as SMA[20] and Duchenne muscular dystrophy.[21] KIDSCREEN-27 is

a generic measure of HRQoL of children and adolescents aged 8 to 18 years. It encompasses 27 questions, each described in five levels, covering five domains: Physical well-being, Psychological well-being, Autonomy & parents, Peers & social support, and School environment. Item scores are transformed into Rasch-derived standardized domain and total scores ranging from 0 to 100, with a mean of 50 and a standard deviation of 10 (higher score = better HRQoL). KIDSCREEN-27 has been frequently employed in research studies, clinical practice, and public health initiatives to assess and monitor HRQoL of children and adolescents and has been shown to exhibit excellent cross-cultural comparative validity.[8] Finally, the HUI is a family of generic preference-based systems for measuring HRQoL. It covers eight dimensions – Vision, Hearing, Speech, Ambulation/mobility, Pain, Dexterity, Emotion, and Cognition – each described in three to six levels. The HUI is scored using preference measurements from the general population representing mean interval-level utilities (see below for details).[19] If needed, patients were permitted to get help from a caregiver for reading and typing only.

The study was approved by the regional Ethics Committee from the Saarland Medical Association (protocol number 09/20), registered in the German clinical trial registry on October 19, 2020 (DRKS00022876), and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Informed consent to participate (designated per the Saarland Medical Association) was self-provided by all legal guardians/parents (all adults). For patients between 12–17 years of age, informed consent was provided by the patient *and* their legal guardian/parent. For patients <12 years of age, informed consent was provided by the legal guardian/parent of the patient.

## Statistical Analysis

Continuous demographic and clinical characteristics were summarized using means, standard deviations (SDs), and ranges (ie, minimum value to maximum value) and categorial characteristics using frequencies and percentages. All measures of HRQoL were scored according to their respective manual. For the HUI, we estimated single-attribute utilities (ranging between 0 and 1) and multi-attribute utilities (ranging between −0.36 and 1) using the HUI Mark III algorithm.[22] All estimated utilities were interpreted as follows: 0=health state equal to being dead; 1 = health state of perfect health; and <0 = health state worse than being dead. Agreement between child- and parent proxy-ratings of ordinal measures (ie, responses to individual items) was estimated using Cohen's κ,[23] ranging between 0 (indicating agreement by chance) and 1 (indicating perfect agreement), with intermediate values interpreted as proposed by Landis et al[24] (ie, 0–0.20 as slight, 0.21–0.40 as fair, 0.41–0.60 as moderate, and 0.61–0.80 as substantial agreement). Agreement for continuous measures (ie, domain and total scores) was assessed by estimating intraclass correlation coefficients (ICCs) from one-way random-effects models. We considered ICC <0.40 to indicate poor/fair agreement, 0.40–0.60 moderate agreement, 0.61–0.80 good agreement, and >0.80 excellent agreement.[12,13,25,26] To provide data and facilitate interpretation of the magnitude of observed differences at the item-level, for KIDSCREEN-27 and the PedsQL 3.0 NMM, we also summarized the questions with the largest positive discrepancy in estimated scores between children and parents (ie, where children noted *less* problems than their parents), as well as questions with the largest negative discrepancy (ie, where children noted *more* problems than their parents). In this analysis, to facilitate comparison across scales, response categories for KIDSCREEN-27 were transferred from 5–1 to 100–0 (ie, the PedsQL 3.0 NMM item-level scoring structure). For the HUI, we instead summarized the proportion of children and parents reporting any problems (equal to a single-attribute utility of <1) in each domain. Data analysis was performed using Stata 15 (StataCorp, College Station, TX, USA).

# Results

A total of 17 children with SMA and their parents participated in the study. Demographic and clinical characteristics of the final patient sample are summarized in Table 1. All 17 patient-caregiver pairs completed the PedsQL 3.0 NMM, and 10 pairs completed the KIDSCREEN (since the latter is self-administered from 8 years of age). The mean age of the patient cohort was 9.88 years (SD: 4.33, range 5 to 16) and 59% (10/17) were female. All but two patients (88%, 15/17) were receiving disease-modifying therapy (73% [11/15] received nusinersen and 27% [4/15] risdiplam).

