

# Exploring functional strength changes during nusinersen treatment in symptomatic children with SMA types 2 and 3.

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## ABSTRACT

The Hammersmith Functional Motor Scale-Expanded (HFMSE) is a validated outcome measure for monitoring changes in functional strength in patients with spinal muscular atrophy (SMA). The objective of this study was to explore changes in HFMSE item-scores in children with SMA types 2 and 3a treated with nusinersen over a period of six to twenty months. We stratified patients according to motor ability (sitting and walking), and calculated numbers and percentages for each specific improvement (positive score change) or decrease (negative score change) for the total group and each subgroup and calculated frequency distributions of specific score changes. Ninety-one percent of the children showed improvement in at least 1 item, twenty-eight percent showed a score decrease in 1 or more items. In the first six to twenty months of nusinersen treatment motor function change was characterized by the acquisition of the ability to perform specific tasks with compensation strategies (score changes from 0 to 1). Children with the ability to sit were most likely to improve in items that assess rolling, whilst children with the ability to walk most likely improved in items that assess half-kneeling. The ability most frequently lost was hip flexion in supine position.

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## 1. Introduction

Spinal muscular atrophy (SMA) is an autosomal recessive neuromuscular disease caused by loss of function of the survival motor neuron 1 (*SMN1*) gene. The key characteristic of SMA is degeneration of alpha motor neurons in the anterior horns of the spinal cord resulting in progressive generalized muscle weakness [1,2]. The variability in disease severity in SMA is striking. It ranges from infantile-onset with virtually no gross motor development (i.e. type 1), to two childhood-onset forms with impaired gross motor development (type 2 and type 3a with sitting and walking as highest achieved motor milestones respectively) and late-onset forms characterized by limb-girdle pattern weakness (types 3b and 4) [3,4]. Variability in disease severity between patients can be partly explained by the inverse correlation with the *SMN2* copy number [5]. The disease course in all treatment-naïve patients is characterized by deteriorating muscle strength and motor function throughout life [6–8].

Since 2017, the introduction of disease modifying treatments (DMT) for SMA has altered the disease course and the outlook for patients [9–16]. Nusinersen (Spinraza®), the first DMT for SMA, is an antisense oligonucleotide that modifies *SMN2* splicing, thereby increasing functional *SMN* protein production. Nusinersen was the first approved DMT in the Netherlands and started in May 2017 for children with SMA type 1, and in August 2018 treatment became available for patients up to 9.5 years of age.

Sham-controlled clinical trials showed that nusinersen improves motor function of infants and children with SMA types 1 and 2 as reflected by changes in relevant age-specific motor function scales, i.e., the total scores of CHOP INTEND and the Hammersmith Functional Motor Scale-Expanded (HFMSE), respectively [10,11,13]. The HFMSE is a validated motor function measurement consisting of 33 gross-motor skill items; its use in reflecting and analysing disease trajectories in children with SMA types 2 and 3 has been proven [6,9,10,17,18].

Weakness in patients with SMA is generalized but predominates in axial and specific proximal muscle groups, i.e., deltoid, triceps, iliopsoas, and quadriceps muscles, possibly due to differences in vulnerability of motor neuron pools [6,19,20]. Response of motor neurons to treatment might be equally

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variable. This could be reflected by differences of motor function improvement as indicated by the predominance of changes in specific HFMSE item-scores. In addition, insight into potential patterns of motor function improvement could help to manage treatment expectations, develop training programs, and facilitate goal-setting in physiotherapy and rehabilitation.

The goal of this study was, therefore, to explore changes in HFMSE item-scores in children with SMA types 1c-3a treated with nusinersen.

2. Patients and methods

We performed an observational prospective study to evaluate treatment response in children with SMA types 2–3a treated with nusinersen. Treatment of children with SMA in the Netherlands (population size approximately 17.6 million) is centralized at the Netherlands SMA Center in the University Medical Center Utrecht (UMCU), a tertiary neuromuscular referral center for children and adults. Between May 2017 and August 2019, we enrolled all patients with SMA in the Netherlands who, according to reimbursement criteria, were eligible for treatment. At the time of this study, reimbursement in the Netherlands was confined to patients with infantile onset and a disease duration shorter than 26 weeks, children with disease onset between the ages of 6 and 20 months who were younger than 9.5 years at start of treatment, and presymptomatic cases with 2 or 3 SMN2 copies. All patients in this cohort had previously been included in an ongoing prospective population-based prevalence cohort study in the Netherlands, approved by the local Medical Ethical Committee (registered at the Dutch registry for clinical studies and trials, NL29692.041.09). All parents had given written and oral informed consent [5,12,21].

