

# An expanded version of the Hammersmith Functional Motor Scale for SMA II and III patients

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## Abstract

**Purpose:** To develop and evaluate an expanded version of the Hammersmith Functional Motor Scale allowing for evaluation of ambulatory SMA patients.

**Procedures:** Thirty-eight patients with SMA type II or III were evaluated using the Gross Motor Function Measure and the Hammersmith Functional Motor Scale. Based on statistical and clinical criteria, we selected 13 Gross Motor Function Measure items to develop an expanded HFMS. The expanded Hammersmith Functional Motor Scale was validated by comparison with the Gross Motor Function Measure minus the 13 items (GMFM-75) and an assessment of clinical function. The reliability of the expanded Hammersmith Functional Motor Scale in 36 patients was established.

**Findings:** The expanded Hammersmith Functional Motor Scale was highly correlated with the GMFM-75 and the clinical function assessment ( $p = 0.97$ , and  $p = 0.90$ ). The expanded Hammersmith Functional Motor Scale showed excellent test–retest reliability (International Coordinating Committee = 0.99).

**Conclusions:** The expanded Hammersmith Functional Motor Scale allows assessment of high functioning SMA type II and III patients. Ease of administration and correlation with established motor function measures justify use in future SMA clinical trials.

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**Keywords:** Spinal Muscular Atrophy; Gross Motor Function Measure; Hammersmith Functional Motor Scale; Outcome measure; Physical therapy

## 1. Introduction

Spinal Muscular Atrophy (SMA) is one of the most devastating neurological diseases of childhood. Affected

infants and children suffer from progressive muscle weakness caused by degeneration of lower motor neurons in the spinal cord and brainstem. SMA is caused by homozygous deletion of the Survival of Motor Neurons-1 (SMN1) gene [1,2]. A related gene, SMN2, produces low levels of full-length SMN protein due to inefficient splicing. There is an inverse correlation between SMN2 copy number and disease severity, presumably mediated by SMN2 derived full-length SMN protein [3]. Therefore, increasing the amount of full-length SMN protein is a promising

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treatment strategy [4]. Several drugs targeting gene expression have resulted in increased SMN protein in preclinical assays and are now being investigated as pharmacological candidates for clinical trials in humans [5–8]. To test these drugs, well-designed clinical trials using valid, reliable and responsive outcome measures are needed.

Clinically, SMA patients are classified according to the highest motor function ever achieved: Those with SMA type I never achieve independent sitting; those with type II can sit and may stand but do not walk independently; and those with SMA type III can walk without assistance. The retention of these motor milestones is not considered in their classification. Many individuals with type III later lose the ability to functionally ambulate [1]. The wide range of functional skills in SMA patients, both between and within types, and their limited endurance pose obstacles in designing motor function assessments. Clinical trials in a relatively rare disease would preferably allow the enrollment of a wide phenotypic range of the disease population in order to facilitate recruitment and a broad application of results. Therefore, a motor function measure would ideally allow for the assessment of both SMA type II and type III patients. The Gross Motor Function Measure (GMFM) and Motor Function Measure (MFM) both cover the wide range of functional abilities seen in SMA type II and type III patients, but these tests typically take more time than the Hammersmith Functional Motor Scale (HFMS), an instrument developed for the evaluation of SMA type II patients [9–11].

The MFM was developed and validated for use in neuromuscular disorders. It shows excellent correlations with a visual analogue scale given by professionals, as well as, the Vignos and Brooke scales and the Functional Independence Measure. The MFM is able to discriminate amongst the various diagnostic groups that were included in the validation study and it showed adequate internal consistency. However, SMA accounted for only 10% of the tested population. In addition, the time to administer the test is considerable. The test time exceeds 30 min in the majority of cases, and some patients take more than an hour to complete the MFM [12]. The length of time to administer the test is significant because children with SMA fatigue easily. In any clinical trial the selected motor measure will be one of a number of outcomes and testing time and tolerability will be important considerations.

The GMFM was designed at McMaster University for the assessment of gross motor skills in patients with cerebral palsy. It consists of a group of tasks that span the range of skills typically seen in SMA type II and III patients. In previous studies, the reliability of the GMFM was established in patients with SMA ages 2–18 [9,11,13]. The convergent validity of the GMFM was established by correlation with muscle strength in patients from 5 to 18 years of age. The discriminant validity was established by demonstrating the tests ability to differentiate between SMA patients with varying degrees of clinical severity [9]. The testing inventory includes 88 items, which are each

scored on a 4 point (0–3) Likert scale, and divided into 5 dimensions: (1) lying and rolling, (2) sitting, (3) crawling and kneeling, (4) standing, (5) walking, running, and jumping. In addition to the raw score, the results are expressed as a percent of the maximum possible score for each dimension (ranging from 0 to 100 across the 5 dimensions).

The GMFM provides a sensitive measure of gross motor function in children with type II and III SMA. However, since it was developed for children with cerebral palsy not all the items are appropriate for children with SMA. For example, items requiring prone positioning cannot be administered effectively in those with hip flexion contractures. The GMFM can take 45 min to complete which is a disadvantage for its use in SMA clinical trials.

