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Upper limb function changes over 12 months in untreated SMA II and III individuals: an item-level analysis using the Revised Upper Limb Module

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ABSTRACT

The Revised upper limb module (RULM) has been increasingly used in clinical trials and in clinical settings. The aim of this study was to use the 'shift analysis' to assess the patterns of lost or gained abilities for each item on the RULM in an untreated cohort, stratified by SMA type, age, *SMN2* copy number, and motor functional status. The analysis was performed on 222 12-month paired assessments from 129 individuals (115 assessment from type II and 107 from type III) who had at least two assessments at yearly intervals. There was a loss of one or more activities in 54% in type II and in 29% type III. A gain of one or more activities was found in 42% type II and in 22% type III. There were concomitant gains and losses in 27% in SMA II and in 9% in SMA III. Our results, measuring the number of abilities that are lost or gained, provide an additional method of detecting changes that can be used for the interpretation of the longitudinal data collected in treated SMA individuals.

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1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neurodegenerative condition caused by mutations in the survival motor neuron 1 gene (*SMN1*). This disorder leads to the degeneration of α-motor neurons found in the spinal cord and brain stem. Traditionally, before the advent of disease modifying therapies, SMA was categorized into types 0-IV [1]. Individual with type II SMA, typically had onset of symptoms between 6 and 18 months of age and never achieved the ability to walk independently. In type III SMA, associated with onset after the age of 18 months, independent ambulation was achieved but there was also progression of weakness and loss of function over time [2,3]. In most of the previous studies, disease progression has been assessed using changes in total scores of functional scales such as the Hammersmith Functional Motor Scale Expanded (HFMSE) but also, more recently, using the Revised Upper Limb Module (RULM), a scale specifically designed to assess upper limb function in SMA [4,5].

Several studies have shown that the overall motor progression rate varies both between different types and within each type. Specifically, the natural history progression patterns over 12 and 24 months differ between type II and type III, as well as between ambulant and non-ambulant type III individuals [6-17].

In recent years, there has been a growing interest on employing alternative methods to better understand the impact of gain or loss of functional abilities, notably through shift analysis, which categorizes changes into a binary system—either transitioning from an inability to perform a task to being able to do so with or without compensations, or vice versa [18-20]. This approach becomes particularly pertinent, especially in scenarios where changes on the RULM, such as those observed in type III at 12 and 24 months, are minimal [8,14,15]. The use of such approach is strongly supported not only by Rasch analysis that has suggested that a number of items are more appropriate using a binary system, but also by individuals and carers who report that the change in the modality used to perform the activity (compensation or non-compensation) is far less relevant than a partial gain or complete loss of the activity [21]. Understanding the patterns of lost or gained abilities therefore becomes crucial in accurately reflecting the true impact of disease progression in these individuals.

The aim of this analysis is to comprehensively examine the patterns of lost or gained abilities for each item on the RULM in an untreated cohort of SMA type II and III, stratified by SMA type, age, *SMN2* copy number, and motor functional status.

2. Materials and methods

A retrospective study was conducted by using prospectively collected data from the International SMA registry group [22]. The study examined data collected between July 2014 and February 2024 and included individuals with genetically confirmed SMA who were clinically diagnosed with type II or III, with an age at baseline $\geq$ 30 months, had not received any disease modifying therapy (DMTs), and had undergone at least two assessments within a one-year follow-up period (supplementary figure 1). The analysis was performed solely on anonymous and de-identified data, and clinical investigations were conducted in accordance with the Declaration of Helsinki principles. Written informed consent and/or assent was obtained as appropriate from all participants or their guardians, and the study was approved by institutional review boards in compliance with ethical requirements. The coordinating centres' IRB protocol number is 0024731/22.

2.1. RULM

The RULM was developed as a comprehensive tool to evaluate upper limb function in individuals with SMA, with the aim of improving upon the previously used upper limb module (ULM), that was originally developed to assess young and weak infants with type II and had a ceiling effect in stronger individuals [5]. The revised module includes additional tasks for the ambulant/stronger population. The RULM comprises an entry item and 19 activities that assess various upper limb functions on a 3-point scoring system, with a score range of 0 to 2 indicating the level of functional ability. The scores range from 0 to 37 with higher numbers indicating a higher level of function. The RULM's validity and reliability have been established, and it is being used as an outcome measure in clinical trials [5,23]. For the purposes of this research, missing data at the item level resulted in the exclusion of the entire assessment.