**Table 1** Demographic and Clinical Characteristics of Children with SMA

| | Measure of HRQoL | |
|---|---|---|
| | **KIDSCREEN-27 and Health Utilities Index (age: 8–18 years)** | **PedsQL 3.0 NMM (age: 5–18 years)** |
| **n (%)** | 10 (59%) | 17 (100%) |
| **Age, in years** | 12.8 (3.12) (8 to 16) | 9.88 (4.33) (5 to 16) |
| **Female sex, n (%)** | 6 (60%) | 10 (59%) |
| **Age at first symptoms, in years** | 1.20 (1.14) (0 to 3) | 1.12 (0.99) (0 to 3) |
| **Age at SMA diagnosis, in years** | 2.00 (2.00) (0 to 6) | 1.65 (1.66) (0 to 6) |
| **Best motor function, n (%)** | | |
| Non-sitter | 4 (40%) | 4 (24%) |
| Sitter | 3 (30%) | 7 (41%) |
| Walker | 3 (30%) | 6 (35%) |
| **Type of SMA, n (%)** | | |
| Type I | 1 (10%) | 3 (18%) |
| Type II | 5 (50%) | 8 (47%) |
| Type III | 4 (40%) | 6 (35%) |
| **Disease-modifying therapy, n (%)** | 8 (80%) | 15 (88%) |

**Note**: Data reported as mean (SD) (range) unless otherwise stated.

## The Pediatric Quality of Life Inventory 3.0 Neuromuscular Module

A total of 17 child-parent pairs completed the PedsQL 3.0 NMM (Table 1). Estimated mean scale and total scores are presented in Figure 1. The ICC for the total score was estimated at 0.85 (95% CI: 0.64 to 0.94, $p < 0.001$), indicative of excellent agreement. Based on the assessment of Cohen's κ, the questions exhibiting the highest level of overall agreement were "It is hard for me to ask the doctors and nurses questions" ($\kappa = 1.00$), "It is hard for me to tell the doctors and nurses how I feel" ($\kappa = 0.61$), "It is hard for me to explain my illness to other people" ($\kappa = 0.55$), and "It is hard to breathe" ($\kappa = 0.54$). The questions exhibiting the lowest level of overall agreement were "I do not have the equipment I need" ($\kappa = -0.17$), "I get sick easily" ($\kappa = -0.01$), "It is hard for my family to get enough rest" ($\kappa = 0.05$), and "I get sores and/or rashes" ($\kappa = 0.08$).

The questions with the largest positive discrepancy in estimated scores between children and parents (ie, where children noted *less* problems than their parents) on average at the cohort level were "My hands were weak" (mean score difference: 22.06), "I think my family has a lot of problems" (21.43), "It is hard for my family to get enough rest" (17.86), "It takes me a long time to bathe or shower" (16.18), and "It is hard to turn myself during the night" (16.18). The questions with the largest negative discrepancy (ie, where children noted *more* problems than their parents) were "It is hard to gain or lose weight when I want to" (−4.41) and "My back feels stiff" (−2.94). Additional PedsQL 3.0 NMM item-level agreement results are available as supplemental material (online) (eTable 1).

