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ORIGINAL RESEARCH

Validation of a Set of Instruments to Assess Patient- and Caregiver-Oriented Measurements in Spinal Muscular Atrophy: Results of the SMA-TOOL Study

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ABSTRACT

Introduction: Outcome measures traditionally used in spinal muscular atrophy (SMA) clinical trials are inadequate to assess the full range of disease severity. The aim of this study was to assess the psychometric properties of a set of existing questionnaires and new items, gathering information on the impact of SMA from the patient and caregiver perspectives.

Methods: This was a multicenter, prospective, noninterventional study including patients with a confirmed diagnosis of 5q-autosomal-recessive SMA aged 8 years and above, or their

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parents (if aged between 2 and 8 years). The set of outcome measurements included the SMA Independence Scale (SMAIS) patient and caregiver versions, the Neuro-QoL Fatigue Computer Adaptive Test (CAT), the Neuro-QoL Pain Short Form—Pediatric Pain, the PROMIS adult Pain Interference CAT, and new items developed by Fundación Atrofia Muscular España: perceived fatigability, breathing and voice, sleep and rest, and vulnerability. Reliability, construct validity, discriminant validity, and sensitivity to change (4 months from baseline) were measured.

Results: A total of 113 patients were included (59.3% 2–17 years old, 59.3% male, and 50.4% with SMA type II). Patients required moderate assistance [mean patient and caregiver SMAIS (SD) scores were 31.1 (12.8) and 7.6 (11.1), respectively]. Perceived fatigability was the most impacted domain, followed by vulnerability. Cronbach's alpha coefficient for perceived fatigability, breathing and voice, and vulnerability total scores were 0.92, 0.88, and 0.85, respectively. The exploratory factor analysis identified the main factors considered in the design, except in the sleep and rest domain. All questionnaires were able to discriminate between the Clinical Global Impression—Severity scores and SMA types. Sensitivity to change was only found for the SMAIS caregiver version and vulnerability items.

Conclusions: This set of outcome measures showed adequate reliability, construct validity, and discriminant validity and may constitute a valuable option to measure symptom severity in patients with SMA.

Keywords: Spinal muscular atrophy; Patients and caregivers; Outcome measures; Quality of life; Symptom assessment; Disease burden

Key Summary Points

Outcome measures traditionally used in clinical practice and research are insufficient to assess the full range of disease severity

There is a need to develop sensitive scales capable of detecting small changes in a spectrum of dimensions beyond motor function

This study provided a validated set of measurements incorporating patients' and parent caregivers' meaningful outcomes

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INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal-recessive disorder characterized by motor neuron loss in the spinal cord and lower brainstem, leading to progressive proximal muscle weakness and atrophy [1]. The cause of SMA is a biallelic mutation in the survival motor neuron 1 (*SMN1*) gene, located on chromosome 5q13 [1, 2]. The incidence of all types of SMA is around 1/12,000 live births, with a prevalence of 1–2/100,000 and a carrier frequency of 1/40–1/60 [2]. The prognosis of SMA has changed dramatically in the last decade with the development of disease-modifying therapies, allowing patient improvement or stabilization

of motor and respiratory functions, and extended survival [3, 4]. However, treatment decisions are complex because of the lack of direct comparisons between therapies and the uncertainty of long-term outcomes [5–7].

Multiple clinician-rated instruments administered in research and routine clinical practice are available to assess patients with SMA, such as the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders, Hammersmith Infant Neurological Examination, Hammersmith Functional Motor Scale-Expanded, Revised Upper Limb Module, Six-Minute Walk Test, and the Motor Function Measure 32 [8–12]. Although these scales assess motor function, they show significant limitations in some subgroups of patients [13]. In addition, tools assessing the impact on other meaningful areas for patients and their caregivers are still lacking [14–17]. Bulbar functions, mobility, ability to perform daily activities, swallowing, endurance, self-toileting and feeding, spending time alone, and being engaged in social activities are areas that matter to patients and caregivers, but are frequently neglected in usual outcome measures [18–20]. Thus, there is a need to complement them by incorporating the perspectives of patients and caregivers, especially in the domains essential for autonomy and quality of life. The aim of this study was to assess the psychometric properties of a set of existing questionnaires and new items, gathering information on the impact of SMA on physical, psychological, functional, and social domains from the patient and caregiver perspectives.

METHODS

Design

The SMA-TOOL was a prospective, noninterventional study conducted at 12 hospital-based neuromuscular clinics specialized in the management of patients with SMA in Spain. People with a confirmed diagnosis of 5q-autosomal-recessive SMA (genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the *SMN1* gene) aged 8 years and above, or their parents in the case of patients aged between 2 and 8 years, were included. Participants were recruited consecutively from October 2020 to October 2021.

This study was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation and the ethical principles of the Declaration of Helsinki, and was approved by the investigational review board of the Hospital Universitari de Bellvitge (Barcelona, Spain; reference code: PR264/20). Written informed consent was obtained from all subjects.