2.2. Statistical analysis

In order to investigate the differences in RULM changes at 12 months in type II and type III individuals, we analyzed a longitudinal dataset of paired visits at 12 months. To maximize participant populations, we considered each paired assessment according to the time the assessments were performed. As performed in previous studies, participants with multiple assessments at different ages and different stages were represented independently in each subgroup [24].

Quantitative variables were described using minimum, maximum, range, mean, and standard deviation measures.

Taking into consideration pairs of RULM assessments 12 months apart, each item of the scale was classified as follows:

- Shift up (gain of function): item scores increased from 0 to either 1 or 2;
- No change: item scores remained the same or had changes between 1 and 2 or vice-versa;
- Shift down (loss of function): item scores decreased from 1 or 2 to 0.

Frequency of item distribution and loss progression was calculated on each item.

3. Results

The cohort included 222 12-month paired assessments from 129 individuals who had at least two assessments within a one-year follow-up period. Table 1 shows information on patients' assessments at baseline.

At 12 months, in SMA II, there was a loss of one or more activities in 63 of the 115 paired assessments (54%) and a gain of one or more activities in 49 of the 115 (42%). In 31 of the 115 assessments (27%) there were concomitant gains and losses. Individuals who gained more than 2 points in the RULM had a mean of 0 activities lost and 3.2 gained, while those who lost more than 2 points had 0.24 activities gained and 3.1 lost. At baseline, 14 of 115 assessments (12%) had total RULM score of 0 and none had a maximum score.

At 12 months, in SMA III, there was a loss of one or more activities in 31 of the 107 paired assessments (29%) and a gain of one or more activities in 24 of the 107 (22%). In 10 of the 107 assessments (9%) there were concomitant gains and losses. Individuals who gained more than 2 points in the RULM had a mean of 0.10 activities lost and 2.80 gained, while those who lost more than 2 points had 0.12 activities gained and 2.41 lost. At baseline, none of the 107 assessments had total score of 0 and 35 (32.71%) had a maximum score.

Table 1
Information on patients' assessments at baseline.

	SMA II (n=115)	SMA III (n=107)
Age (Mean (SD)) – Median [Range]	17.1 (11.0) – 13.5 [2.69, 59.0]	22.9 (16.6) – 17.2 [2.88, 66.2]
Sex assigned at birth assigned at birth (N, %)		
Female (N (%))	57 (49.6%)	52 (48.6%)
Male (N (%))	58 (50.4%)	55 (51.4%)
Total RULM (Mean (SD)) – Median [Range]	12.1 (8.00) – 13.0 [0, 35.0]	29.4 (7.87) – 32.0 [12.0, 37.0]
Functional status (N, %)		
Non sitter (N (%))	39 (33.9%)	4 (3.7%)
Sitter (N (%))	76 (66.1%)	41 (38.3%)
Walker (N (%))	0 (0%)	62 (57.9%)
SMN2 copy number (N, %)		
2	25 (21.7%)	6 (5.6%)
3	63 (54.8%)	43 (40.2%)
4+	3 (2.6%)	44 (41.1%)
Unknown	24 (20.8%)	14 (13.1%)

Table 2
Number of activities lost or gained in relation to the overall RULM change. Key to table: The overall change in RULM is determined by the number of activities lost, gained, or the net result of simultaneous gains and losses. Specific details on the exact number of gains, losses, or concurrent gains and losses can be found in the previous paragraph.