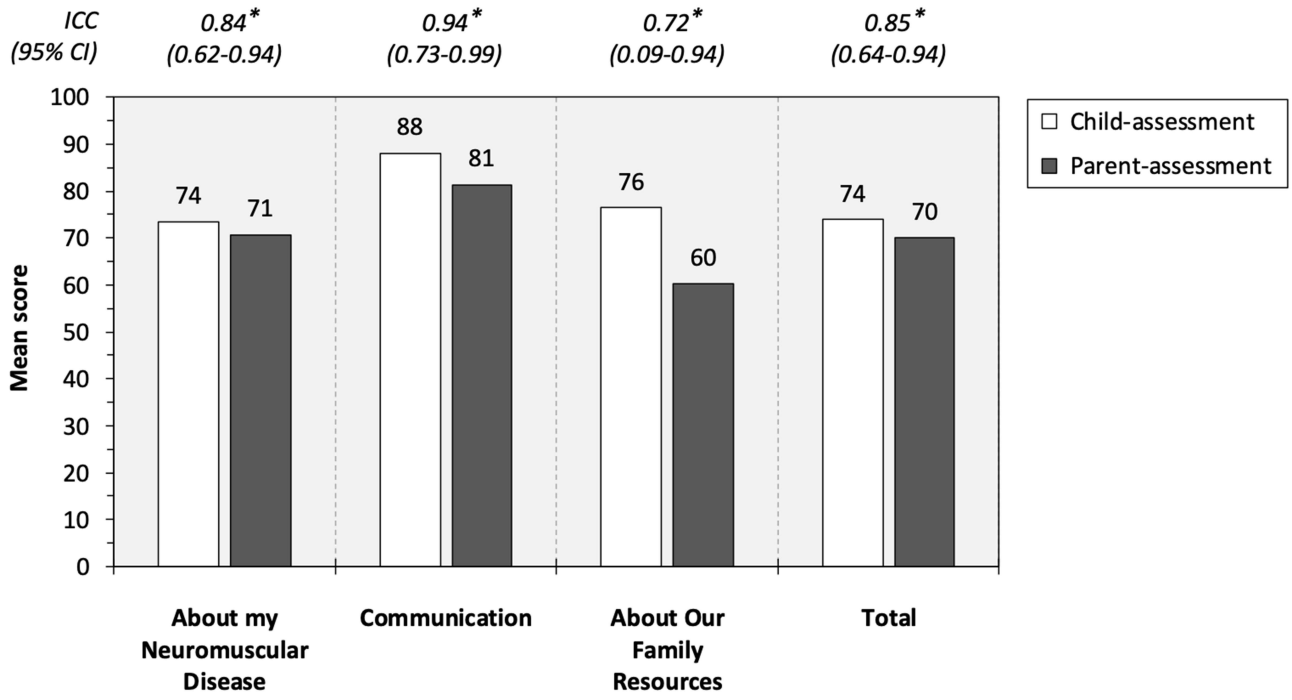


**Figure 1** Child self- and parent proxy-reported PedsQL 3.0 NMM scores.
**Notes**: PedsQL 3.0 NMM scores range from 0 to 100 (higher score = better health status/higher HRQoL). *Statistically significant.
**Abbreviations**: CI, Confidence interval; ICC, Intraclass correlation coefficient; PedsQL 3.0 NMM, Pediatric Quality of Life Inventory 3.0 Neuromuscular Module.

## KIDSCREEN-27

A total of 10 child-parent pairs completed the KIDSCREEN-27 (Table 1). Estimated domain and total scores are presented in Figure 2. The ICC for the total score was estimated at 0.27 (95% CI: 0.00 to 0.75, p = 0.197), indicative of poor/fair agreement. The questions exhibiting the highest level of overall agreement were "Have you been in a good mood?" (κ = 0.63), "Have your parent(s) had enough time for you?" (κ = 0.62), and "Have you had fun with your

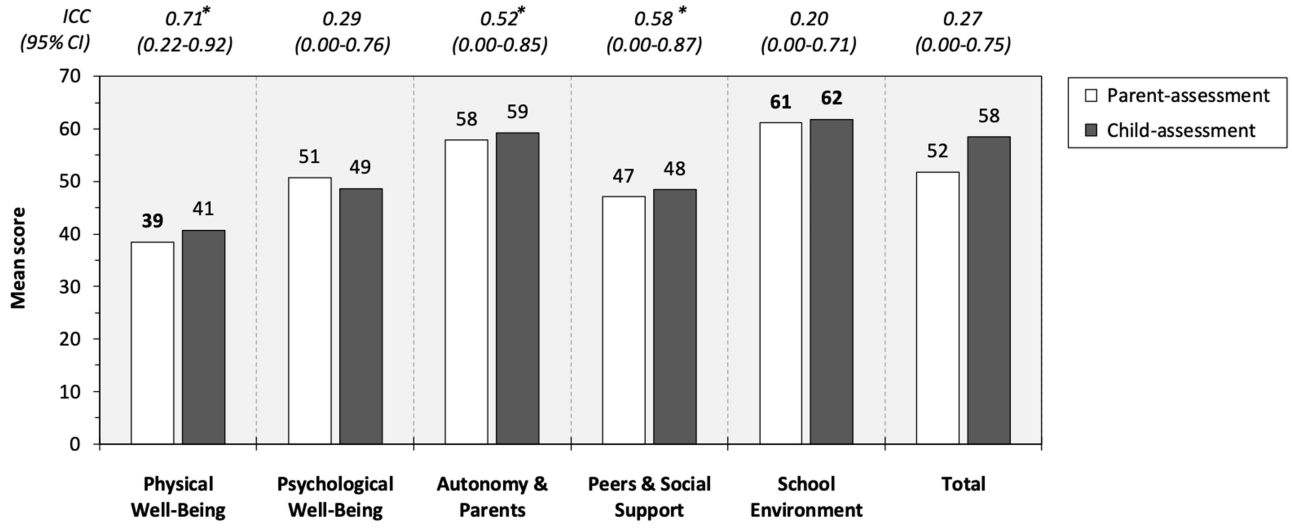


**Figure 2** Child self- and parent proxy-reported KIDSCREEN scores.
**Notes**: KIDSCREEN scores range from 0 to 100 (higher score = better health status/higher HRQoL). Bold numbers are significantly different from general population KIDSCREEN reference scores (mean: 50, SD: 10). *Statistically significant.
**Abbreviations**: CI, Confidence interval; ICC, Intraclass correlation coefficient.


https://doi.org/10.2147/PROM.S517362

friends?" (κ = 0.56). The questions exhibiting the lowest level of overall agreement were "In general, how would you say your health is?" (κ = −0.13), "Have you had enough money for your expenses?" (κ = −0.11), and "Have you had enough money to do the same things as your friends?" (κ = −0.05).

