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INTRODUCTION

There is an urgent need of outcome measures for assessing disease progression and response to treatment in adolescents and adult patients with Spinal Muscular Atrophy (SMA).

OBJECTIVE

The SMA Life study aims to develop and validate a new clinical multidimensional tool “toolkit” to assess key motor and beyond motor function dimensions relevant to the functional status of adolescent and adult patients with spinal muscular atrophy (SMA).

MATERIAL AND METHODS

This prospective, non-interventional ongoing study is being conducted at five centers in Spain and includes patients aged 16 years or older with a confirmed diagnosis of SMA 5q. 107 patients were recruited and 106 eligible for evaluation. A panel of neurologists, physiatrists, and patient representatives designed a 53-item clinical tool assessing seven key dimensions (bulbar function, breathing, axial, lower and upper limb function, fatigability, and other symptoms). This instrument was administered at baseline, 12 months, and 24 months. An interim Rasch analysis was conducted after the initial visit to evaluate its psychometric properties, such as model fit, dependency, reliability and construct validity.

RESULTS

After a Rasch analysis, 35 selected items were chosen, along with 2 objective clinical measures (myopinch and FVC) and signs of lower motor neuron (LMN) involvement in 4 regions (bulbar, respiratory, axial, and upper limbs). A final Rasch analysis was performed with the 41 items (Figure 1) to estimate an overall score with different weightings for each item (Table 1). Additionally, an unweighted global score of 0-100 was estimated (Table 2). The Toolkit items demonstrated local independence according to the adjusted Q3 statistic, with a mean (SD) of 0.0001 (0.1542), and a MADaQ3 close to 0.1 with a significant adjusted p-value using Holm's method ($p < 0.001$). Reliability: Cronbach's alpha was excellent at 0.939, and for all domains, the intraclass correlation coefficient (ICC) was between good and excellent ($ICC > 0.75$).

Table 1. Mean score, item difficulty, infit and weight for each item of the Toolkit

Item	Mean(SD)	Item difficulty*	Infit	Weight (p=100) ***
BULB1	1.972 (0.216)	-5.301	0.854	76.6
BULB2	1.925 (0.299)	-5.100	0.706	34
BULB3	1.925 (0.299)	-5.100	0.797	59.8
BULB4	1.906 (0.325)	-5.025	0.890	86.1
BULB6	1.925 (0.329)	-4.749	0.881	83.8
BULB12	1.943 (0.333)	-4.619	1.624	0.8
BULB10	1.887 (0.373)	-4.603	0.965	98.5
AX1	1.840 (0.417)	-4.429	0.691	30.2
BULB11	1.887 (0.398)	-4.398	1.459	7.2
BULB5	1.792 (0.472)	-4.060	0.823	67.5
MS2	1.811 (0.480)	-3.983	0.998	100
MS3	1.802 (0.486)	-3.951	1.031	98.8
BULB7	1.755 (0.513)	-3.788	0.945	96.3
MS1	1.698 (0.555)	-3.487	0.981	99.5
BULB14	1.689 (0.558)	-3.455	1.337	24.2
AX2	1.708 (0.568)	-3.433	0.909	90.1
BULB13	1.547 (0.588)	-2.956	1.093	89.7
FAT1	1.575 (0.647)	-2.800	0.997	100
MS5	1.462 (0.783)	-2.134	0.945	96.3
AX4	1.415 (0.815)	-1.930	1.121	83.4
MS6	1.396 (0.789)	-1.885	0.754	47
MS4	1.396 (0.824)	-1.853	1.063	95.1
AX3	1.330 (0.825)	-1.603	1.069	94.3
BULB9	1.226 (0.929)	-1.178	1.737	0.1
BULBYN	1.094 (1.000)	-0.693	1.294	33.9
FVC	1.100 (0.859)	-0.567	1.007	99.9
MS7	1.028 (0.889)	-0.368	1.024	99.3
Myopinch	1.000 (0.711)	0.079	1.159	72.9
BULB80YN	0.849 (0.993)	0.293	1.503	4.3
MS10	0.774 (0.939)	0.668	0.967	98.7
MS14	0.745 (0.895)	0.839	0.523	5.8
MS	0.745 (0.874)	0.864	0.594	12.7
MI1	0.670 (0.902)	1.163	0.582	11.3
MI7	0.613 (0.823)	1.511	0.811	64.1
AXYN	0.528 (0.886)	1.816	1.490	5
MI6	0.538 (0.841)	1.822	0.523	5.8
MI9	0.472 (0.795)	2.176	0.566	9.5
MI11	0.292 (0.534)	3.729	0.696	31.4
MSYN	0.132 (0.499)	4.231	0.978	99.4
MI12	0.151 (0.385)	5.151	0.977	99.4
MI13	0.066 (0.317)	5.294	1.167	70.7