	SMA II						
	<-2 (N=21)	-2 (N=11)	-1 (N=16)	0 (N=32)	1 (N=17)	2 (N=13)	>2 (N=5)
N° activities lost							
Mean	3.10	1.27	1.00	0.34	0.82	0.23	0
(SD)	(1.41)	(1.01)	(0.730)	(0.545)	(0.951)	(0.439)	(0)
Median	3.00	1.00	1.00	0	0	0	0
[Min, Max]	[1.00, 6.00]	[0, 3.00]	[0, 2.00]	[0, 2.00]	[0, 2.00]	[0, 1.00]	[0, 0]
N° activities gained							
Mean	0.24	0.27	0.37	0.41	1.24	1.54	3.20
(SD)	(0.539)	(0.647)	(0.619)	(0.712)	(1.03)	(1.13)	(0.837)
Median	0	0	0	0	1.00	1.00	3.00
[Min, Max]	[0, 2.00]	[0, 2.00]	[0, 2.00]	[0, 2.00]	[0, 3.00]	[0, 4.00]	[2.00, 4.00]
	SMA III						
	<-2 (N=17)	-2 (N=12)	-1 (N=11)	0 (N=40)	1 (N=10)	2 (N=7)	>2 (N=10)
N° activities lost							
Mean	2.41	0.67	0.36	0.05	0.40	0	0.10
(SD)	(1.33)	(0.888)	(0.674)	(0.22)	(0.70)	(0)	(0.32)
Median	2.00	0	0	0	0	0	0
[Min, Max]	[1.00, 5.00]	[0, 2.00]	[0, 2.00]	[0, 1.00]	[0, 2.00]	[0, 0]	[0, 1.00]
N° activities gained							
Mean	0.12	0.25	0.18	0.08	0.40	0.29	2.80
(SD)	(0.332)	(0.452)	(0.405)	(0.267)	(0.699)	(0.488)	(1.81)
Median	0	0	0	0	0	0	2.00
[Min, Max]	[0, 1.00]	[0, 1.00]	[0, 1.00]	[0, 1.00]	[0, 2.00]	[0, 1.00]	[0, 5.00]

Table 2 reports the mean and median number of activities lost and gained subgrouped by the overall RULM change.

3.1. Shift of total scores and SMA type: individual item

At baseline, none of the Type II individuals were able to complete all RULM items. Regardless of age, most SMA type II individuals failed to perform items weighing over 500 grams at baseline. The distribution of unperformed items at baseline appeared to be age-dependent.

At baseline, the majority (>80%) of SMA type III individuals could complete all RULM items, except for shoulder abduction 1 kg.

A frequency analysis to evaluate which abilities were achieved or lost at 12 months on the RULM was conducted both across the entire cohort and in type II and III separately (table 3).

Supplementary table 1 show details of the individual items shifted up, down or remaining stable after 12 months categorized into three functional domains of upper limb function [25] and subdivided by SMA type and age at baseline.

Table 4 shows details of the individual items shifted up, down or remaining stable after 12 months subdivided by SMA type and functional status at baseline.

Supplementary table 2 show details of the individual items shifted up, down or remaining stable after 12 months categorized into three functional domains of upper limb function [25] and subdivided by SMA type and functional status at baseline.

Table 5 shows details of the individual items shifted up, down or remaining stable after 12 months subdivided by SMA type and entry item at baseline.

Supplementary table 3 show details of the individual items shifted up, down or remaining stable after 12 months categorized into three functional domains of upper limb function [25] and subdivided by SMA type and entry item at baseline.

4. Discussion

'Shift analysis', providing additional information on gains and losses of individual activities, has been increasingly used in clinical trials in Duchenne Muscular dystrophy (DMD) and has also applied to the Hammersmith Functional Motor Scale Expanded in type II SMA patients [18,19]. Here we report its application to the RULM

Table 3
Details of the frequency analysis at 12-month change from baseline for individual items subdivided by SMA type and age. Key to table: Dark red cells represent >10% of negative shifts (from score 2 to score 0 or from score 1 to score 0), light red cells represent 0-9% negative shifts. Dark green cells represent >10% of positive shifts (from score 0 to score 2 or from score 0 to score 1), light green cells represent 0-9% positive shifts.