Measurements

The set of outcome measurements included the SMA Independence Scale (SMAIS), the Neuro-QoL Fatigue Computer Adaptive Test (CAT), the Neuro-QoL Pain Short Form–Pediatric Pain, the PROMIS adult Pain Interference CAT, and new items developed using qualitative methods by Fundación Atrofia Muscular España (FundAME) to assess perceived fatigability, breathing and voice, sleep and rest, and vulnerability [21–27]. This set was selected by a multidisciplinary research team of pediatric and adult neurologists, rehabilitation physicians, and a patient representative [27]. Patients and parents completed the study questionnaires in person during their regular follow-up visits at the neuromuscular units. Sociodemographic and clinical characteristics and the severity of patient illness in the last 7 days using Clinical Global Impression–Severity scale (CGI-S) were collected by investigators [28]. Patients were classified into type 1–4 SMA as defined elsewhere, as well as into functional subgroups: walkers (able to walk at least five steps without assistance), sitters (able to sit without assistance or head support for more than 10 s), and non-sitters [15, 29]. At the 4-month follow-up, all measures were collected again, adding the Clinical Global Impression–Improvement scale, (CGI-I) [28].

The SMAIS is a 29-item self-reported questionnaire to assess the ability of patients with SMA type 2 or 3 to independently perform activities of daily-living [21, 22]. The SMAIS has

a patient version for patients aged 12 years or over and a caregiver-report version for caregivers of patients aged over 2 years. The total score ranges from 0 to 44, with higher values indicating greater independence. The Neuro-QoL Fatigue CAT is a self-reported measurement to assess fatigue across neurological conditions [23, 24]. Higher scores indicate worse self-reported fatigue. The Neuro-QoL Pain Short Form–Pediatric Pain is a ten-item self-reported questionnaire to measure pain in patients aged 8–17 years [25]. The PROMIS adult Pain Interference CAT is a 40-item self-reported measurement to assess pain in adult patients [26]. Higher scores in both scales indicate worse self-reported pain. The perceived fatigability, breathing and voice, sleep and rest, and vulnerability assessments consist of 10–11, 8, 3, and 9 self-reported items, respectively [27]. Neuro-QoL tests and FundAME's items were fulfilled by caregivers in the case of patients under 8 years of age. Additional details on the measurements included in the set can be found elsewhere [27].

Statistical Analysis

Different variables were analyzed in the total sample and by grouping patients aged 0–7 years (parents responded to the questionnaires), 8–-17 years, and 18 years and older. The reliability, construct validity, and discriminant validity of both versions of the SMAIS and the new items included in the set (perceived fatigability, breathing and voice, sleep and rest, and vulnerability) were measured. For the new items, it was first necessary to group them into dimensions and questionnaires according to the previous hypothesized structure, and to perform an exploratory factorial analysis to assess construct validity. The scores of each questionnaire were calculated on a 0–100 scale. The construct validity of both versions of the SMAIS was assessed by conducting confirmatory factorial analysis to determine the dimensional structure of the original version of the questionnaire and by conducting exploratory factorial analysis for the new items. Reliability was assessed in terms of internal consistency by means of Cronbach's alpha coefficient in both versions of the SMAIS and in the new items, which must be more than 0.70. Discriminant validity was assessed in both versions of the SMAIS and in the new items by comparing the scores of the questionnaires between different patient groups according to previous hypotheses: scores were compared according to the type of SMA and CGI-S scale using one-way ANOVA. Sensitivity to change or longitudinal validity was assessed by comparing the scores of the questionnaires at the first and second visits in the group of patients who changed their clinical status according to investigator opinion, using the CGI-I for both versions of the SMAIS and the new items.

RESULTS

A total of 113 patients were included. The mean age (SD) was 19.7 (15.7) years, 59.3% were male, and 50.4% had SMA type II. The median disease duration was 75 months (interquartile range 33.7, 157.3). The main sociodemographic and clinical characteristics of the sample are shown in Table 1.

The mean SMAIS total scores (SD) were 31.1 (12.8) and 27.6 (11.1) for the patient and caregiver versions, respectively. Perceived fatigability was the most impacted domain, followed by vulnerability. The mean scores of the questionnaires of the set are presented in Table 2 and in Figs. 1 and 2, comparing scores between the baseline and follow-up visits. For the new items related to sleep and rest, it was not possible to establish a total score, and the distribution of answers for each item is presented in Table 3.