All patients had a homozygous deletion of the SMN1 gene. SMN1 and SMN2 copy number were determined by Multiplex Ligand Probe amplification (MLPA) (SALSA MLPA kit P021-B1-01 (MRC-Holland), followed by sequencing analysis for c.859G>C mutations. SMA type was defined according to the age at onset and highest achieved motor milestone [5,12,21,22]. In case of discrepancy between age at onset and highest motor milestone, the latter was used to define the final type. Patients with SMA type 2 have, by definition, a disease onset between the ages of 6 and 18 months and learn to sit independently (type 2a) and sometimes stand or walk with support (but never independently) (i.e. type 2b). Patients with SMA type 3a experience onset of weakness between the ages of 18 months and 3 years and learn to walk independently [2,22].

All included patients were over 2 years of age and started treatment symptomatically. They were treated with nusinersen according to the manufacturer's schedule [23]. After starting treatment, children were assessed at least once a year using HFMSE.

We included all children with at least two HFMSE assessments, but only 1) when the first assessment had been performed within six months, up to two weeks after the start of treatment, 2) if the second assessment had been performed after at least the full loading dose and 5th injection, and 3) provided no spinal surgery had been performed between the two assessments.

2.1. HFMSE

The HFMSE consists of 33 items and a 3-point scale (0–2 points per item; range 0–66 points) and documents the functional motor abilities of patients with SMA. An item score of 2 represents the ability to perform the task without modification or compensation, a score of 1 the ability to perform the task with modification or compensation, and a score of 0 is given when a patient is unable to perform the task [24]. HFMSE measurements were assessed by three experienced pediatric physical therapists from the same department (MS, BB and DW).

2.2. Data analysis

We used descriptive statistics for clinical and demographic data. We stratified patients in three groups according to current highest basic motor skill, i.e. independent sitting or walking (Table 1). We calculated numbers and percentages for each specific improvement (positive score change) or decrease (negative score change) for the total group and each subgroup and calculated frequency distributions of specific score changes (i.e. from 0–1, 0–2, 1–2, 2–1, 2–0, 0–0, 1–1, 2–2) for each item for the total group and each subgroup.

Statistical analyses were performed with SPSS V26 software.

3. RESULTS

We included forty-six patients with SMA types 2–3a in this study. Clinical characteristics and functional scores at baseline and during treatment of all included children are presented in Table 2. The median age at baseline was 5.2 years (range 1.5–9.9). The mean interval between measurements was 15.0 months (range 7.0–20.0). Patients received 5 to 8 doses of nusinersen, the majority (54 %) receiving 7 doses. Median HFMSE total score increased by 4.5 points (range –2–18) (Table 2).

One patient was on ventilation >16 h a day at baseline.

3.1. HFMSE items sensitive to change

3.1.1. Total group

The majority of children, 42 of 46 (91 %), showed improvement in at least 1 item, while only 28 % (13 of 46) showed a score decrease in one or more items. Twelve children (26 %) showed both improvement in some item scores, as well as decreases in others. Of these twelve, six (13 %) had a stable (three children) or decreased (three children) HFMSE total score.

Most changes in item scores were from 0 to 1 (105 of 201 changes, 52 %), while decreases usually involved a change from 1 to 0 (10 of 18 changes, 56 %) (Table 3). A score change from 2 to 0 was only found in one patient, in item 13 (props on extended arms), due to hip flexion contractures. Number of doses nusinersen and SMN2 copy number did not influence the pattern of score changes, with the highest percentage of changes being changes from 0 to 1, followed by changes from 1 to 2 and then changes from 0 to 2.

Item 7 (rolling from prone to supine over left) was most sensitive for score improvement (14 of 46 patients, 30 %) followed by items 8 and 9 (rolling from supine to prone over both sides) (in

Table 1  
Definition of functional subgroups based on HFMSE item scores.

Non-sitters	HFMSE item 1 “sitting” score < 2
Sitters	HFMSE item 1 “sitting” score = 2 and HFMSE items 20 score < 2
Walkers	HFMSE item 20 “Stepping” score = 2