	SMA II											
	<5 years (N=5)			5-9 years (N=21)			10-17 years (N=54)			>18 years (N=36)		
Items	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month
B. Hands lap to table	0%	0%	0%	0%	0%	0%	15%	11.3%	5.7%	58%	8.3%	2.8%
C. Trace path	20%	0%	20.0%	0%	0%	0%	6%	1.9%	1.9%	42%	2.8%	2.8%
D. Pick up tokens	0%	0%	0%	5%	0%	0%	6%	0%	0%	36%	5.6%	0%
E. Tokens in cup	20%	0%	20.0%	0%	9.5%	0%	20%	9.4%	7.5%	61%	13.9%	2.8%
F. Reach to side	60%	20.0%	0%	48%	9.5%	4.8%	72%	15.1%	5.7%	94%	2.8%	8.3%
G. Push on light	80%	0%	40.0%	19%	4.8%	9.5%	22%	9.4%	1.9%	72%	13.9%	2.8%
H. Tear paper	100%	0%	0%	38%	0%	14.3%	32%	5.7%	11.3%	78%	2.8%	0%
I. Open Ziploc	100%	0%	0%	76%	4.8%	9.5%	72%	7.5%	18.9%	97%	2.8%	5.6%
J. Cup to mouth	60%	0%	20.0%	5%	9.5%	4.8%	15%	7.5%	5.7%	58%	11.1%	0%
K. Lift 200 g horizontally	60%	0%	20.0%	5%	19.0%	4.8%	20%	7.5%	5.7%	69%	8.3%	0%
L. Lift 500 g horizontally	80%	0%	0%	24%	23.8%	0%	35%	7.5%	9.4%	72%	8.3%	0%
M. Lift 200 g diagonally	60%	0%	0%	24%	4.8%	0%	39%	18.9%	7.5%	78%	5.6%	2.8%
N. Lift weight from lap	60%	0%	0%	33%	9.5%	4.8%	41%	7.5%	7.5%	75%	0%	0%
O. Shoulder abduction	80%	0%	0%	71%	14.3%	4.8%	98%	0%	0%	97%	2.8%	0%
P. Shoulder abduction 500 g	100%	0%	0%	86%	0%	4.8%	98%	0%	0%	97%	2.8%	0%
Q. Shoulder abduction 1 kg	100%	0%	0%	86%	4.8%	4.8%	98%	0%	0%	100%	0%	0%
R. Shoulder flexion	100%	0%	20.0%	57%	23.8%	4.8%	98%	0%	1.9%	94%	2.8%	0%
S. Shoulder flexion 500 g	100%	0%	20.0%	91%	0%	4.8%	98%	0%	0%	97%	2.8%	0%
T. Shoulder flexion 1 kg	100%	0%	0%	95%	0%	4.8%	100%	0%	1.9%	100%	0%	0%
	SMA III											
	<5 years (N=5)			5-9 years (N=21)			10-17 years (N=54)			>18 years (N=36)		
Items	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score = 0 at baseline	lost at 12 month	gain at 12 month
B. Hands lap to table	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
C. Trace path	20%	0%	20%	0%	0%	0%	0%	0%	0%	0%	0%	0%
D. Pick up tokens	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
E. Tokens in cup	0%	0%	0%	0%	0%	0%	0%	0%	0%	6%	8%	4%
F. Reach to side	0%	0%	0%	5%	0%	5%	10%	10%	3%	35%	2%	2%
G. Push on light	20%	0%	20%	0%	0%	0%	3%	0%	3%	2%	2%	2%
H. Tear paper	20%	0%	20%	0%	0%	0%	0%	0%	0%	0%	2%	0%
I. Open Ziploc	20%	0%	20%	0%	0%	0%	0%	3%	0%	15%	6%	4%
J. Cup to mouth	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	0%
K. Lift 200 g horizontally	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	2%	0%
L. Lift 500 g horizontally	0%	0%	0%	0%	0%	0%	0%	0%	0%	4%	4%	2%
M. Lift 200 g diagonally	0%	0%	0%	0%	0%	0%	3%	7%	3%	8%	4%	0%
N. Lift weight from lap	0%	0%	0%	0%	0%	0%	0%	3%	0%	6%	2%	4%
O. Shoulder abduction	0%	0%	0%	0%	0%	0%	27%	20%	0%	46%	8%	2%
P. Shoulder abduction 500 g	0%	0%	0%	0%	0%	0%	30%	13%	3%	50%	6%	4%
Q. Shoulder abduction 1 kg	80%	20%	60%	20%	10%	20%	57%	0%	0%	56%	2%	2%
R. Shoulder flexion	0%	0%	0%	5%	0%	5%	23%	10%	3%	44%	2%	0%
S. Shoulder flexion 500 g	20%	0%	20%	5%	0%	5%	37%	7%	0%	50%	6%	2%
T. Shoulder flexion 1 kg	60%	20%	40%	20%	10%	20%	50%	10%	10%	60%	0%	2%

in both type II and III patients, trying to establish patterns of gains and losses in relation to different variables.