An alternative disease specific measure of motor function designed for SMA type II patients is the HFMS [10]. Motor skills are scored on 20 items using a 3 point (0–2) Likert scale. It is feasible (taking approximately 15 min to administer), requires minimal equipment, is clinically meaningful, and has good inter-rater reliability [10,14]. However, the limited range of skills that can be assessed (independent sitting to taking 4 steps) can result in a ceiling effect in higher functioning SMA patients.

The aim of this study is to create a GMFM-derived module that could be added to the HFMS to allow testing of patients with type II and type III SMA. Creating one scale with items that span the observed skill levels would allow both groups of patients to participate in the same trial using the same motor function scale. We initially presented the reliability of the first version of HFMS at the Families of SMA meeting in 2005. Here, we further refine that measure providing a valid and reliable test that permits the evaluation of SMA type II and III patients while at the same time being more rapidly administered and thus, better tolerated than the full GMFM assessment.

## 2. Patients and methods

### 2.1. Subjects

Fifty-four subjects with genetically confirmed SMA were evaluated at three study sites, as part of the Pediatric Neuromuscular Clinical Research (PNCr) SMA network. 38 of these 54 had type II ( $n = 21$ , median age = 5.7 years, range 2.3–32.5 years) or III ( $n = 17$  median age = 9.1 years, range 3.9–45.1 years). The remaining 16 subjects had type I. They were not evaluated using either the HFMS or the GMFM, and therefore are not included in any analysis. Informed consent was obtained from all parents and where appropriate, assent was obtained.

### 2.2. Clinical evaluators

Trained pediatric physical and occupational therapists within the PNCr Network had previously undergone training in the HFMS and the GMFM. Inter-rater reliability was established.

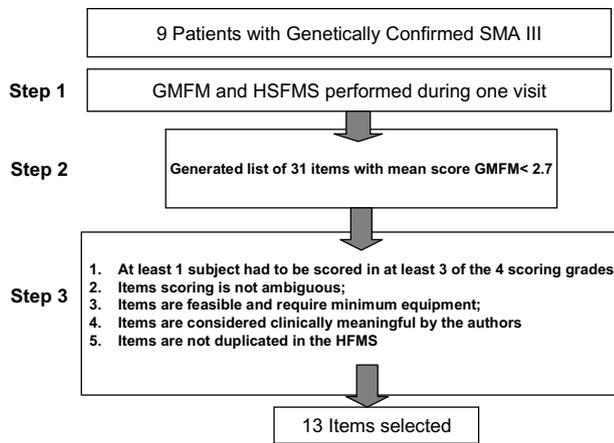


Fig. 1. Schematic description of methods used to determine add-on module to expand the HFMS.

### 3. Item selection

The 38 patients with SMA type II or III enrolled in an ongoing longitudinal cohort study were evaluated using the GMFM and the HFMS. Data from the first 9 patients with SMA III were examined to identify GMFM items that would be sensitive to change in these ambulatory patients. A selection process was designed to choose the most appropriate GMFM items (Fig. 1). First descriptive statistical analyses were used to eliminate those items with a ceiling effect in this population. A list of 31 items with a mean score of less than 2.7 on the GMFM scale was then generated. This cut-off point was determined to indicate those items with sufficient sensitivity in the subjects studied. Each of these 31 items was then analyzed individually using its mean, standard deviation and frequency distribution as a measure of that item’s sensitivity in the type III subjects. Items were selected based on fulfillment of the following selection criteria: (1) at least 1 subject had to be scored in 3 of the 4 scoring grades. This distribution of subject scores indicates an optimal level of operational definition sensitivity. (2) Items were not ambiguous as determined by clinical evaluators. (3) Items were feasible and required minimum equipment. (4) Items were considered clinically meaningful

by the clinical evaluators. (5) Items were not duplicated in the HFMS. This analysis generated 13 items (Table 1) that would be useful as an addition to the HFMS and allowing the assessment of advanced skills seen in ambulatory SMA patients.

### 4. Scoring

The scoring scale of the selected 13 GMFM items needed to be collapsed from a 4-point to a 3-point scale in order to be equivalent to the HFMS. To accomplish this, GMFM grades 1 and 2, both indicating partial task performance, were collapsed to grade 1, and grade 3 (full response) was changed to grade 2. Zero is scored for no response.

This 13-item expansion module was added to the HFMS to become the Expanded Hammersmith Functional Motor Scale (HFMS-E).

### 5. Statistical analysis

The validity and reliability of the HFMS-E were examined in the entire sample of 38 patients with type II or type III SMA. Although the intent of this scale development was to evaluate patients with SMA type II and type III, the HFMS-E was directed towards higher functioning skills. Therefore, the analyses were repeated for the subset of type III patients. Concurrent validity was examined by computing the Pearson rank correlation between the HFMS-E and the only validated motor measure for patients with SMA, the GMFM. Since the HFMS-E contains 13 items from the GMFM, we correlated the HFMS-E with the sum of the remaining 75 GMFM items (GMFM-75) rather than the full GMFM instrument as to not artificially inflate the score.