**Table 2**  
Patient characteristics.

	Type 2a (n = 23)	Type 2b (n = 9)	Type 3a (n = 14)	Total (n = 46)
Age at onset, mean (SD)	8.3 (3.9)	13.3 (2.7)	22.1 (6.6)	13.5 (7.6)
Age at start of treatment, years	4.4 (1.5–9.9)	7.6 (3.9–9.4)	5.6 (3.3–9.1)	5.2 (1.5–9.9)
Disease duration	41.8 (11.5–106.9)	79.1 (28.5–100.6)	45.2 (12.1–91.2)	47.5 (11–111)
Sex, no (%)				
Male	12 (52)	6 (67)	7 (50)	25 (54)
Female	11 (48)	3 (33)	7 (50)	21 (46)
Nusinersen doses	7 (5–8)	7 (6–8)	7 (5–8)	7 (5–8)
Time between measurements	14.8 (7.4–20)	15 (13.6–20.1)	15.4 (6.9–20.1)	15 (7–20)
Treatment duration, mean (SD)	13.7 (3.4)	12.9 (1.8)	13.6 (3.2)	13.5 (3.1)
HFMSE score at first recorded measurement	9 (0–21)	24 (5–38)	48 (35–62)	18 (0–62)
HFMSE score after treatment	15 (0–34)	26 (5–44)	55 (34–65)	25 (0–65)
HFMSE score change after treatment	4 (–1–18)	5 (–2–8)	4.5 (–2–10)	4.5 (–2–18)
RULM at start of treatment (no)	7 (5–10) n = 4	24 (13–31) n = 5	36 (29–27) n = 6	27 (5–37) n = 15
SMN2 copy numbers, no (%)				
2	1 (4.3 %)	0 (0 %)	1* (7.1 %)	2 (4.3 %)
3	22 (95.7 %)	9 (100 %)	4 (28.6 %)	35 (76.0 %)
4	0 (0 %)	0 (0 %)	9 (64.3 %)	9 (19.6 %)
Total	23 (100 %)	9 (100 %)	14 (100 %)	46 (100 %)
Subgroup**, no (%)				
Non-sitters	4 (17.4 %)	0 (0 %)	0 (0 %)	4 (8.7 %)
Sitters	19 (82.6 %)	9 (100 %)	2 (14.3 %)	30 (65.2 %)
Walkers	0 (0 %)	0 (0 %)	12 (85.7 %)	12 (26.1 %)

All data are described as median (range) and months, unless otherwise specified.

\*This patient has a c.859G>C mutation in the SMN2 copies, which is a positive modifier for disease severity and explains the SMA type 3 phenotype on a 2-copy background.

\*\* Subgroups based on highest achieved HFMSE-item at start of treatment. Non-sitters; item 1 < 2, sitters; item 1 = 2, item 20 < 2, walkers; item 20 = 2.

**Table 3**  
Distribution of score changes.

Specified number of changes from – to	Non-sitters, n (%)	Sitters, n (%)	Walkers, n (%)	Total, n (%)
<b>Increase</b>				
<b>0–1</b>	9 (69 %)	59 (48 %)	37 (56 %)	105 (52 %)
<b>1–2</b>	1 (8 %)	35 (29 %)	27 (41 %)	63 (31 %)
<b>0–2</b>	3 (23 %)	28 (23 %)	2 (3 %)	33 (16 %)
<b>Total</b>	13 (100 %)	122 (100 %)	66 (100 %)	201 (100 %)
<b>Decrease</b>				
<b>1–0</b>	0	9 (56 %)	1 (50 %)	10 (56 %)
<b>2–1</b>	0	6 (38 %)	1 (50 %)	7 (39 %)
<b>2–0</b>	0	1 (6 %)	0	1 (5 %)
<b>Total</b>	0	16 (100 %)	2 (100 %)	18 (100 %)

Number of observed score changes. Cumulative result of all observed changes within each subgroup and total group expressed as total, and percentages.

both cases, 12 of 46 patients, 26 %). Items 21 (3 of 46 patients, 7 %) and 22 (4 of 46 patients, 9 %) (right and left hip flexion, respectively) were most sensitive for a decline in score (Fig. 1a). There were no changes in item 18, no children achieved the ability to stand with support, and only 1 patient showed an improvement in score in items 16, 19 and 20 (crawling, standing without support and stepping).

### 3.1.2. Non-sitters

Of the 4 children, 2 (50 %) improved in 1 or more HFMSE items, none showed a decrease in HFMSE items, and 2 were unable to make a negative change (e.g. because they had 0 points at start of treatment).

Item 1, sitting, and item 3, bringing 1 hand to the head, were most sensitive to improvement: 2 of 4 (50 %) of the non-sitters improved on these items (Fig. 1b).

### 3.1.3. Sitters

Of the 30 children, 28 (93 %) improved in 1 or more HFMSE items and 11 (37 %) had a decrease in score in at least 1 item.

In items 6 and 7, rolling from prone to supine over right and left side, there was an improvement in score in, respectively, 10 (33 %) and 12 (40 %) of the 30 children in this subgroup. In items 8 and 9, rolling from supine to prone over right and left side, 11 of 30 (37 %) children showed improvement. In the group of patients who did not achieve maximal item score (i.e., item score <2) at the start, most improvement in score was seen in item 2, long-sitting (6 of 12 patients, 50 %), item 5, supine to side-lying (3 of 6 patients, 50 %), and items 8 and 9 (11 of 21 patients, 52 %).

Items most sensitive to a decline in score were items 21 and 22, right and left hip flexion, 3 (10 %) and 4 (13 %) of the 30 children showing a decline, also, in both item 4, two hands to the head, and item 14, lying to sitting, 2 of 30 (6 %) children showed a decline in score (Fig. 1c).