The questions with the largest positive discrepancy in estimated scores between children and parents (ie, where children noted *less* problems than their parents) on average at the cohort level were "Have you been able to do the things that you want to do in your free time?" (mean score difference: 15.00) and "Have you had fun with your friends?" (15.00). The questions with the largest negative discrepancy (ie, where children noted *more* problems than their parents) were "Has your life been enjoyable?" (−25.00), "Have you felt so bad that you didn't want to do anything?" (−10.00), and "Have you had enough money for your expenses?" (−10.00). Additional KIDSCREEN-27 item-level agreement results are available as supplemental material (online) (eTable 2).

## The HUI

A total of 10 child-parent pairs completed the HUI (Table 1). Estimated mean HUI single-attribute utilities (ranging from 0 to 1, where a lower value indicates greater impairment and lower HRQoL) are shown in Figure 3. The proportion of children and parents reporting any problems (equal to a single-attribute utility of <1) in the Vision domain was 30% (3/10) and 70% (7/10), respectively (mainly related to a need for glasses or contact lenses). Corresponding estimates for Hearing was 0% (0/10) and 0% (0/10); Speech 30% (3/10) and 10% (1/10); Ambulation 70% (7/10) and 90% (9/10); Dexterity 40% (4/10) and 50% (5/10); Emotion 40% (4/10) and 0% (0/10); Cognition 20% (2/10) and 20% (2/10), and Pain 40% (4/10) and 60% (6/10), respectively. The mean child-reported global HUI utility was estimated at 0.43 (SD: 0.36, range: 0.02 to 0.95), and the mean parent-reported global HUI utility at 0.44 (SD: 0.40, range: −0.02 to 1.00). The ICC for global HUI utility was estimated at 0.98 (95% CI: 0.93 to 0.9952, p < 0.001), indicative of excellent agreement. ICCs for the single-attribute utilities were 0.25 (−0.39 to 0.74, p = 0.219) for Vision, 0.91 (0.69 to 0.98, p < 0.001) for Speech, 0.98 (0.92 to 0.99, p < 0.001) for Ambulation, 0.93 (0.77 to 0.98, p < 0.001) for Dexterity, −0.20 (−0.7 to 0.45, p = 0.723) for Emotion, 0.86 (0.57 to 0.96, p < 0.001) for Cognition, and 0.97 (0.91 to 0.99, p < 0.001) for Pain (with perfect concordance for Hearing).

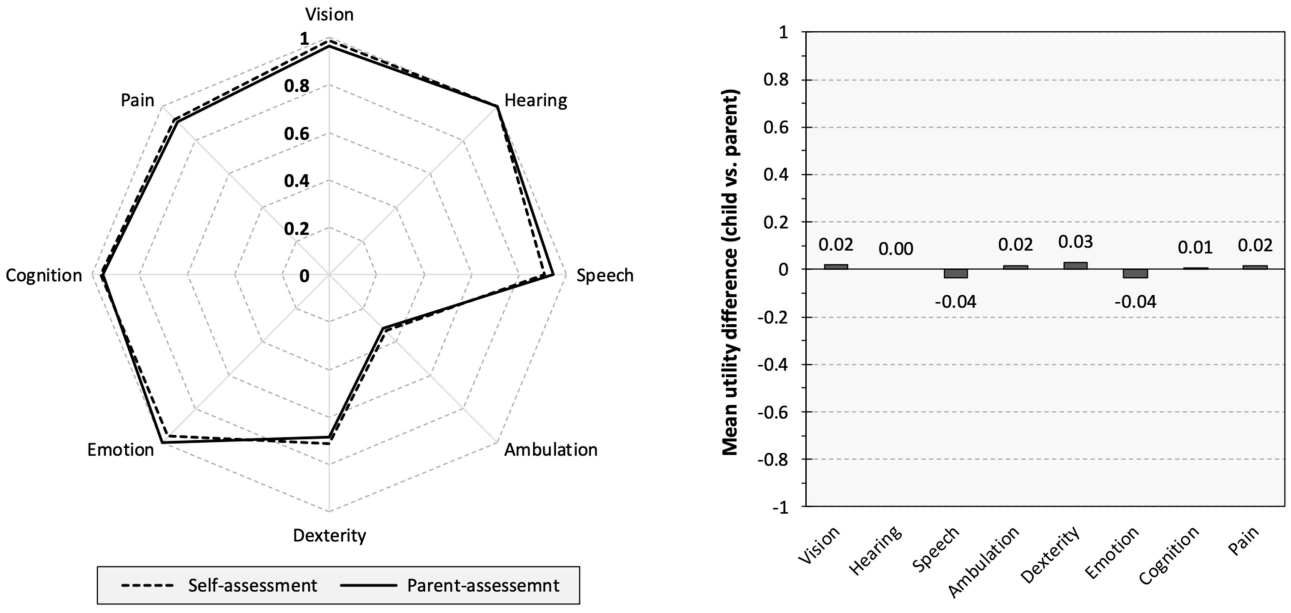


**Figure 3** Child self- and parent proxy-reported single-attribute HUI (Mark III) utilities.
**Note**: Single-attribute HUI utilities range between 0 and 1 (higher value = better health status/higher HRQoL).
**Abbreviation**: HUI, Health Utilities Index.