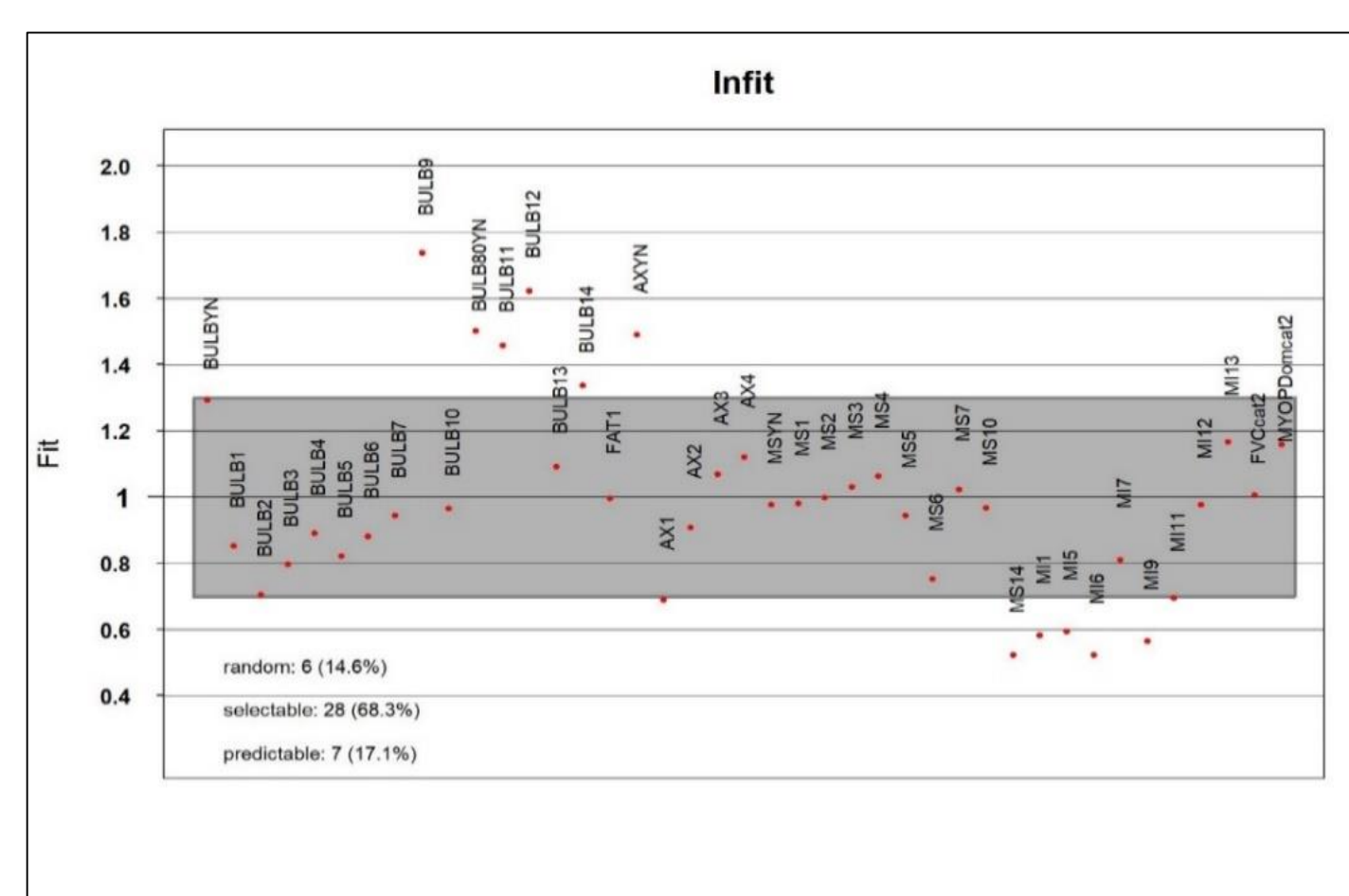
Table 2. Scores (0-100) of each area of the Toolkit