Our results confirm, as previously observed when analysing raw total scores, that there are more changes in type II compared to type III, with the latter showing more stable findings over 12 months [8,15]. The pattern of activities susceptible to changes were dependent on functional abilities at baseline. In type II, most individuals already have a score of 0 on many items (such as opening Ziploc container and all the 6 final items involving more proximal abilities) therefore limiting the number of items in the scale which may show losses (shifts down) at follow up (table 3). This was also reflected by the fact that only very few individuals had an entry item of 6 or 5, reflecting antigravity movements at shoulder level (table 5). Items assessing abilities at middle domain were progressively lost with increasing age and, in parallel, with a progressive reduction of the score on the entry item, indicating a progression with a proximal to distal gradient.

In our cohort of untreated type II individuals, gains were overall less frequent and gains in more than one activity were more often observed in the very young children, probably as a result of development or increasing ability to lift heavier weights.

Table 4
Details of the frequency analysis at 12-month change from baseline for individual items subdivided by SMA type and functional status at baseline. Key to table: Dark red cells represent >10% of negative shifts (from score 2 to score 0 or from score 1 to score 0), light red cells represent 0-9% negative shifts. Dark green cells represent >10% of positive shifts (from score 0 to score 2 or from score 0 to score 1), light green cells represent 0-9% positive shifts.

	SMA II								
	Non Sitter (N=39)			Sitter (N=76)			Walker (N=0)		
Items	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month
B. Hands lap to table	69%	13%	5%	3%	5%	3%	N/A	N/A	N/A
C. Trace path	44%	3%	3%	3%	1%	3%	N/A	N/A	N/A
D. Pick up tokens	41%	5%	0%	1%	0%	0%	N/A	N/A	N/A
E. Tokens in cup	69%	15%	8%	9%	8%	4%	N/A	N/A	N/A
F. Reach to side	95%	5%	3%	63%	13%	8%	N/A	N/A	N/A
G. Push on light	74%	8%	3%	21%	11%	7%	N/A	N/A	N/A
H. Tear paper	90%	3%	5%	30%	4%	9%	N/A	N/A	N/A
I. Open Ziploc	97%	3%	5%	74%	7%	16%	N/A	N/A	N/A
J. Cup to mouth	64%	15%	5%	9%	5%	4%	N/A	N/A	N/A
K. Lift 200 g horizontally	77%	3%	3%	13%	13%	5%	N/A	N/A	N/A
L. Lift 500 g horizontally	87%	3%	5%	26%	14%	4%	N/A	N/A	N/A
M. Lift 200 g diagonally	85%	10%	3%	30%	12%	5%	N/A	N/A	N/A
N. Lift weight from lap	90%	3%	3%	30%	7%	5%	N/A	N/A	N/A
O. Shoulder abduction	100%	0%	0%	88%	5%	1%	N/A	N/A	N/A
P. Shoulder abduction 500 g	100%	0%	0%	93%	1%	1%	N/A	N/A	N/A
Q. Shoulder abduction 1 kg	100%	0%	0%	95%	1%	1%	N/A	N/A	N/A
R. Shoulder flexion	97%	3%	0%	86%	7%	4%	N/A	N/A	N/A
S. Shoulder flexion 500 g	100%	0%	0%	95%	1%	3%	N/A	N/A	N/A
T. Shoulder flexion 1 kg	100%	0%	0%	99%	0%	3%	N/A	N/A	N/A
	SMA III								
	Non Sitter (N=4)			Sitter (N=41)			Walker (N=62)		
Items	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month	score 0 at baseline	lost at 12 month	gain at 12 month
B. Hands lap to table	0%	0%	0%	0%	0%	0%	0%	0%	0%
C. Trace path	0%	0%	0%	0%	0%	0%	2%	0%	2%
D. Pick up tokens	0%	0%	0%	0%	0%	0%	0%	0%	0%
E. Tokens in cup	50%	25%	50%	2%	7%	0%	0%	0%	0%
F. Reach to side	100%	0%	0%	44%	10%	7%	0%	0%	0%
G. Push on light	0%	25%	0%	5%	0%	5%	2%	0%	2%
H. Tear paper	0%	0%	0%	0%	2%	0%	2%	0%	2%
I. Open Ziploc	50%	25%	0%	15%	7%	5%	2%	0%	2%
J. Cup to mouth	0%	25%	0%	0%	0%	0%	0%	0%	0%
K. Lift 200 g horizontally	0%	25%	0%	0%	0%	0%	0%	0%	0%
L. Lift 500 g horizontally	0%	25%	0%	5%	2%	2%	0%	0%	0%
M. Lift 200 g diagonally	75%	25%	0%	5%	7%	2%	0%	0%	0%
N. Lift weight from lap	25%	0%	0%	5%	5%	5%	0%	0%	0%
O. Shoulder abduction	75%	25%	0%	66%	12%	0%	3%	6%	2%
P. Shoulder abduction 500 g	100%	0%	0%	68%	12%	5%	5%	3%	2%
Q. Shoulder abduction 1 kg	100%	0%	0%	90%	5%	5%	21%	3%	10%
R. Shoulder flexion	100%	0%	0%	61%	7%	2%	3%	2%	2%
S. Shoulder flexion 500 g	100%	0%	0%	73%	10%	2%	8%	2%	3%
T. Shoulder flexion 1 kg	100%	0%	0%	90%	7%	10%	19%	5%	10%