### 3.1.4. Walkers

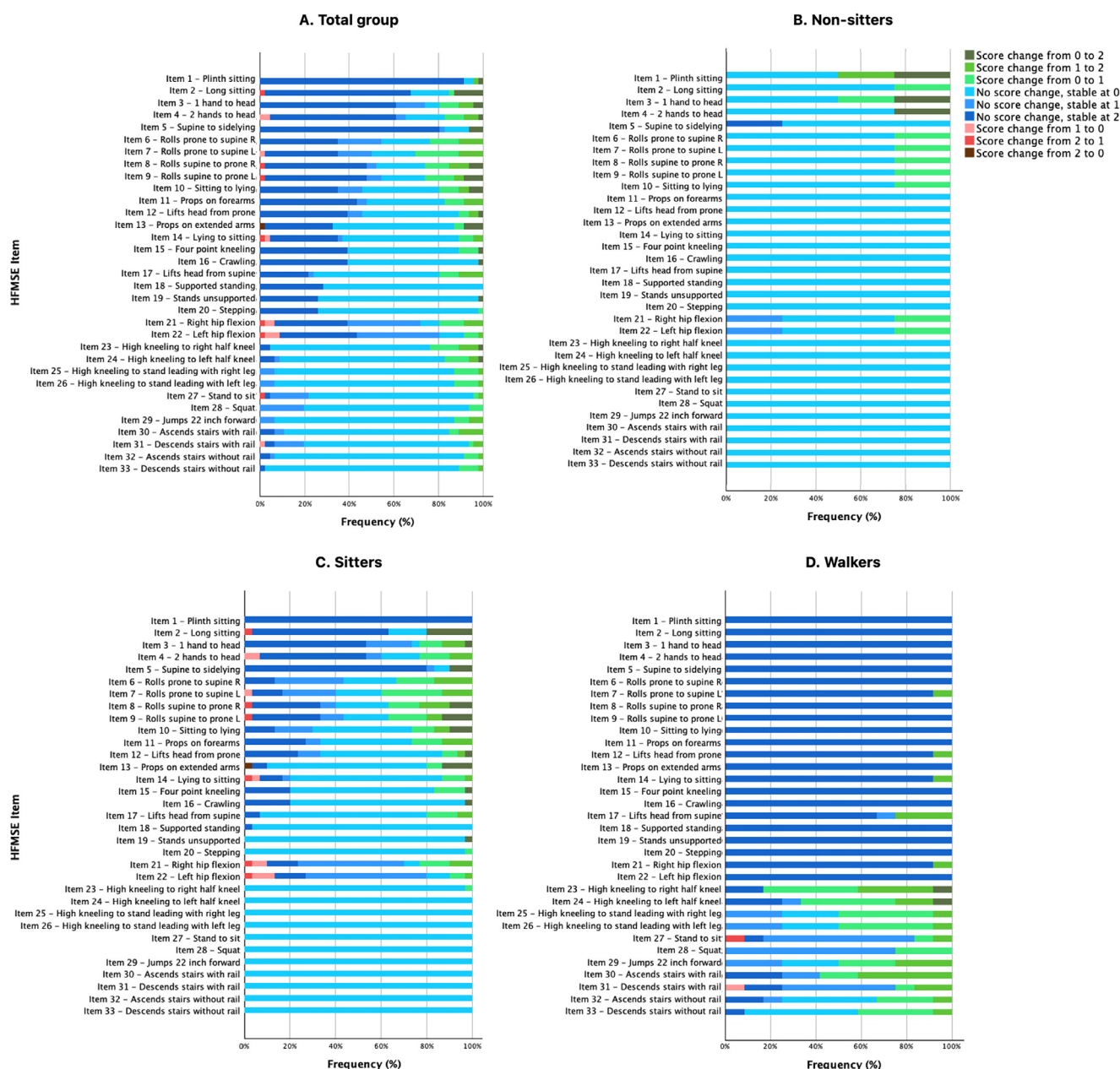
All twelve children improved in 1 or more HFMSE items. In two (17 %), the score decreased in at least 1 item.

In items 23 and 24, high-kneeling to right and left half-kneel, there was an improvement in score in, respectively, 10 (83 %) and 8 (75 %) of the 12 children. In item 30, ascending stairs with handrail, 7 of 12 (58 %) patients showed improvement. In the group who did not achieve maximal item score (i.e., items score <2) at the start, all (n = 10) improved in item 23, and all but one in item 24 (89 %).

In items 25 and 26, high-kneeling to stand leading with right and left leg the score improved in 6 of 12 children (50 %). In item 30, ascending the stairs with handrail, 7 of 10 (70 %) children improved and in item 29, jumping 12 inches forward, 6 of 12 (50 %) (Fig. 1d).