## Discussion

In this pilot study, we examined the agreement between child self- and parent proxy-assessment of HRQoL using several commonly employed measures in a cohort of patients receiving novel pharmacological therapies. Looking into results from the PedsQL 3.0 NMM, which generally demonstrated excellent concordance in reports, the highest level of agreement was noted for questions pertaining to the "Communication" domain (ie, communication with doctors and nurses, as well as other people). These findings suggest that children with SMA and their parents have a similar perception and understanding of difficulties related to speech (which is prevalent especially among patients with SMA type I and type II due to weakened respiratory and bulbar muscles, as well as dysarthria) and social interactions more generally. Agreement was also high for the PedsQL 3.0 NMM "It is hard to breathe" (in the "About my neuromuscular disease" domain), which is not surprising given the prevalence of breathing complications in patients with SMA, especially types I and II, who frequently require respiratory support and monitoring equipment in the home. Overall, agreement was the lowest for questions pertaining to access to equipment and family rest (in the "About our family resources" domain) and getting sick easily and sores and/or rashes (in the "About my neuromuscular disease" domain). Potential explanations for these results include that parents may not openly discuss topics relating to family resources and problems with their children, that parents may be better informed about existing (but perhaps not accessible) medical devices and aids, and their own (and other family members) possibility to get rest, as well as differences in vantage points (concerning if the child gets sick easily) and coping with the sores and/or rashes. The questions with the largest positive discrepancy in estimated scores (ie, where children noted *less* problems than their parents) related mainly to hand weakness and problems with bathing/showering and turning at night (in the "About my neuromuscular disease" domain) and family problems/rest (in the "About our family resources" domain). Parents may perceive these areas as more problematic since they would be expected to involve their support and help (eg, help with eating, personal hygiene, and changing position when sleeping). Interestingly, there were only two PedsQL 3.0 NMM questions in which the children indicated *more* problems than their parents, on average, namely losing or gaining weight and back stiffness (in the "About my neuromuscular disease" domain). These findings suggest that parents may underestimate the perceived difficulties associated with weight gain, prevalent among, for example, wheelchair users, as well as back pain/stiffness, common in association with scoliosis and due to difficulty in self-repositioning. It is worth noting, however, that the magnitude in differences for questions in which the children indicated more problems was much lower than for questions in which the children indicated fewer problems.

In contrast to the other scales, agreement for KIDSCREEN-27 outcomes was generally poor/fair. In particular, parents underestimated the subjective impact of SMA on life enjoyment (ie, "Has your life been enjoyable?" and "Have you felt so bad that you didn't want to do anything?" [from the "Psychological well-being" domain]) and overestimated perceived problems associated with pursuing leisure activities and socializing with peers (ie, "Have you been able to do the things that you want to do in your free time?" ["Parent relations & autonomy" domain] and "Have you had fun with your friends?" ["Social support and peers" domain]). These results suggest that children with SMA, compared with their parents, perceive that they have fewer problems with social interactions with friends (which is indeed encouraging) but also that these interactions may not be as fun or enjoyable as parents might hope, and/or that these social interactions cannot help alleviate the emotional toll associated with living with SMA to the degree expected. Poor concordance was also noted concerning general health status (in the "Physical well-being" domain) and problems with money (in the "Parent relations and autonomy" domain). As in the case of the PedsQL 3.0 NMM, child-report scores were higher than the parents' assessments in all domains (with the exception of the "Physical well-being" domain), as well as for the total score, although they were in most cases similar, on average. A potential explanation for the comparatively poor agreement for KIDSCREEN-27 is that the scale focuses more on subjective qualities of mental and social domains of life, for which parents might have comparatively less insight, than on, for example, physical aspects (ie, manifestations which are more directly observable). Children reported noticeably more problems than their parents concerning money (ie, "Have you had enough money for your expenses?"), which may, at least in part, be driven by the substantial household cost burden associated with caring for a child with a severely debilitating neuromuscular disease, such as SMA.[27] Finally, it should be noted that when interpreting the mean total scale scores and each respective ICC in Figure 2, the ICCs are derived at the patient-parent pair level, whereas the mean score is derived independently within each group.