Most of the gains or losses were observed in the type II sitters. The type II individuals who had lost the ability to sit (non-sitters) had a narrower range of shift changes as they were overall much weaker, with lower entry item scores and the great majority of items already scoring 0 at baseline and therefore not susceptible to possible shifts down. Similarly, because they were overall weaker, they also had a low chance of gains. In addition,22% of the type II participants were at the floor of the scale at baseline, only permitting an increase to be identified.

Type III individuals were overall more stable: not surprisingly the most able type III had entry items or 5 or 6 and in a proportion of them we observed a loss of shoulder items that were present at baseline (table 5). With decreasing functional level there were progressive losses of more distal items. In addition, 33% of the type III participants were at the ceiling of the scale at baseline, only permitting a decrease to be identified.

In both types more than one shift up or down was generally observed in individuals who had changes in the raw scores > 2. The shift analysis provides more accurate information on the impact of the changes in raw scores as changes in raw scores is not always associated with an overall loss or gain of function. While a loss (or gain) in 3 or more points on the scale can be theoretically associated with several items showing changes from 2 to 1 or vice versa without loss or gain of the overall function, the shift analyses enables characterization of activities lost (or gained) and not just changes in the modality of performing the activity, providing additional functional information compared to the total score.

Table 5
Details of the frequency analysis at 12-month change from baseline for individual items subdivided by SMA type and entry item at baseline. Key to table: Dark red cells represent >10% of negative shifts (from score 2 to score 0 or from score 1 to score 0), light red cells represent 0-9% negative shifts. Dark green cells represent >10% of positive shifts (from score 0 to score 2 or from score 0 to score 1), light green cells represent 0-9% positive shifts.