## 4. Discussion

This study shows that motor function changes in HFMSE scores are not evenly distributed across the 33 HFMSE items and that responses at item level are mostly partial. We observed limited change in non-sitters, while sitters and walkers primarily showed



**Fig. 1.** Frequency of item score changes plotted for each subgroup. Red columns on the left side represent % of score decrease (from 2–1, 2–0 or 1–0); green columns on the right side represent % of score improvement (from 0–1, 1–2 or 0–2). Blue columns represent % of stable scores (0–0, 1–1 or 2–2).

improvement in items assessing rolling ability and high-kneeling, respectively. Although loss of motor functions was limited, it converged in items 21 and 22 which assesses (right and left) hip flexion. Observed motor function improvements were partial in 52 % of score changes, i.e. score changes from 0 to 1 reflecting the gained ability to perform a new motor function with compensation, while full achievement of new motor functions without compensation, i.e. changes from 0 to 2, was seen in 16 % of score changes.

The HFMSE has been used in many completed and ongoing clinical trials to evaluate efficacy of treatment strategies for SMA [25–27]. The Hammettsmith motor function scale (HMFS) was originally developed to quantify motor ability in children with SMA types 2 and 3, given the wide range of severity of SMA and to monitor clinical disease progression [24]. To circumvent

the problem of ceiling effects and to allow the use of the HMFS for the assessment of patients with milder symptoms, 13 items were added to create an expanded version of the HFMS, i.e. the HFMSE [18]. Although it is used in many clinical studies, Rasch analysis of the HFMSE has shown an unequal distribution of the constituent items in the total score, explained by multidimensionality and dependency of some of the motor function items [28]. Multidimensionality refers to the multiple domains making up the HFMSE and implies that specific motor function scores may show improvement (for example bringing the hands to the head), while other item scores (for example hip flexion in supine position) may show an opposite decrease, leading to an unchanged total score [28]. Dependency of items, on the other hand, explains why scores of some items affect the scores of several other items (for example rolling items),

the score changes in these items are highly related [28]. Our study data suggest that dependency might be seen in the items containing rolling in the subgroup sitters, and items containing half-kneel in the subgroup walkers. Our data indicate that the methodological limitations of HFMSE as shown by Rasch analysis are relevant to the interpretation of treatment effects, since not every item is equally sensitive to capture treatment effects and total scores might conceal or inflate clinically relevant motor function improvements.

To the best of our knowledge, our study is the first to address HFMSE changes at the item level in children with SMA treated with nusinersen. In a recent study, Coratti et al. analyzed the gain and loss of abilities by analysing HFMSE item score change in untreated children and adults with SMA type 2 over a 12-month time span. The cohort consisted of sitters and non-sitters [29]. They labelled gained abilities as score changes from 0 to 1 or 2, and loss of abilities as changes from 2 or 1, to 0. Their results show both similarities and differences with the subgroup of treated sitters in our cohort, which is most similar to the cohort of Coratti et al. Not surprisingly, percentages of gained abilities were higher for most items in our cohort of treated patients compared to what is observed as part of the natural disease course in SMA. In natural history by Coratti, highest percentage of gained abilities for the total group was 6.8 % (sitting to lying), while in our cohort of treated patients this item showed 20 % of children gaining this ability. The group of untreated patients had a higher mean age compared to the treated group, but even when one looks at the youngest group of the natural history study (<5 years of age), none of the items shows comparable percentages of gained abilities. The overall pattern of responsive items, however, appears similar between our subgroup of treated sitters and the untreated patients with SMA type 2 from Coratti et al., with less responsiveness in items involving lying to sitting, crawling and (un)supported standing and walking (e.g. items 14, 16 and 18–20), and higher response rates of the other items concerning the domains sitting and transition/crawling (i.e. items 2–4 and 10–13 and 15).

When comparing our results with those from the untreated group, there are differences in the domain of rolling (items 6–9) and lifting the head in supine position (item 17), in which the patients treated with nusinersen show relatively more gains compared to the other items.

In untreated SMA patients, the most frequently lost ability is that of hip flexion, i.e. items 21 and 22, similar to our cohort of treated patients. All first 22 HFMSE item scores were sensitive to loss of function (i.e. score change from 2 or 1 to 0) in the untreated population, as opposed to only 6 items in the treated group (items 4,7,13,14,21 and 22). This implies that nusinersen treatment may not only improve motor function but may also limit the loss of functional abilities. The loss of item score in items 21 and 22 (hip flexion) is mostly due to increase of hip and knee flexion contractures, present in the majority of 'sitters'. The presence and/or increase of these contractures not only translates to the loss of item scores, it also prevents increase in motor function, with might be one of the main problems when transitioning to standing and walking, as seen in the limited response at items 18, 19 and 20 (i.e. standing with and without support and stepping).