Psychometric Properties of Measurements

SMAIS Patient and Caregiver Versions

Cronbach's alpha coefficient for the total score of the SMAIS patient questionnaire was 0.97 and that of the SMAIS caregiver version, 0.96. The confirmatory factor model, adjusted for the SMAIS patient version, indicated that the prescribed relationships between the variables and the factors were significant, except for items 21 ("Move through the house with wheelchair'')

Table 1 Baseline sociodemographic and clinical characteristics of the sample (N = 113)

		0–7 years (N = 28)	**8–17 years (N = 39)**	**≥ 18 years (N = 46)**	**Total (N = 113)**
Age, years	Mean (SD)	4.54 (1.64)	12.54 (2.89)	35.00 (13.44)	19.70 (15.74)
Age cat n (%)	0–7 years old	28 (100%)	–	–	28 (24.8%)
	8–11 years	–	15 (38.5%)	–	15 (13.3%)
	12–17 years	–	24 (61.5%)	–	24 (21.2%)
	≥ 18 years	–	–	46 (100%)	46 (40.7%)
Gender *n* (%)	Male	17 (60.7%)	26 (66.7%)	24 (52.2%)	67 (59.3%)
Living status *n* (%)	Living with their family or friend or personal assistant	28 (100%)	39 (100%)	41 (89.1%)	108 (95.6%)
Education *n* (%)	Currently not studying	12 (42.9%)	1 (2.6%)	–	14 (19.4%)
	Currently studying primary education	14 (50.0%)	17 (43.6%)	–	31 (43.1%)
	Currently studying secondary education	–	21 (53.8%)	4 (80.0%)	25 (34.7%)
	Not available	2 (7.1%)	–	1 (20.0%)	2 (2.8%)
Time since SMA diagnosis, months	Mean (SD)	42.71 (19.65)	112.55 (52.43)	146.17 (135.26)	108.89 (100.27)
	Median	38.6	112.4	90.9	75.0
	(P25; P75)	(25.3; 61.8)	(77.6; 153.3)	(31.5; 252.1)	(33.7; 157.3)
	(Min; Max)	(15.2; 75.1)	(0.0; 202.9)	(1.9; 518.0)	(0.0; 518.0)
Type of SMA	I	9 (32.1%)	–	–	9 (8.0%)
	II	15 (53.6%)	27 (69.2%)	15 (32.6%)	57 (50.4%)
	IIIa	4 (14.3%)	8 (20.5%)	9 (19.6%)	21 (18.6%)
	IIIb	-	3 (7.7%)	20 (43.5%)	23 (20.4%)
	IV	–	1 (2.6%)*	2 (4.3%)	3 (2.7%)
SMN2 copies	2	10 (35.7%)	3 (7.7%)	5 (10.9%)	17 (15.0%)
	3	16 (57.1%)	28 (71.8%)	24 (52.2%)	69 (61.1%)
	4	1 (3.6%)	8 (20.5%)	16 (34.8%)	25 (22.1%)
	More than 4	1 (3.6%)	–	–	1 (0.9%)
	Unknown	–	–	1 (2.2%)	1 (0.9%)
Functional classification	Non-sitter	1 (3.6%)	5 (12.8%)	8 (17.4%)	14 (12.4%)
	Sitter	21 (75.0%)	23 (59.0%)	19 (41.3%)	63 (55.8%)
	Walker	6 (21.4%)	11 (28.2%)	19 (41.3%)	36 (31.9%)
SMA symptoms (more than one option possible)	Limb weakness	23 (82.1%)	26 (66.7%)	40 (87.0%)	89 (78.8%)
	Hypotonia	22 (78.6%)	28 (71.8%)	16 (34.8%)	66 (58.4%)
	Delay on WHO motor milestones acquisition	18 (64.3%)	22 (56.4%)	15 (32.6%)	55 (48.7%)

Table 1 continued

		0–7years (N = 28)	8–17years (N = 39)	≥ 18years (N = 46)	Total (N = 113)
Muscle strength—elbow flexion	Median MRC value	4.0	4.0	4.0	4.0
	(P25; P75)	(4.0; 4.0)	(3.0; 4.0)	(3.0; 5.0)	(3.0; 4.0)
Muscle strength—knee extension	Median MRC value	3.0	2.0	1.0	2.0
	(P25; P75)	(3.0; 4.0)	(1.0; 3.0)	(0.0; 3.0)	(1.0; 3.0)
Muscle strength—knee flexion	Median MRC value	4.0	3.0	3.0	3.0
	(P25; P75)	(3.0; 4.0)	(2.0; 4.0)	(1.0; 4.0)	(2.0; 4.0)
Ventilatory support	N (%)	11 (39.3%)	17 (43.6%)	8 (17.4%)	36 (31.9%)
Gastrointestinal tube	N (%)	3 (10.7%)	2 (5.1%)	-	5 (4.4%)
Scoliosis surgery	N (%)	1 (3.6%)	14 (35.9%)	16 (34.8%)	31 (27.4%)
Active drug for SMA treatment	N (%)	27 (96.4%)	31 (79.5%)	33 (71.7%)	92 (81.4%)
Clinical Global Impression–Severity of Illness (CGI-S)	1: Normal, not at all ill N (%)	3 (10.7%)	8 (20.5%)	1 (2.2%)	13 (11.5%)
	2: Borderline ill; N (%)	3 (10.7%)	5 (12.8%)	3 (6.5%)	10 (8.8%)
	3: Mildly ill; N (%)	10 (35.7%)	5 (12.8%)	10 (21.7%)	25 (22.1%)
	4: Moderately ill N (%)	10 (35.7%)	13 (33.3%)	19 (41.3%)	42 (37.2%)
	5: Markedly ill; N (%)	2 (7.1%)	6 (15.4%)	11 (23.9%)	19 (16.8%)
	6: Severely ill; N (%)	–	2 (5.1%)	2 (4.3%)	4 (3.5%)
	7: Among the most extremely ill patients; N (%)	–	–	–	–