Results from the HUI exhibited excellent agreement, on average, between child self- and parent proxy-reports. Indeed, estimated mean utilities were almost identical (mean difference: <2%) (Figure 3). Yet, there were some

differences in specific domains, in particular Emotion, in which parents indicated fewer problems than their children, with a corresponding ICC of -0.20 (p = 0.723). These results are in agreement with the findings from the KIDSCREEN-27 (noted above) and may be indicative of parents' challenges in perceiving and recognizing impairment to their child's psychological, as opposed to physical, wellbeing.

Looking into previous research, to the best of our knowledge, only a limited number of studies have investigated the agreement between self- and proxy-reported HRQoL in SMA. Specifically, Iannaccone et al[7] measured HRQoL using two PedsQL modules, namely the PedsQL 3.0 NMM and the PedsQL 4.0 Generic Core Scales (PedsQL 4.0 GCS), in a sample comprising 125 US patients with SMA (distribution of sex and age not reported; SMA type not reported) and their parents. Agreement (examined using ICCs) for the PedsQL 3.0 NMM About My Neuromuscular Disease score was estimated at 0.48, indicative of moderate agreement, markedly lower than our estimate of 0.84. Similar results were noted for the Communication and About Our Family Resources domains, with the lowest ICC found for the latter (as reported in our study). The ICC for the PedsQL 3.0 NMM total score was estimated at 0.45.

In the second study, Weaver et al[28] compared PedsQL 3.0 NMM scores derived from 28 US patients with SMA (distribution of age and sex not reported; 25% with SMA type I, 54% with type II, and 21% with type III) and their parents. Although not statistically significant, similar to our findings, self-reports using this specific instrument were consistently higher than parent proxy-proxy reports across all subscales, as well as for the total scale score. Yet, compared with our results, differences were generally much smaller. For example, the largest mean difference in scores, noted for the Family resources domain in both studies, was estimated at 16 in our study, compared with 5 in Weaver et al.[28]

Finally, and most recently, Aksaralikitsunti et al[29] measured HRQoL using the PedsQL 4.0 GCS in 42 Thai children with SMA (mean age: 10 years, 40% female; 10% with SMA type I, 67% with type II and 24% with type III) and their parents. Again, in agreement with our results, child self-reported scores using this generic instrument were consistently lower than parent proxy-reports. All domains exhibited moderate-to-good correlation between reports except for Physical Health and Social Functioning, for which agreement was only fair.

To provide further context to our results, it may also be of interest to briefly compare the child-parent agreement for generic measures with that observed in research of the general population. For example, using KIDSCREEN-27, Berman et al[30] found the item-by-item agreement generally ranging from slight to fair, although concordance at the dimension-level, as well as for the total score, ranged from good to excellent, in a random sample of 600 Swedish 11–16 year-olds and their parents. Interestingly, analogous to our findings, particularly poor agreement was noted for the item "Has your life been enjoyable?". In a study encompassing 418 Spanish children/adolescents aged 8–18 years and their parents, Rajmil et al[31] found child–parent agreement to range between low and moderate, with better agreement noted for the "Physical well-being" domain. For the HUI, in contrast to our study, a recent systematic review[32] (including studies of different populations) reported of poor agreement for overall Mark III utilities in the literature. Yet, in line with our findings, the lowest level of concordance was generally reported for the Emotion domain. Interestingly, contrary to our results, agreement in the literature for the Vision domain of the HUII generally ranged from substantial to almost perfect.[32] Notwithstanding these observations of variable agreement, more generally, it may be argued that utilizing both self- and proxy-reports can help provide a richer, more comprehensive assessment of the HRQoL of children and adolescents by accounting for different perspectives of a shared life.[5,33]

Our work is subject to three main limitations. First, in concordance with most rare disease research, our cohort was limited in size, encompassing 17 boys and girls with SMA. For this reason, we were unfortunately not able to stratify our results by SMA type. Second, similarly to all studies employing a self-report design, the data recorded as part of our work is subject to potential bias from measurement error due to incorrect reporting. Third, and last, in terms of generalizability, participants in our study were identified and recruited from a nationwide SMA registry in Germany. However, as inclusion into this registry is voluntary and family-initiated, we cannot rule out a degree of selection bias. It should also be noted that severely ill patients may not have been able to, or chosen not to, take part, which means that our estimates of HRQoL are overestimated on average at the population-level.

## Conclusions

We show that the agreement between child self- and parent proxy-reports of HRQoL in SMA varies markedly across HRQoL measures and examined domains, ranging from poor/fair (KIDSCREEN-27) to excellent (PedsQL 3.0 NMM and the HUI) with some limitations. The lowest levels of concordance were generally found for domains capturing school and family life, as well as mental well-being, as opposed to physical functioning and disability. These results indicate that parent proxy-reports of patient HRQoL in SMA are more reliable when using instruments predominantly addressing physical aspects of life, for which the child's experiences and the objective manifestations of the disease are more directly observable. Our preliminary findings will be helpful in informing the design of future research of HRQoL in SMA, including instrument development and selection for proxy reports.