Score changes from 0 to 2 were uncommon, in contrast to changes from 0 to 1. This study shows that improvement is seen over a broader range of items, with no influence of highest achieved motor function, number of doses nusinersen or SMN2 copy number on the type of, or distribution of, type of changes. The pattern of changes (0 to 1 > 1 to 2 > 0 to 2) does not change. This might be explained by the fact that although score changes from 0 to 1 are described as challenging, changes from 0 to 2 should be regarded as a big difference [30]. Most patients prefer, however, multiple small (1 point) improvements

rather than larger improvements in single items, as illustrated by the evaluation of reported meaningful changes by SMA patients using another validated motor function score, the 32-item Motor Function Measure (MFM32) [31]. This preference is not considered or reflected in total score changes that are currently used to define and document treatment efficacy.

The HFMSE has been used successfully as (primary) outcome measure in clinical trials [10,32]. Patients who do not show improvements in motor function scales, such as the HFMSE, are often regarded as 'non-responders' to the investigated therapy. Our data support the idea that the HFMSE will not detect all relevant changes during treatment. To improve the HFMSE, the Revised Hammersmith Scale (RHS) is developed. Although the RHS does decrease the dependency of items, the impact of contractures, differences in responsiveness of the individual items, and the multidimensionality the scale are still not weighed in total scores.

The development of motor function scales that document arm function, such as the revised upper limb module (RULM), or tests that quantify complementary dimensions of motor function, such as endurance, have refined assessments but may still not cover all relevant motor function changes [33–35]. With the introduction of multiple expensive therapies for SMA, healthcare professionals are faced with the additional responsibility of distinguishing responders and non-responders as soon as possible after initiation of treatment. Improvements of the HFMSE total scores are accepted as proof of response to treatment, but this is probably also the case if patients' general motor function does not deteriorate, or even when scores show deterioration in some items but improvement in others. Although negative item-score changes are limited in our cohort, 13 % of the children still show a stable or even decreased HFMSE total score, whilst improvement is also present. These children show improvement in score in 1 item but decrease in score in other items. Our new insight into the HFMSE item responses suggests that comparing only HFMSE total scores is insufficient to identify (non)-responders.

The presented data can be used in physical therapy for expectation management and goal-setting. Goal-setting in reaching new motor functions with compensation in multiple motor functions should be considered over attaining single new motor functions without compensation. Contractures might limit motor function improvement, especially in the domain of standing and walking and should therefore be prevented.

## 5. Limitations

Children included in this study were all symptomatic, with a mean age of 5.2 years at the start of treatment with nusinersen. Younger patients with shorter disease durations tend to show more improvements in motor function than older patients with longer disease duration. We could not assess whether the response in younger patients is different from the population studied here. Our cohort is relatively small, especially for subgroup analysis of non-sitters, or different age groups. We cannot exclude the possibility that response patterns may be slightly different in larger studies. This study focussed on exploring patterns and looking in-depth at changes in HFMSE-items, not to describe or to demonstrate nusinersen treatment effects. Given the nature of the study, and relatively small sample size no extended statistics were used.

## 6. Conclusion

In the first 6 to 20 months of nusinersen treatment, motor function changes are mostly characterized by the acquisition of the ability to perform specific items with compensation strategies. Children with the ability to sit are most likely to improve in items that assess rolling and long-sitting. Children with the ability to

walk are most likely to improve in items that assess half-kneeling and ascending the stairs using a handrail. The most frequently lost ability is hip flexion in supine position.

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The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Danny R. van der Woude, his employer receives fees for SMA-related consultancy activities.

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### CRediT authorship contribution statement

**Danny R. van der Woude:** Writing – review & editing, Writing – original draft, Visualization, Resources, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Renske I. Wadman:** Writing – review & editing, Methodology, Conceptualization. **Fay-Lynn Asselman:** Writing – review & editing, Methodology, Conceptualization. **Marja A.G.C. Schoenmakers:** Investigation, Data curation. **Inge Cuppen:** Methodology, Conceptualization. **W. Ludo van der Pol:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Bart Bartels:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Conceptualization.