*This subject's classification is provisional, since she/he is asymptomatic

and 23 ("Keep your head up without a neck brace or headband") (supplementary material, Table S1). It was the same for the SMAIS caregiver version, except for item 23 ("Keep your head up without a neck brace or headband") (supplementary material, Table S2). The mean total scores of both SMAIS versions comparing patients according to their CGI-S scores and SMA types are shown in Tables 4 and 5, respectively. The scores of both questionnaires showed a high correlation coefficient (0.96). SMAIS patient version scores did not change in the predicted way in relation to the changes observed in the CGI-I; although one patient who had very much improved, showed an increase of 4 points in the SMAIS score and six patients who had much improved, showed slightly lower scores. SMAIS caregiver version scores changed in the predicted way in relation to the changes observed in the CGI-I: five patients who very much improved, showed an increase of 3 points in the SMAIS score and 12 patients who had much improved, showed only slightly higher scores (supplementary material, Table S3).

Perceived Fatigability

Cronbach's alpha coefficient for the total score of perceived fatigability was 0.92. Exploratory factor analysis of items identified six factors with a proportion criterion of 80%; three of them explained 60% of the score variance. The aggregation of items into dimensions can be observed in Table 6. The mean total perceived

Table 2 Baseline scores of the questionnaires included in the set*

Variable		0–7 years (*N* = 28)	8–17 years (*N* = 39)	≥ 18 years (*N* = 46)	Total (*N* = 113)
SMAIS Patient version (for patients aged 12 years or over) Total score (0–44)	Valid *N*	–	23	46	69
	Mean (SD)	–	30.11 (10.22)	31.65 (14.01)	31.14 (12.81)
SMAIS caregiver version (for all caregivers). Total score (0–44)	Valid *N*	28	39	32	99
	Mean (SD)	15.26 (7.55)	27.47 (11.09)	26.78 (13.67)	27.61 (11.09)
Scores (0–100) for perceived fatigability	Valid *N*	28	39	46	113
	Mean (SD)	21.64 (18.53)	20.32 (17.16)	23.31 (22.43)	21.86 (19.66)
Scores (0–100) for breathing and voice	Valid *N*	28	39	46	113
	Mean (SD)	15.55 (24.32)	5.98 (7.07)	7.27 (11.80)	8.88 (15.18)
Scores (0–100) for vulnerability	Valid *N*	28	39	46	113
	Mean (SD)	19.18 (19.16)	10.21 (17.75)	12.60 (17.94)	13.41 (18.36)
T-scores for Neuro-QoL Fatigue CAT for children	Valid *N*	28	38	–	66
	Mean (SD)	46.97 (8.94)	45.01 (7.36)	–	45.84 (8.06)
T-scores for Neuro-QoL Fatigue CAT for adults	Valid *N*	–	–	46	46
	Mean (SD)	–	–	43.55 (7.47)	43.55 (7.47)
T-Scores for Neuro-QoL Pain children SF for children	Valid *N*	28	39	2	69
	Mean (SD)	44.22 (6.50)	47.54 (6.97)	49.76 (14.87)	46.26 (7.09)
T-Scores for PROMIS adult Pain Interference CAT	Valid *N*	–	–	44	44
	Mean (SD)	–	–	47.73 (8.77)	47.73 (8.77)

*except sleep and rest

fatigability scores comparing patients according to their CGI-S scores and SMA types are presented in Tables 4 and 5, respectively. Perceived fatigability scores did not change in the predicted way with respect to CGI-I: five patients who had very much improved, showed a decrease of 6 points, but patients who had much improved or minimally improved,

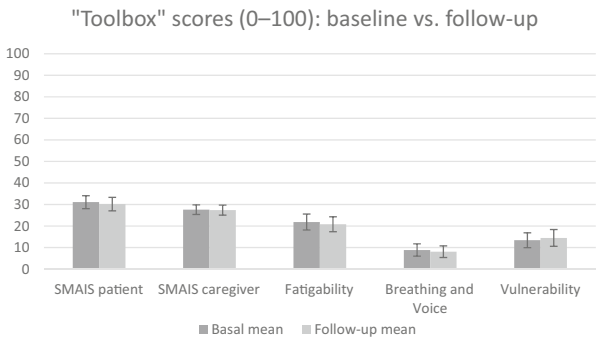

Fig. 1 Changes in scores between baseline and follow-up visits for 0–100 scores of SMAIS patient and caregiver versions, perceived fatigability, breathing and voice, and vulnerability questionnaires