Score per Area*		Absolute score	Relative score (0-100)
Bulbar Impairment (11 items)	Mean (SD)	19,0 (3,8)	86,3 (17,2)
Respiratory impairment (5 items)	Mean (SD)	7,9 (2,0)	79,2 (20,4)
Axial function (5 items)	Mean (SD)	6,8 (2,7)	68,2 (27,2)
Upper limb movility (10 items)	Mean (SD)	12,2 (5,5)	61,2 (27,7)
Lower limb mobility (8 items)	Mean (SD)	3,5 (4,8)	22,2 (30,2)
Fatigability (4 items)	Mean (SD)	5,6 (2,1)	70,3 (26,0)

Table 3. Spearman correlation coefficients between global scores and dimension scores and HFMSE, RULM and SMAIS

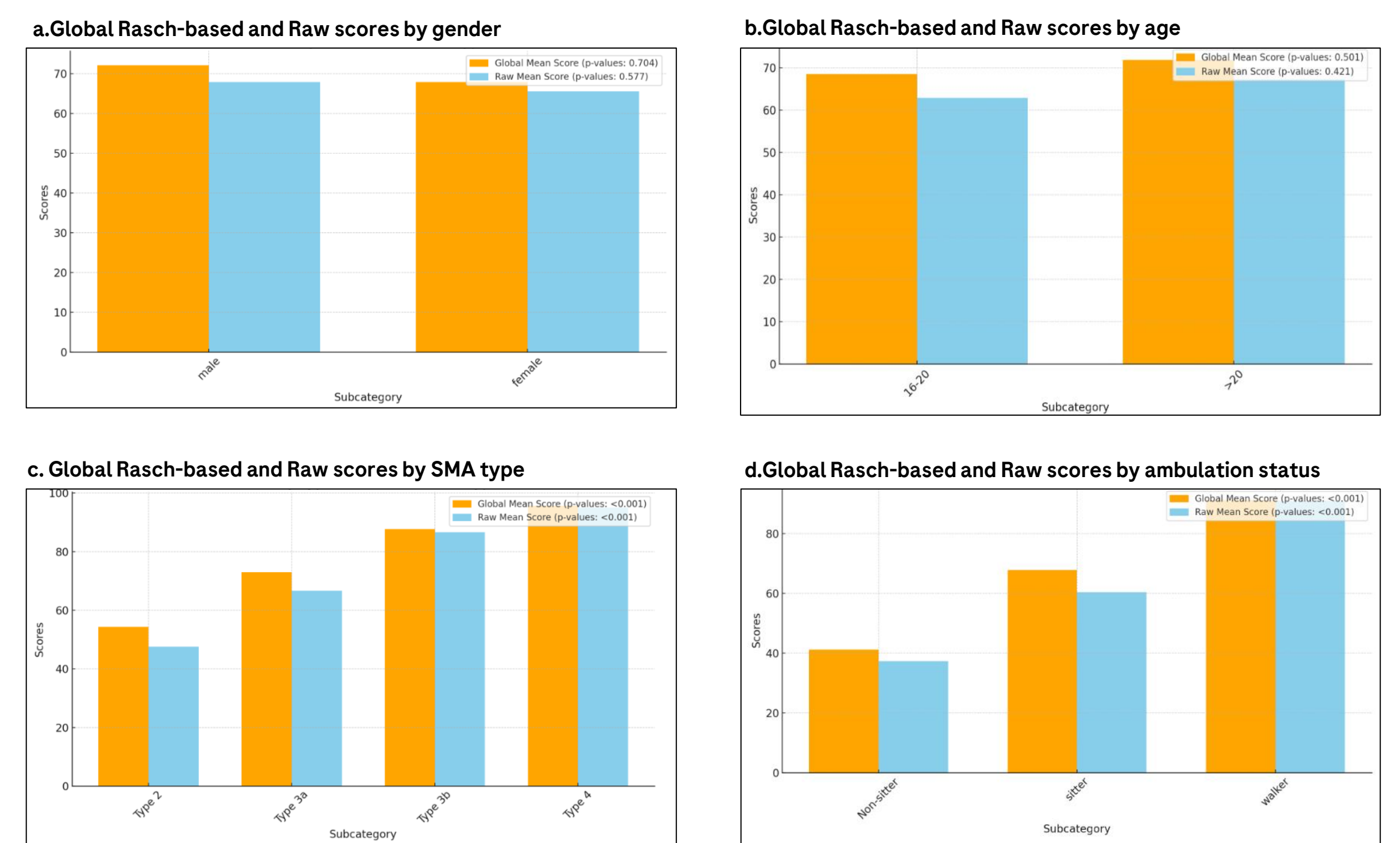
Test to correlate		HFMSE		RULM		SMAIS	
		Pearson	Spearman	Pearson	Spearman	Pearson	Spearman
Global score of the "toolkit"	r	0.8038	0.9208	0.9019	0.9372	0.848	0.9097
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	83	83	93	93	54	54
Raw score	r	0.8892	0.9228	0.9222	0.9218	0.8588	0.8832
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	83	83	93	93	54	54
Bulbar dimension	r	0.5855	0.7212	0.6525	0.7141	0.5475	0.6141
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	94	94	103	103	62	62
Vital dimension	r	0.7189	0.7412	0.7213	0.7115	0.6021	0.5406
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	94	94	103	103	62	62
Axial dimension	r	0.7548	0.8504	0.8103	0.8374	0.7297	0.76
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	94	94	103	103	62	62
Superior mobility dimension	r	0.7923	0.866	0.9226	0.9399	0.8788	0.8893
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	94	94	103	103	62	62
Inferior mobility dimension	r	0.9672	0.8891	0.8197	0.8527	0.7172	0.7226
	p-value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	N valid	94	94	103	103	62	62