SMA II														
	0		1		2		3		4		5		6	
	(N=3)		(N=20)		(N=8)		(N=67)		(N=9)		(N=5)		(N=3)	
	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month
A. Entry item	N/A	33%	15%	5%	12%	62%	12%	3%	44%	0%	40%	20%	66%	N/A
B. Hands lap to table	0%	0%	5%	0%	25%	0%	9%	6%	0%	0%	0%	0%	0%	0%
C. Trace path	0%	0%	5%	0%	12%	12%	0%	1%	0%	0%	0%	20%	0%	0%
D. Pick up tokens	0%	0%	10%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
E. Tokens in cup	0%	0%	10%	0%	0%	12%	13%	7%	0%	0%	20%	0%	0%	0%
F. Reach to side	0%	0%	0%	0%	0%	0%	12%	10%	33%	0%	20%	0%	0%	0%
G. Push on light	0%	0%	10%	0%	12%	12%	10%	6%	11%	11%	0%	0%	0%	0%
H. Tear paper	0%	0%	0%	0%	0%	12%	6%	12%	0%	0%	0%	0%	0%	0%
I. Open Ziploc	0%	0%	0%	0%	0%	0%	6%	18%	11%	11%	20%	0%	0%	33%
J. Cup to mouth	0%	0%	0%	0%	0%	62%	13%	0%	11%	0%	0%	0%	0%	0%
K. Lift 200 g horizontally	0%	0%	5%	0%	12%	25%	12%	4%	11%	0%	0%	0%	0%	0%
L. Lift 500 g horizontally	0%	0%	0%	0%	0%	12%	13%	6%	22%	0%	20%	0%	0%	0%
M. Lift 200 g diagonally	0%	0%	0%	0%	0%	12%	18%	6%	11%	0%	0%	0%	0%	0%
N. Lift weight from lap	0%	0%	0%	0%	0%	0%	7%	7%	0%	0%	20%	0%	0%	0%
O. Shoulder abduction	0%	0%	0%	0%	0%	0%	0%	1%	11%	0%	20%	0%	67%	0%
P. Shoulder abduction 500 g	0%	0%	0%	0%	0%	0%	0%	0%	11%	0%	0%	0%	0%	33%
Q. Shoulder abduction 1 kg	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	20%	33%	0%
R. Shoulder flexion	0%	0%	5%	0%	0%	0%	1%	1%	11%	0%	40%	20%	33%	33%
S. Shoulder flexion 500 g	0%	0%	0%	0%	0%	0%	0%	0%	11%	0%	0%	20%	0%	33%
T. Shoulder flexion 1 kg	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	40%	0%	0%
SMA III														
	0		1		2		3		4		5		6	
	(N=0)		(N=0)		(N=0)		(N=29)		(N=7)		(N=13)		(N=58)	
	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month	lost at 12 month	gain at 12 month
A. Entry item							3%	7%	71%	14%	54%	8%	9%	N/A
B. Hands lap to table							0%	0%	0%	0%	0%	0%	0%	0%
C. Trace path							0%	0%	0%	0%	0%	8%	0%	0%
D. Pick up tokens							0%	0%	0%	0%	0%	0%	0%	0%
E. Tokens in cup							14%	3%	0%	14%	0%	0%	0%	0%
F. Reach to side							7%	7%	14%	0%	8%	8%	0%	0%
G. Push on light							0%	3%	14%	0%	0%	8%	0%	2%
H. Tear paper							3%	0%	0%	0%	0%	0%	0%	2%
I. Open Ziploc							14%	7%	0%	0%	0%	8%	0%	0%
J. Cup to mouth							3%	0%	0%	0%	0%	0%	0%	0%
K. Lift 200 g horizontally							3%	0%	0%	0%	0%	0%	0%	0%
L. Lift 500 g horizontally							7%	3%	0%	0%	0%	0%	0%	0%
M. Lift 200 g diagonally							10%	3%	14%	0%	0%	0%	0%	0%
N. Lift weight from lap							3%	7%	0%	0%	8%	0%	0%	0%
O. Shoulder abduction							10%	3%	0%	0%	54%	0%	0%	0%
P. Shoulder abduction 500 g							3%	3%	14%	29%	31%	0%	2%	0%
Q. Shoulder abduction 1 kg							0%	3%	0%	0%	15%	15%	3%	9%
R. Shoulder flexion							0%	0%	29%	0%	15%	15%	0%	0%
S. Shoulder flexion 500 g							0%	3%	29%	0%	15%	15%	2%	0%
T. Shoulder flexion 1 kg							3%	7%	14%	0%	8%	15%	5%	10%

In conclusion, the number of assessments that showed shifts in more than one activity was relatively low, reflecting the small percentage of patients who showed large changes (>2) in raw scores. These shifts seems to be influenced by several factors, including the baseline functional abilities, age, and disease severity. For instance, younger children in the type II group exhibited more gains, likely due to developmental progress, while older individuals showed more losses, especially in those with weaker baseline abilities. The distribution of baseline scores also played a crucial role, with individuals starting at the floor or ceiling of the scale having limited capacity for further shifts. Disease progression, particularly the proximal-to-distal gradient of muscle weakness, further contributed to these observed changes.

One of the limitations in this study was that the RULM was developed in 2015, at the time of the first clinical trials and before DMTs became commercially available. This has reduced the possibility to obtain data in larger cohorts and with longer follow up data where larger changes would have probably been observed and predictors of changes could have been analyzed more effectively. Even with these limitations, our findings provide an additional method of interpreting possible changes on the RULM that reflect the gain and the loss of activities that are

meaningful to the families and will provide reference data for the interpretation of clinical trials or real world RULM data.

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Supplementary materials

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