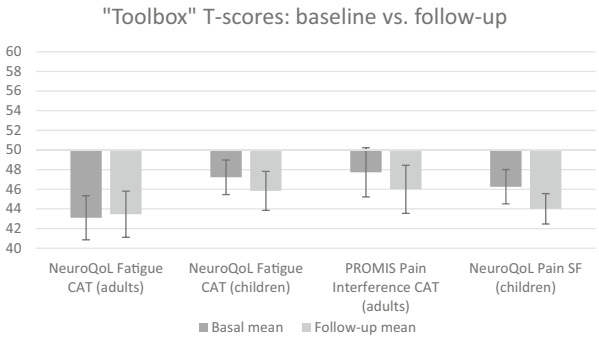

Fig. 2 Changes in scores between baseline and follow-up visits for T-scores of Neuro-Qol Fatigue CATs for children and adults, PROMIS Pain Interference CAT for adults and Neuro-QoL Pain short form for children

showed higher scores (supplementary material, Table S3).

Breathing and Voice

Cronbach's alpha coefficient for the total score of breathing and voice was 0.88. Exploratory factor analysis identified three factors with a proportion criterion of 80%; the first of them explained 60% of the score variance. The way in which items are aggregated into dimensions can be observed in Table 7. The first item ("Could you talk?") alone formed a separate factor, while the rest of the items were aggregated into the two other factors. Mean total breathing and voice scores comparing patients according to their CGI-S scores and SMA types are presented in Tables 4 and 5, respectively. Breathing and voice total scores did not change in the predicted way with respect to CGI-I, being higher in patients who had very much improved and lower in patients who had much improved or minimally improved (supplementary material, Table S3).

Sleep and Rest

The three items assessing sleep and rest explore different aspects related to sleep in patients with SMA and, according to the exploratory factor analysis, it seems that they would form three different factors. Hence, the three items must be considered separately to describe the impact of SMA on three different aspects of sleep and rest (Table 8).

Vulnerability

Cronbach's alpha coefficient for the total score of vulnerability was 0.85. Exploratory factor analysis identified four factors with a proportion criterion of 80%; two of them explained 60% of the score variance. The aggregation of items into dimensions is presented in Table 9. These items were designed to assess three aspects: the risk associated with choking, postural changes, and infections. Although the structure seems to be somewhat different, the three most important factors from the exploratory factor analysis coincided with this structure. Mean total vulnerability scores comparing patients according to their CGI-S scores and SMA types are presented in Tables 4 and 5, respectively. Vulnerability scores changed in the predicted way in relation to the changes observed in the CGI-I (supplementary material, Table S3).

DISCUSSION

SMA is a heterogeneous disorder affecting a range of patients, from non-ambulant children

Table 3 Baseline scores of items of sleep and rest

Variable		0–7 years (*N* = 28)	8–17 years (*N* = 39)	≥ 18 years (*N* = 46)	Total (*N* = 113)
1. Have you woken up during the night to ask for help and to be able to move in bed?	Valid *N*	28 (100%)	39 (100%)	46 (100%)	113 (100%)
	Never	15 (53.6%)	10 (25.6%)	24 (52.2%)	49 (43.4%)
	Rarely	5 (17.9%)	3 (7.7%)	2 (4.3%)	10 (8.8%)
	Sometimes	1 (3.6%)	6 (15.4%)	5 (10.9%)	12 (10.6%)
	Very often	3 (10.7%)	7 (17.9%)	4 (8.7%)	14 (12.4%)
	Always	3 (10.7%)	13 (33.3%)	11 (23.9%)	27 (23.9%)
	Not applicable	1 (3.6%)	–	–	1 (0.9%)
1a.* The nights that you have woken up, how many times is it usual?	Valid *N*	12 (100%)	29 (100%)	22 (100%)	63 (100%)
	1 time	4 (33.3%)	7 (24.1%)	11 (50.0%)	22 (34.9%)
	2–3 times	6 (50.0%)	10 (34.5%)	10 (45.5%)	26 (41.3%)
	4+ times	2 (16.7%)	12 (41.4%)	1 (4.5%)	15 (23.8%)
2. If you use a ventilation device, did you wake up during the night because it bothered you?	Valid *N*	28 (100%)	39 (100%)	46 (100%)	113 (100%)
	Never	5 (17.9%)	24 (61.5%)	15 (32.6%)	44 (38.9%)
	Rarely	3 (10.7%)	2 (5.1%)	1 (2.2%)	6 (5.3%)
	Sometimes	3 (10.7%)	2 (5.1%)	4 (8.7%)	9 (8.0%)
	Very often	2 (7.1%)	1 (2.6%)	–	3 (2.7%)
	Always	1 (3.6%)	1 (2.6%)	–	2 (1.8%)
	Not applicable	14 (50.0%)	9 (23.1%)	26 (56.5%)	49 (43.4%)
3. Have you woke up tired after sleeping at night?	Valid *N*	28 (100%)	39 (100%)	46 (100%)	113 (100%)
	Never	14 (50.0%)	22 (56.4%)	18 (39.1%)	54 (47.8%)
	Rarely	9 (32.1%)	11 (28.2%)	8 (17.4%)	28 (24.8%)
	Sometimes	3 (10.7%)	5 (12.8%)	18 (39.1%)	26 (23.0%)
	Very often	1 (3.6%)	1 (2.6%)	2 (4.3%)	4 (3.5%)
	Always	1 (3.6%)	–	–	1 (0.9%)

to ambulant adults. Of note, current assessment tools are insufficient, especially for the detection of subtle, but potentially key changes in patient autonomy [5–7]. There is a need to develop new measures or a set of different instruments suitable to capture SMA patient and parent caregiver preferences and meaningful outcomes [16, 20, 30–33].