Figure 1. Final Rasch analysis with 41 items of the Toolkit



Divergent validity: The stability of raw and Rasch-based scores and their divergent validity were demonstrated by comparing scores based on various characteristics (Figures 2a to 2d).

Figures 2a to 2D. Differences on global Rasch-based and raw scores by different groups: gender, age, SMA type, functional classification and current ambulation stage.



Convergent validity: All scores and dimensions showed strong or very strong correlation with other scales, with floor and ceiling effects observed in the HFMSE and RULM scales (Table 3, Figures 3 and 4)

Figure 3. Correlation figures MMSS score with RULM and SMAIS

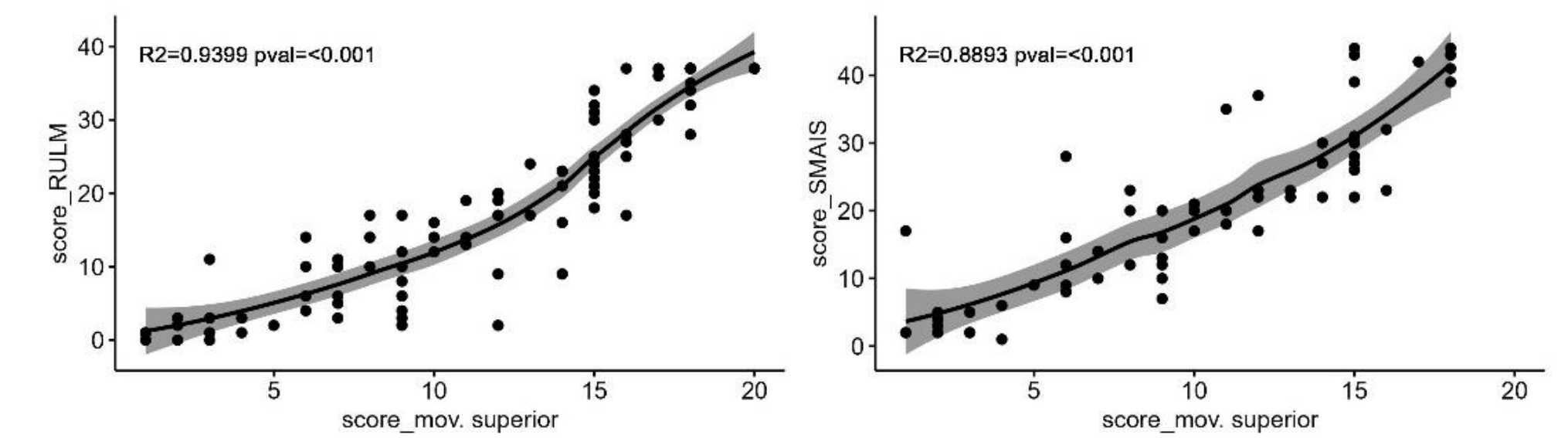
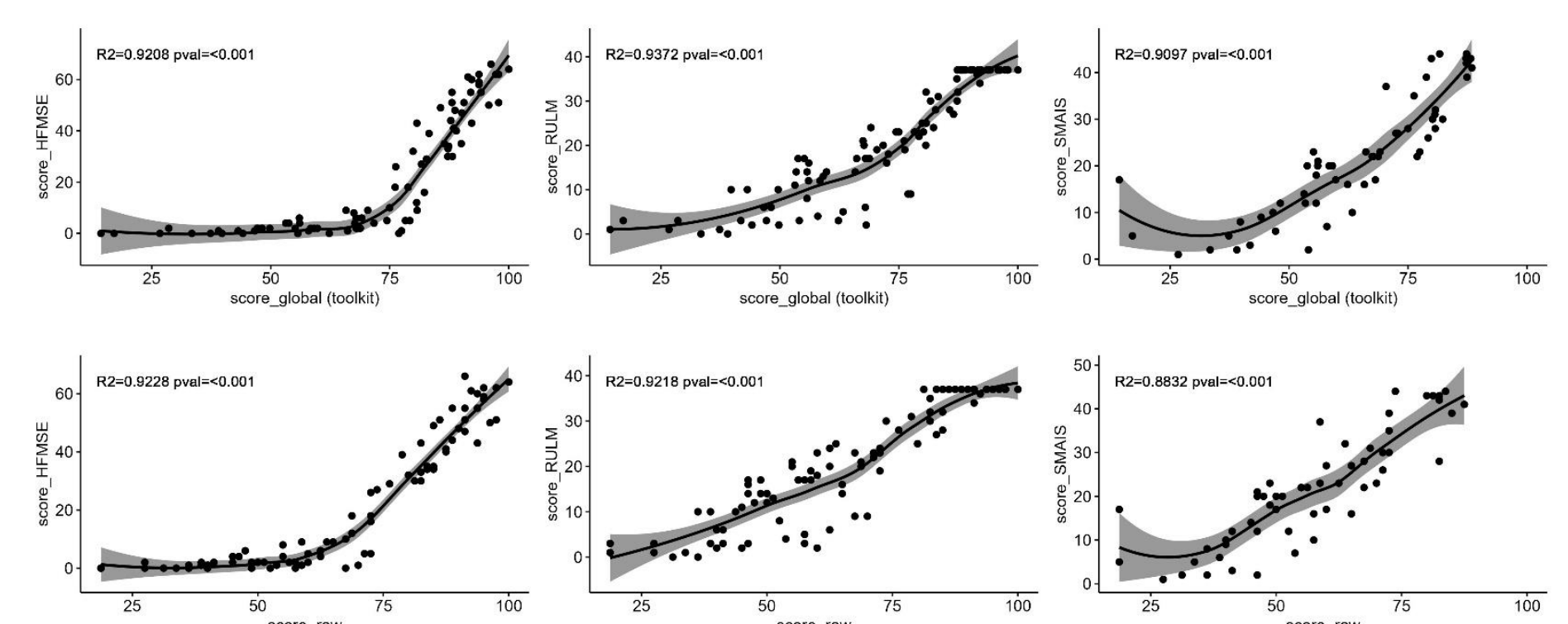


Figure 4. Correlation figures total score and HFMSE, RULM and SMAIS



CONCLUSIONS

This interim baseline validation showed a reliable 41-item clinical tool with strong psychometric properties, effectively assessing functional status in adolescents and adults with SMA. Further prospective assessments are necessary to confirm these findings supporting its use in clinical and research settings.