### References

- [1] Lefebvre S, Bürglen L, Reboullet S, Clermont O, Burlet P, Viollet L, et al. Identification and characterization of a spinal muscular atrophy-determining gene. *Cell* 1995;80:155–65. doi:10.1016/0092-8674(95)90460-3.
- [2] D'Amico A, Mercuri E, Tiziano FD, Bertini E. Spinal muscular atrophy. *Orphanet J Rare Dis* 2011;6:71. doi:10.1186/1750-1172-6-71.
- [3] Kolb SJ, Kissel JT. Spinal Muscular Atrophy. *Neurol Clin* 2015;33:831–46. doi:10.1016/j.ncl.2015.07.004.
- [4] Piepers S, Van Den Berg LH, Brugman F, Scheffer H, Ruiterkamp-Versteeg M, Van Engelen BG, et al. A natural history study of late onset spinal muscular atrophy types 3b and 4. *J Neurol* 2008;255:1400–4. doi:10.1007/s00415-008-0929-0.
- [5] Wadman RI, Stam M, Gijzen M, Lemmink HH, Snoeck IN, Wijngaarde CA, et al. Association of motor milestones, SMN2 copy and outcome in spinal muscular atrophy types 0–4. *J Neurol Neurosurg Psychiatry* 2017;88:364–7. doi:10.1136/jnnp-2016-314292.
- [6] Wadman RI, Wijngaarde CA, Stam M, Bartels B, Otto LAM, Lemmink HH, et al. Muscle strength and motor function throughout life in a cross-sectional cohort of 180 patients with spinal muscular atrophy types 1c–4. *Eur J Neurol* 2018;25:512–18. doi:10.1111/ene.13534.
- [7] Wijngaarde CA, Stam M, Otto LAM, Bartels B, Asselman F-L, van Eijk RPA, et al. Muscle strength and motor function in adolescents and adults with spinal muscular atrophy. *Neurology* 2020;95:e1988. doi:10.1212/WNL.000000000010540.
- [8] Kolb SJ, Coffey CS, Yankey JW, Krosschell K, Arnold WD, Rutkove SB, et al. Baseline results of the NeuroNEXT spinal muscular atrophy infant biomarker study. *Ann Clin Transl Neurol* 2016;3:132–45. doi:10.1002/ajcn3.283.
- [9] Hagenacker T, Wurster CD, Günther R, Schreiber-Katz O, Osmanovic A, Petri S, et al. Nusinersen in adults with 5q spinal muscular atrophy: a non-interventional, multicentre, observational cohort study. *Lancet Neurol* 2020;19:317–25. doi:10.1016/S1474-4422(20)30037-5.
- [10] Mercuri E, Darras BT, Chiriboga CA, Day JW, Campbell C, Connolly AM, et al. Nusinersen versus sham control in later-onset spinal muscular atrophy. *N Engl J Med* 2018;378:625–35. doi:10.1056/nejmoa1710504.
- [11] Finkel RS, Mercuri E, Darras BT, Connolly AM, Kuntz NL, Kirschner J, et al. Nusinersen versus sham control in infantile-onset spinal muscular atrophy. *N Engl J Med* 2017;377:1723–32. doi:10.1056/nejmoa1702752.
- [12] Scheijmans FE V, Cuppen I, van Eijk RPA, Wijngaarde CA, Schoenmakers MAGC, van der Woude DR, et al. Population-based assessment of nusinersen efficacy in children with spinal muscular atrophy: a 3-year follow-up study. *Brain Commun* 2022;4:fcac269–fcac269. doi:10.1093/braincomms/fcac269.
- [13] Coratti G, Cutrona C, Pera MC, Bovis F, Ponzano M, Chieppa F, et al. Motor function in type 2 and 3 SMA patients treated with Nusinersen: a critical review and meta-analysis. *Orphanet J Rare Dis* 2021;16:430. doi:10.1186/s13023-021-02065-z.
- [14] Mendell JR, Al-Zaidy S, Shell R, Arnold WD, Rodino-Klapac LR, Prior TW, et al. Single-dose gene-replacement therapy for spinal muscular atrophy. *N Engl J Med* 2017;377:1713–22. doi:10.1056/NEJMoa1706198.
- [15] Darras BT, Masson R, Mazurkiewicz-Beldzińska M, Rose K, Xiong H, Zanoteli E, et al. Risdiplam-treated infants with Type 1 spinal muscular atrophy versus historical controls. *N Engl J Med* 2021;385:427–35. doi:10.1056/NEJMoa2102047.
- [16] Day JW, Finkel RS, Chiriboga CA, Connolly AM, Crawford TO, Darras BT, et al. Onasemnogene abeparvovec gene therapy for symptomatic infantile-onset spinal muscular atrophy in patients with two copies of SMN2 (STRIVE): an open-label, single-arm, multicentre, phase 3 trial. *Lancet Neurol* 2021;20:284–93. doi:10.1016/S1474-4422(21)00001-6.
- [17] Coratti G, Pane M, Lucibello S, Pera MC, Pasternak A, Montes J, et al. Age related treatment effect in type II spinal muscular atrophy pediatric patients treated with nusinersen. *Neuromuscul Disord* 2021;31:596–602. doi:10.1016/j.nmd.2021.03.012.
- [18] O'Hagen JM, Glanzman AM, McDermott MP, Ryan PA, Flickinger J, Quigley J, et al. An expanded version of the hammersmith functional motor scale for SMA II and III patients. *Neuromuscul Disord* 2007;17:693–7. doi:10.1016/j.nmd.2007.05.009.
- [19] Piepers S, der Pol W-L van, Brugman F, Wokke JHJ, Berg LH van den. Natural history of SMA IIIB: muscle strength decreases in a predictable sequence and magnitude. *Neurology* 2009;72:2057. doi:10.1212/01.wnl.0000349698.94744.1e.
- [20] Deymeier F, Serdaroglu P, Parman Y, Poda M. Natural history of SMA IIIB. *Neurology* 2008;71:644. doi:10.1212/01.wnl.0000324623.89105.c4.
- [21] Wijngaarde CA, Stam M, Otto LAM, van Eijk RPA, Cuppen I, Veldhoen ES, et al. Population-based analysis of survival in spinal muscular atrophy. *Neurology* 2020;94:e1634. doi:10.1212/WNL.0000000000009248.
- [22] Mercuri E, Bertini E, Iannaccone ST. Childhood spinal muscular atrophy: controversies and challenges. *Lancet Neurol* 2012;11:443–52. doi:10.1016/S1474-4422(12)70061-3.
- [23] . Spinraza: EPAR–Product information. Annex 1, Summary of product characteristics; 2021. p. 1–31.
- [24] Main M, Kairon H, Mercuri E, Muntoni F. The Hammersmith functional motor scale for children with spinal muscular atrophy: a scale to test ability and monitor progress in children with limited ambulation. *Eur J Paediatr Neurol* 2003;7:155–9. doi:10.1016/S1090-3798(03)00060-6.
- [25] Day JW, Howell K, Place A, Long K, Rossello J, Kertesz N, et al. Advances and limitations for the treatment of spinal muscular atrophy. *BMC Pediatr* 2022;22:632. doi:10.1186/s12887-022-03671-x.
- [26] Finkel RS, Darras BT, Mendell JR, Day JW, Kuntz NL, Connolly AM, et al. Intrathecal Onasemnogene Abeparvovec for Sitting, Nonambulatory Patients with Spinal Muscular Atrophy: phase I Ascending-Dose Study (STRONG). *J Neuromuscul Dis* 2023;10:389–404. doi:10.3233/JND-221560.
- [27] Wadman RI, van der Pol WL, Bosboom WMJ, Asselman FL, van den Berg LH, Iannaccone ST, et al. Drug treatment for spinal muscular atrophy types II and III. *Cochrane Database Syst Rev* 2020. doi:10.1002/14651858.CD006282.pub5.
- [28] Cano SJ, Mayhew A, Glanzman AM, Krosschell KJ, Swoboda KJ, Main M, et al. Rasch analysis of clinical outcome measures in spinal muscular atrophy. *Muscle Nerve* 2014;49:422–30. doi:10.1002/mus.23937.
- [29] Coratti G, Lucibello S, Pera MC, Duong T, Muni Lofra R, Civitello M, et al. Gain and loss of abilities in type II SMA: a 12-month natural history study. *Neuromuscul Disord* 2020;30:765–71. doi:10.1016/j.nmd.2020.07.004.
- [30] McGraw S, Qian Y, Henne J, Jarecki J, Hobby K, Yeh W-S. A qualitative study of perceptions of meaningful change in spinal muscular atrophy. *BMC Neurol* 2017;17:68. doi:10.1186/s12883-017-0853-y.
- [31] Duong T, Staunton H, Braid J, Barriere A, Trzaskoma B, Gao L, et al. A patient-centered evaluation of meaningful change on the 32-item motor function measure in spinal muscular atrophy using qualitative and quantitative data. *Front Neurol* 2022;12. doi:10.3389/fneur.2021.770423.