Zizzi et al. recently developed and validated the Spinal Muscular Atrophy Health Index (SMA-HI), a disease-specific, patient-reported outcome measure to assess the overall disease burden and 15 key domains, including motor functions, mobility, fatigue, pain, swallowing, breathing, sleep, social satisfaction, and emotional health [34, 35]. This instrument showed adequate internal consistency (Cronbach's

Table 4 Scores of the questionnaires of the set compared according to Clinical Global Impressions Scale, Severity of illness (CGI-S)

Variable		1–2	3	4	5–7	Total	*p*-Value
SMAIS patient	Valid *N*	13	13	26	17	69	
total score (0–44)	Mean (SD)	36.16 (9.21)	42.69 (2.50)	33.90 (8.67)	14.24 (8.20)	31.14 (12.81)	< 0.0001
SMAIS caregiver	Valid *N*	20	19	38	22	99	
total score (0–44)	Mean (SD)	33.34 (8.87)	34.37 (7.60)	28.70 (8.58)	14.66 (8.57)	27.61 (11.09)	< 0.0001
Perceived fatigability total score (0–100)	Valid *N*	23	25	42	23	113	
	Mean (SD)	9.63 (8.73)	19.82 (14.61)	19.36 (15.97)	40.88 (25.12)	21.86 (19.66)	< 0.0001
Breathing and voice total score (0–100)	Valid *N*	23	25	42	23	113	
	Mean (SD)	1.63 (3.26)	10.17 (15.88)	7.66 (16.63)	16.94 (15.65)	8.88 (15.18)	0.0056
Vulnerability total score (0–100)	Valid *N*	23	25	42	23	113	
	Mean (SD)	7.84 (19.17)	12.78 (17.48)	10.70 (10.68)	24,60 (24,97)	13.41 (18.36)	0.0074

1: normal; 2: borderline ill; 3: mildly ill; 4: moderately ill; 5: markedly ill; 6: severely ill; 7: extremely ill

alpha = 0.77–0.96), high test–retest reliability (intraclass correlation coefficient = 0.60–0.96), and an ability to differentiate between SMA groups with different disease severities in a sample of adults, adolescents, and children 8 years of age and older (range = 8–79 years) [34]. However, the SMA-HI was validated using remote surveys, wherein demographic and clinical information was reported by the participants themselves, with the subsequent risk of bias or misclassification of SMA types [34].

Our study showed that this new set of outcome measures, including the SMAIS together with specific questionnaires for perceived fatigability, breathing and voice, and vulnerability domains, has adequate reliability, construct validity, and discriminant validity. In addition, it was validated in a sample of 113 patients routinely managed at 12 neuromuscular clinics specialized in SMA care throughout the country.

The SMAIS is a validated, disease-specific instrument to assess different activities of daily living such as washing and hygiene, dressing, eating and drinking, picking up and moving objects, mobility and strength, chores, writing and using a computer [21]. In our study, the internal consistency of the SMAIS was good, with Cronbach's alpha scores similar to those of the self-reported and caregiver original versions (0.97 and 0.96 in this study compared with 0.90 and 0.91, respectively). It was also confirmed that the construct validity showed a moderate model fit with the original structure of the questionnaire and adequate discriminant validity. Differences between the four groups of patients according to their CGI-S score or their type of SMA were greater than or equal to the change between 1 and 5 points proposed as meaningful in the original validation study [21]. Both versions showed a high correlation in the total score (> 0.90), in the mobility/strength score (> 0.80), and in the chore items (0.80).

Table 5 Scores of the questionnaires of the set compared according to SMA type classification

Variable		I	II	IIIa	IIIb	IV	Total	*p*-Value
SMAIS patient	Valid *N*		30	13	23	3	69	
total score (0–44)	Mean (SD)		19.39 (9.22)	38.69 (6.09)	40.52 (6.22)	44.00 (0.00)	31.14 (12.81)	< 0.0001
SMAIS caregiver	Valid *N*	9	56	18	14	2	99	
total score (0–44)	Mean (SD)	24.97 (7.84)	22.31 (9.88)	36.56 (6.05)	36.64 (7,96)	44.00 (0,00)	27.61 (11.09)	< 0.0001
Perceived fatigability total score (0–100)	Valid *N*	9	57	21	23	3	113	
	Mean (SD)	23.66 (24.04)	25.35 (21.11)	19.91 (12.92)	16.91 (18,79)	1.87 (3,23)	21.86 (19.66)	0.1557
Breathing and voice total score (0–100)	Valid N	9	57	21	23	3	113	
	Mean (SD)	34.50 (34.45)	9.50 (11.13)	3.61 (6.08)	3.26 (7.32)	0.00 (0.00)	8.88 (15.18)	< 0.0001
Vulnerability total score (0–100)	Valid *N*	9	57	21	23	3	113	
	Mean (SD)	36.79 (22.22)	16.46 (19.81)	5.59 (8.33)	5,57 (8,89)	0,00 (0,00)	13.41 (18.36)	< 0.0001