## Abbreviations

CI, Confidence interval; HRQoL, Health-related quality of life; HUI, Health Utilities Index; ICC, Intraclass correlation coefficient; PedsQL, Pediatric Quality of Life Inventory; PedsQL 3.0 NMM, Pediatric Quality of Life Inventory 3.0 Neuromuscular Module; PedsQL 4.0 GCS, Pediatric Quality of Life Inventory 4.0 Generic Core Scales; SMA, Spinal muscular atrophy.

## Data Sharing Statement

The data supporting the findings of this study are not publicly available due to ethical restrictions.

## Ethics Approval and Consent to Participate

The study was approved by the regional Ethics Committee from the Saarland Medical Association (protocol number 09/20), registered in the German clinical trial registry (DRKS00022876), and conducted in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

## Funding

The non-profit patient association "Initiative SMA – Gemeinsam für eine Therapie" within the "Deutsche Gesellschaft für Muskelkranke e.V." provided financial support for the license fees of the proprietary HRQoL instruments, as well as the allowance for the SMA patient registry. We acknowledge financial support from University of Saarland for the publication of this article.

## Disclosure

Dr Marina Flotats-Bastardas has received consultant fees from Roche and Biogen. Dr Landfeldt is an employee of IQVIA, a contract research organization. Dr Maggie C. Walter has served on advisory boards for Avexis, Biogen, Novartis, Pfizer, Roche, Santhera, Sarepta, Pharnext, PTC Therapeutics, Ultragenyx, Wave Sciences, received funding for Travel or Speaker Honoraria from Avexis, Biogen, PTC Therapeutics, Ultragenyx, Santhera, Sarepta, and worked as an ad-hoc consultant for AskBio, Audentes Therapeutics, Avexis, Biogen Pharma GmbH, Fulcrum Therapeutics, GLG Consult, Guidepoint Global, Gruenenthal Pharma, Novartis, Pharnext, PTC Therapeutics, Roche. The other authors declare that there is no conflict of interest.

## References

1. Lunn MR, Wang CH. Spinal muscular atrophy. *Lancet*. 2008;371(9630):2120–2133.
2. Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol*. 2012;11(5):443–452.