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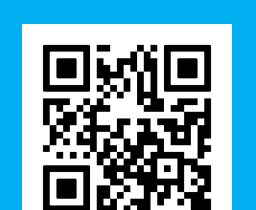


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DISCLOSURES

AT, EG, RC and SG are employees of Roche Pharma Spain. PR & AR are employees of IQVIA Spain. JFVC has received personal fees from Biogen and Roche outside the submitted work. None of the other authors report any conflict of interest.



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Supplemental materials

Items included in the “toolkit”:

▪ Bulbar function

Does the patient have clinical signs of bulbar disease?

Yes/No

Do not continue if the answer is negative

To what extent can the patient perform the following activities of daily living?

1. Make themselves understood when talking to an acquaintance?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

2. Make himself/herself understood when talking to a stranger?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

3. Make himself/herself understood when speaking on the phone?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

4. Talk for hours?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

5. Speak louder to make himself/herself understood in a noisy room?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

6. Drink liquids without choking or coughing?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

7. Swallow pills?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

8. Does the patient notice excess saliva in the mouth?

Never/occasionally/continually

9. Does the patient need nutritional supplements (nutritional shakes)?

He/she doesn't need them/they are a nutritional supplement/they make up the majority of your diet

▪ Axial function

Does the patient have clinical signs of NIM in the axial region?

Yes/No

Do not continue if the answer is negative

1. Shake the head to say yes or no?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

2. Does the patient need to rest his head on the headrest when sitting in the wheelchair?

Needs support continually/needs support at times/does not need support

3. Does the patient need to lean on the backrest when sitting in the wheelchair?

Needs support continually/needs support at times/does not need support To what extent can the patient perform the following activities of daily living?

4. Keep sitting in the toilet?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

▪ Breathing function

Does the patient have a vital capacity greater than 80?

Yes/No

Do not continue if the answer is positive

1. Does the patient have a feeling of shortness of breath?

At rest/when carrying out activities or efforts/never

2. Can the patient cough effectively (expelling mucus) in daily life?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

3. Does the patient use cough assist?

Daily/occasionally (with respiratory infections)/never

4. Does the patient use ventilatory support (invasive and non-invasive ventilation)?

More than 16 h a day/8–16 h a day (at night and occasionally during the day)/less than 8 h a day

▪ Upper limb function

Does the patient have clinical signs of lower motor neuron involvement in the upper limbs?

Yes/No

Do not continue if the answer is negative

1. Use a touchscreen phone or tablet?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

2. Does the patient use the electric chair joystick?

Unable to do it without help/can do it with difficulty or needs an adapted joystick/can do it without difficulty To what extent can the patient perform the following activities of daily living?

3. Use a computer?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

4. Press a switch on the wall (light, elevator, etc.)?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

5. Brush his/her teeth with any type of toothbrush?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

6. Eat and drink independently?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

7. Use a knife and fork (to cut food)?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

8. Move around his/her house in a non-motorized wheelchair?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

9. Reaching for objects on a high shelf:

Unable to do it without help / can do it with difficulty (includes using alternative methods but not help from others) / can do it without difficulty

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Supplemental materials

Lower limb function

To what extent can the patient perform the following activities of daily living?

1. Stay up?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

2. Roll over in bed?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

3. Walk around his/her house?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

4. Can he/she wash his/her body in the shower?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

5. Walk down the street on a flat surface?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

6. Go up a stretch of staircases?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

7. Get up from the ground?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

8. Run?

Incapable of doing it without help/can do it with difficulty (includes the use of substitute methods, but not help from third parties)/can do it without difficulty

Fatigability

1. How long does it take the patient to complete a meal?

Same as the rest of the people (about 30 min)/up to 15 min more than the rest (about 45 min)/more than 15 min more than the rest (more than 45 min)

2. If the patient has applied more effort than usual, does the fatigue last until the next day?

Often/sometimes/never

3. Are there any activities that the patient has been able to do in the morning and that he/she has not been able to do in the afternoon or at night (has he/she run out of battery throughout the day)?

Often/sometimes/never

4. When the patient performs a repetitive daily task (such as writing or walking), do they notice that, after doing it for a while, they perform it increasingly worse or have to stop?

Frequently / sometimes / never

5. Have they been able to maintain their level of energy and activity throughout the entire day?

Frequently / sometimes / never

Other

1. Does he/she have cramps?

Often/sometimes/never

2. Does his/her functionality worsen with cold or humidity?

A lot/some/nothing