However, only the caregiver version score changed in the predicted way in relation to the changes in the CGI-I. Conversely, in the original validation study, both versions showed similar responsiveness [21]. However, in that study, only 22 of the 29 original items were considered. Our data suggest that if the original 29-item version were used, the caregiver version would be more reliable for assessing the degree of independence of SMA patients in daily living activities. Previous research shows that perceptions of children and parents as to the degree of illness in SMA may often differ [36].

The need to assess other relevant domains that are not fully addressed by the usual measures of motor function and the SMAIS has led us to include four new areas (perceived fatigability, breathing and voice, sleep and rest, and vulnerability) identified in a qualitative study previously conducted by FundAME [27]. Perceived fatigability scores were similar in the three age groups, suggesting that fatigability is not related to aging or disease duration. Remarkably, perceived fatigability scores strongly worsened with disease severity, suggesting that they are actually related to motor neuron reserve, in line with previous studies [37, 38]. Breathing and voice and vulnerability scores were higher in the group of patients aged 0–7 years than in the other age groups, indicating a higher impact in younger patients. Interestingly, a considerable increase in their scores was only appreciable in severely ill patients, suggesting that these items are especially relevant in this subgroup of patients. The percentage of patients who woke up during the night to ask for help and to be able to move in bed (from "very often'' to "always'') was higher in the group of patients aged 8–17 years, showing a greater impact on sleep and rest in patients of that age group. Exploratory factor analysis of perceived fatigability items identified six factors, with the use of hands, sitting position, and body movements being the three most relevant. These three factors were related to the three main areas included in the design of the group of items (those related to the use of hands, sitting position, and body movements).

Table 6 Rotated factor pattern of perceived fatigability items

	Factor 1		Factor 2		Factor 3		Factor 4		Factor 5		Factor 6	
1. Take notes on paper	75	*	15		−1		10		20		45	
2. Send text messages	24		−7		14		8		17		92	*
3. Combing your hair	81	*	−6		21		11		−12		5	
4. Brush your teeth	88	*	4		3		−5		5		1	
5. Eat alone	85	*	17		7		0		11		14	
6. Joystick use	19		-5		−3		5		82	*	21	
7. Move in a wheelchair	−6		22		−10		−9		84	*	0	
8. Straighten up in the seat when your back is supported	43		81	*	−4		−6		4		−9	
9. Maintain head position	−2		91	*	−2		−8		0		2	
10. Repeat specific movements when you are playing	−1		87	*	−7		7		15		−1	
11. Climb an entire flight of stairs	−8		8		32		86	*	10		−1	
12. Keep up when you walk	16		−14		28		82	*	−16		14	
13. Get up from the seat or bed	12		−4		90	*	25		−14		10	
14. Get in or out of the car	14		−10		84	*	41		−1		6	

Values are multiplied by 100 and rounded to the nearest integer. *Values greater than 0.6

Moreover, only one item showed an item-total correlation below 0.4, indicating that it makes sense to calculate a total dimension score for this group of items, although it would be good to explore the possibility of getting on top of that, other three-dimension scores. Perceived fatigability showed good reliability and discriminant validity. However, the analysis of the sensitivity to change had the same pitfalls as the patient version of the SMAIS. The factorial structure of the breathing and voice items was logical, according to the original design of these items, with one main question ("Could you talk?") that formed a separate factor. Those items showed very good reliability and discriminant validity. However, they failed in the assessment of sensitivity to change. The exploratory factor analysis of vulnerability items identified three relevant factors that were related to the three main areas included in the design of the group of items: choking, infection risk, and the ability to change posture. Thus, the factorial structure fits with the design of the questionnaire, which assesses the not usually explored but relevant area of patients with SMA. The reliability of vulnerability was fairly good, although not reaching 0.90. The discriminant validity of vulnerability was also good, and the sensitivity to changes could be proved with CGI-I. According to the analysis presented in the results section, it was not possible to establish an overall score with the three items assessing sleep and rest.