3. Pechmann A, Behrens M, Dörnbrack K, et al. Effect of nusinersen on motor, respiratory and bulbar function in early-onset spinal muscular atrophy. *Brain*. 2023;146(2):668–677.
4. Pechmann A, Behrens M, Dörnbrack K, et al. Improved upper limb function in non-ambulant children with SMA type 2 and 3 during nusinersen treatment: a prospective 3-years SMArtCARE registry study. *Orphanet J Rare Dis*. 2022;17(1):384.
5. Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. *Health Technol Assess*. 2001;5(4):1–57.
6. Spieth LE, Harris CV. Assessment of health-related quality of life in children and adolescents: an integrative review. *J Pediatr Psychol*. 1996;21:175–193.
7. Iannaccone ST, Hynan LS, Morton A, Buchanan R, Limbers CA, Varni JW. The PedsQL in pediatric patients with spinal muscular atrophy: feasibility, reliability, and validity of the pediatric quality of life inventory generic core scales and neuromuscular module. *Neuromuscul Disord*. 2009;19(12):805–812.
8. Ravens-Sieberer U, Herdman M, Devine J, et al. The European KIDSCREEN approach to measure quality of life and well-being in children: development, current application, and future advances. *Qual Life Res*. 2014;23(3):791–803.
9. Jardine J, Glinianaia SV, McConachie H, et al. Self-reported quality of life of young children with conditions from early infancy: a systematic review. *Pediatrics*. 2014;134(4):e1129–48.
10. Ravens-Sieberer U, Erhart M, Wille N, et al. Generic health-related quality-of-life assessment in children and adolescents: methodological considerations. *Pharmacoeconomics*. 2006;24:1199–1220.
11. Bray P, Bundy AC, Ryan MM, North KN, Everett A. Health-related quality of life in boys with Duchenne muscular dystrophy: agreement between parents and their sons. *J Child Neurol*. 2010;25(10):1188–1194. Epub 2010 Oct 12. PMID: 20179004. doi:10.1177/0883073809357624
12. Davis SE, Hynan LS, Limbers CA, et al. The PedsQL in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the pediatric quality of life inventory neuromuscular module and generic core scales. *J Clin Neuromuscul Dis*. 2010;11(3):97–109.
13. Uzark K, King E, Cripe L, et al. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. *Pediatrics*. 2012;130 (6):e1559–66. Epub 2012 Nov 5. PMID: 23129083. doi:10.1542/peds.2012-0858
14. Hu J, Jiang L, Hong S, Cheng L, Kong M, Ye Y. Reliability and validity of the Chinese version of the pediatric quality of life inventorytm (PedsQLTM) 3.0 neuromuscular module in children with Duchenne muscular dystrophy. *Health Qual Life Outcomes*. 2013;11:47. PMID: 23497421; PMCID: PMC3606306. doi:10.1186/1477-7525-11-47
15. Lim Y, Velozo C, Bendixen RM. The level of agreement between child self-reports and parent proxy-reports of health-related quality of life in boys with Duchenne muscular dystrophy. *Qual Life Res*. 2014;23(7):1945–1952. Epub 2014 Feb 25. PMID: 24566887; PMCID: PMC4140965. doi:10.1007/s11136-014-0642-7
16. Leibrock B, Landfeldt E, Hussong J, et al. Areas of improvement in the medical care of SMA: evidence from a nationwide patient registry in Germany. *Orphanet J Rare Dis*. 2023;18(1):32.
17. Landfeldt E, Leibrock B, Hussong J, et al. Self-reported health-related quality of life of children with spinal muscular atrophy: insights from a nationwide patient registry in Germany. *J Neuromuscul Dis*. 2024;11(1):117–128.
18. Landfeldt E, Leibrock B, Hussong J, et al. Health-related quality of life of adults with spinal muscular atrophy: insights from a nationwide patient registry in Germany. *Qual Life Res*. 2024. doi:10.1007/s11136-024-03665-5
19. Horsman J, Furlong W, Feeny D, Torrance G. The health utilities index (HUI): concepts, measurement properties and applications. *Health Qual Life Outcomes*. 2003;1:54.
20. Landfeldt E, Edström J, Sejersen T, Tulinius M, Lochmüller H, Kirschner J. Quality of life of patients with spinal muscular atrophy: a systematic review. *Eur J Paediatr Neurol*. 2019;23(3):347–356.
21. Landfeldt E. Measuring health-related quality of life in Duchenne muscular dystrophy: current perspectives and recommendations. *J Neurol Sci*. 2023;446:120545.
22. Feeny DH, Furlong WJ, Torrance GW, et al. Multi-attribute and single-attribute utility functions for the health utilities index mark 3 system. *Medical Care*. 2002;40:113–128.
23. Viera AJ, Garrett JM. Understanding interobserver agreement: the kappa statistic. *Fam Med*. 2005;37(5):360–363.
24. Landis JR, Koch GG. The measurement of observer agreement for categorical data. *Biometrics*. 1977;33(1):159–174.
25. Landfeldt E, Udo C, Lövgren M, Sejersen T, Kreicbergs U. Health-related quality of life of children with spinal muscular atrophy in Sweden: a prospective cohort study in the era of disease-modifying therapy. *Eur J Paediatr Neurol*. 2023;46:67–73.
26. Landfeldt E, Lindgren P, Bell CF, et al. Health-related quality of life in patients with Duchenne muscular dystrophy: a multinational, cross-sectional study. *Dev Med Child Neurol*. 2016;58(5):508–515.
27. Landfeldt E, Abner S, Pechmann A, et al. Caregiver burden of spinal muscular atrophy: a systematic review. *Pharmacoeconomics*. 2023;41 (3):275–293.
28. Weaver MS, Hanna R, Hetzel S, et al. A prospective, crossover survey study of child- and proxy-reported quality of life according to spinal muscular atrophy type and medical interventions. *J Child Neurol*. 2020;35(5):322–330.
29. Aksaralikitsunti M, Sanmaneechai O. Health-related quality of life in Thai children with spinal muscular atrophy. *Pediatr Neonatol*. 2022;63 (3):291–297.
30. Berman AH, Liu B, Ullman S, Jadbäck I, Engström K. Children's quality of life based on the KIDSCREEN-27: child self-report, parent ratings and child-parent agreement in a Swedish random population sample. *PLoS One*. 2016;11(3):e0150545.
31. Rajmil L, López AR, López-Aguilà S, Alonso J. Parent-child agreement on health-related quality of life (HRQOL): a longitudinal study. *Health Qual Life Outcomes*. 2013;11:101.
32. Khanna D, Khadka J, Mpundu-Kaambwa C, Lay K, Russo R, Ratcliffe J. Quality of life in kids: key evidence to strengthen decisions in Australia (QUOKKA) project team. are we agreed? Self- versus proxy-reporting of paediatric health-related quality of life (HRQoL) using generic preference-based measures: a systematic review and meta-analysis. *Pharmacoeconomics*. 2022;40(11):1043–1067.
33. Haverman L, Limperg PF, Young NL, Grootenhuis MA, Klaassen RJ. Paediatric health-related quality of life: what is it and why should we measure it? *Arch Dis Child*. 2017;102(5):393–400.