- [32] Oskoui M, Day JW, Deconinck N, Mazzone ES, Nascimento A, Saito K, et al. Two-year efficacy and safety of risdiplam in patients with type 2 or non-ambulant type 3 spinal muscular atrophy (SMA). *J Neurol* 2023. doi:[10.1007/s00415-023-11560-1](https://doi.org/10.1007/s00415-023-11560-1).
- [33] Bartels B, De Groot JF, Habets LE, Wijngaarde CA, Vink W, Stam M, et al. Fatigability in spinal muscular atrophy: validity and reliability of endurance shuttle tests. *Orphanet J Rare Dis* 2020;15. doi:[10.1186/s13023-020-1348-2](https://doi.org/10.1186/s13023-020-1348-2) [LK](#).
- [34] Stam M, Wijngaarde CA, Bartels B, Asselman F-L, Otto LAM, Habets LE, et al. Randomized double-blind placebo-controlled crossover trial with pyridostigmine in spinal muscular atrophy types 2–4. *Brain Commun* 2023;5:fcac324. doi:[10.1093/braincomms/fcac324](https://doi.org/10.1093/braincomms/fcac324).
- [35] Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised upper limb module for spinal muscular atrophy: development of a new module. *Muscle Nerve* 2017;55:869–74. doi:[10.1002/mus.25430](https://doi.org/10.1002/mus.25430).