The Neuro-QoL Fatigue CAT mean T-scores were similar for all patients in the study across all age groups. However, adult patients had mean T-scores slightly lower than the reference population (outpatients with neurological

Table 7 Rotated factor pattern of breathing and voice items

	Factor 1		Factor 2		Factor 3	
1. Could you talk?	26		8		94	*
2. Can you cough effectively (coughing up mucus)?	13		89	*	19	
3. How much difficulty do you have to make yourself understood when speaking with an acquaintance?	84	*	24		34	
4. How much difficulty do you have in making yourself understood when talking to a stranger?	89	*	18		17	
5. How much difficulty do you have to make yourself understood when talking on the phone?	85	*	34		23	
6. How much difficulty do you have participating in group conversations?	88	*	32		9	
7. How much difficulty do you have to make yourself understood with background noise?	60		62	*	3	
8. Do you have changes in the quality of your voice apparently caused by discharge from the throat	37		69	*	−4	

Values are multiplied by 100 and rounded to the nearest integer. *Values greater than 0.6

Table 8 Rotated factor pattern of sleep and rest items

	Factor 1		Factor 2		Factor 3	
1. Have you woken up during the night to ask for help and to be able to move in bed?	2		99	*	11	
2. If you use a ventilation machine, did you wake up during the night because it bothered you?	3		11		99	*
3. Have you woke up tired after sleeping at night?	100	*	2		3	

Values are multiplied by 100 and rounded to the nearest integer. *Values greater than 0.6

disorders) [24]. The Neuro-QoL Pediatric Pain mean T-score was lower than that in the reference population (children with epilepsy and muscular dystrophy), but within the 1-SD limit [39]. In the case of the PROMIS adult Pain Interference CAT, the mean T-score was similar to that in the general population [26]. Considering the different reference populations applied in the calculation of T-scores, pain seemed to be more relevant for children than for adults, and vice versa for fatigue.

Overall, this study shows the overall good reliability and discriminant validity of this set of measurements in a large cohort of patients routinely followed-up in neuromuscular clinics. Furthermore, the longitudinal validity was also shown for a few of its items. All this suggests its usefulness in routine clinical practice to assess

Table 9 Rotated factor pattern of vulnerability items

	Factor 1		Factor 2		Factor 3		Factor 4	
1. How many times have you choked in the last month?	27		12		94	*	2	
2. Has the risk of choking made you always eat with your regular assistant?	76	*	13		29		22	
3. Has the risk of choking limited the type of food you eat in the company of someone other than you?	91	*	12		7		4	
4. Has the risk of choking limited the type of food you can eat alone?	92	*	19		24		3	
5. During the last month, has the risk of having respiratory infections limited your school/social life?	12		13		2		98	*
6. During the past month, how many times have you been unable to regain an upright posture?	7		94	*	16		7	
7. During the last month of not being able to recover your posture, have you felt at risk?	27		12		94	*	2	

domains that are not captured by current motor function scales.

The main limitations of the study are a short follow-up period and a highly heterogeneous sample of patients with a wide range of ages and disabilities, with and without treatment. This may have affected the longitudinal validity of a few items. Considering their diverse clinical characteristics and symptoms, children and adults might require different measurement instruments. The effect of treatment could affect the discriminant validity according to SMA type, which could explain the lack of differences in the scores found between some subtypes. However, this should not affect its validity according to functionality and CGI-S score, as the latter already captures the treatment effects. In addition, no information was collected on standard non-pharmacological care received by patients, such as rehabilitation, including that could have an impact on the different dimensions assessed.

CONCLUSIONS

Understanding the impact of disease from patient and caregiver perspectives may facilitate shared decision-making in SMA care. This new set of instruments is a comprehensive and reliable tool to assess the severity of symptoms in clinical practice. Further studies, stratified by patient subgroup (e.g., children versus adults, ambulant versus non-ambulant, treated versus non-treated) and with longer follow-up are needed to determine its sensitivity to detect changes. Moreover, the validation of this tool against other clinical tests or biomarkers may help to confirm its construct validity.

Declarations

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version to be published; all agreed on the journal to which the article was submitted; and all agreed to be held accountable for all aspects of the work.

Conflict of Interests María Branas-Pampillón, Rosana Cabello-Moruno, Paola Díaz-Abós, Victoria Sánchez-Menéndez, and Jorge Maurino are employees of Roche Farma, Spain. Pablo Rebollo is an employee of IQVIA Spain. Juan F Vázquez-Costa, Julita Medina-Cantillo, Mónica Povedano, Inmaculada Pitarch-Castellano, Mercedes López-Lobato, Joaquín A Fernández-Ramos, Miguel Lafuente-Hidalgo, Ricard Rojas-García, José M Caballero-Caballero, Ignacio Málaga, Jesús Eirís-Puñal, Mencía De Lemus, María G Cattinari, and Marco Madruga-Garrido declare no conflict of interest.

Compliance with Ethics Guidelines The SMA-TOOL study was conducted in accordance with the Good Clinical Practice Guidelines of the International Conference on Harmonisation and with the ethical principles of the Declaration of Helsinki and was approved by the investigational review board of the Hospital Universitari de Bellvitge (Barcelona, Spain; reference code: PR264/20). Written informed consent was obtained from all subjects.

Data Availability Qualified researchers may request access to individual patient-level data through the corresponding author. The datasets generated during the analysis of the study are available from the corresponding author on reasonable request.

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