The validity of the HFMS-E was further examined by computing its Spearman rank correlation with a functional rating of the severity of each of the patients. This was accomplished by having a panel of experts rank the motor skills of each participant using a 10-point functional rating scale (Table 2). The panel consisted of 9 members, one

Table 1  
13 Item expansion module

| GMFM item number | GMFM dimension             | Item description   |
|------------------|----------------------------|--|
| 4                | Lying & rolling            | Supine: flexes right hip and knee through full range                                   |
| 5                | Lying & rolling            | Supine: flexes left hip and knee through full range                                    |
| 49               | Crawling & kneeling        | High kneeling: attains half kneel on right knee using arms, maintains, arms free, 10 s |
| 50               | Crawling & kneeling        | Attains half kneel on left knee using arms, maintains, arms free, 10 s                 |
| 60               | Standing                   | High kneeling: attains standing through half kneeling on right knee, with using arms   |
| 61               | Standing                   | High kneeling: attains standing through half kneeling on left knee, with using arms    |
| 62               | Standing                   | Standing; lowers to sitting on floor with control, arms free                           |
| 63               | Standing                   | Standing: attains squat, arms free   |
| 81               | Walking, running & jumping | Jumps forward 30 cm (12 in.), both feet simultaneously                                 |
| 84               | Walking, running & jumping | Standing, holding one rail: walks up four steps, holding one rail, alternating feet    |
| 85               | Walking, running & jumping | Standing, holding one rail: walks down four steps, holding one rail, alternating feet  |
| 86               | Walking, running & jumping | Standing, walks up four steps, alternating feet  |
| 87               | Walking, running & jumping | Standing, walks down four steps, alternating feet                                      |

Table 2  
Functional Rating Scale

|    |  |
|----|--|
| 1  | Unable to sit independently  |
| 2  | Sits independently   |
| 3  | Pulls to sit   |
| 4  | Supine to sit  |
| 5  | Stands but does not walk   |
| 6  | Takes >4 steps (with or without braces and assistive devices)                    |
| 7  | Household ambulatory-with or without orthotics and assistive devices for 50 feet |
| 8  | Community ambulator-with or without orthotics and assistive devices for >50 feet |
| 9  | Runs   |
| 10 | Age-appropriate in motor skills  |

neurologist specializing in pediatric neuromuscular disease, and two clinical evaluators from each of the three sites, blinded to the patient's HFMS and GMFM scores. On this ordinal scale, "10" indicates the ability to perform age appropriate motor skills and "1" indicates an inability to sit independently, the floor level for SMA type II.

The test-retest (intra-rater) reliability of the HFMSE, HFMS, and GMFM was evaluated using data from the baseline and month 2 visits. Gross motor function appears to be clinically stable, as measured by the HFMS [14] over a 3–6 month interval and by highly correlated test-retest scores using the GMFM over a two week period [11,13]. Reliability was quantified using Interclass Correlation Coefficients (ICCs) estimated from a random-effects one-way analysis of variance model.

## 6. Results

Of the 38 subjects evaluated, 21 subjects had SMA type II and 17 had SMA type III. There were 22 females and 16 males with a mean age of 10.7 years (range 2.3–45.1 years).

All participants completed the testing safely at the baseline evaluation and the 2 month visit. Each subject attempted each item and none were omitted in error. Rest periods were provided to ensure that the full GMFM and HFMS were performed without patient fatigue. In a stronger participant with SMA type III, this testing could take up to an hour, particularly in younger children. A weaker participant with SMA type II could be tested in about 20 min.

In the combined group of patients, the mean ( $\pm$ standard deviation) HFMS score was  $21.0 \pm 16.0$  out of a maximum total score of 40. The mean GMFM total score was  $43.7 \pm 35.7$  out of a maximum total score of 100. The mean HFMSE score was  $27.7 \pm 22.9$  out of a maximum total score of 66. As shown in Table 3, the HFMSE was highly correlated with the GMFM ( $\rho = 0.98$ ) and the GMFM-75

Table 3  
Spearman Rank Correlations between expanded Hammersmith (HFMSE) and GMFM and Functional Rating Scores

|                         | HFMSE Type II/III | HFMSE Type III |
|-------------------------|-------------------|----------------|
| GMFM-75                 | 0.97              | 0.94           |
| Functional Rating Score | 0.90              | 0.88           |

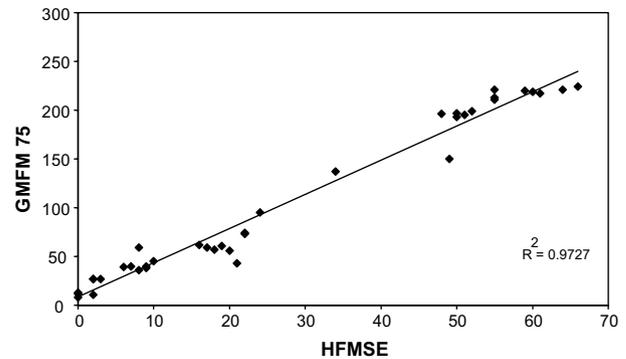


Fig. 2. Relationship of the HFMSE to the GMFM-75.

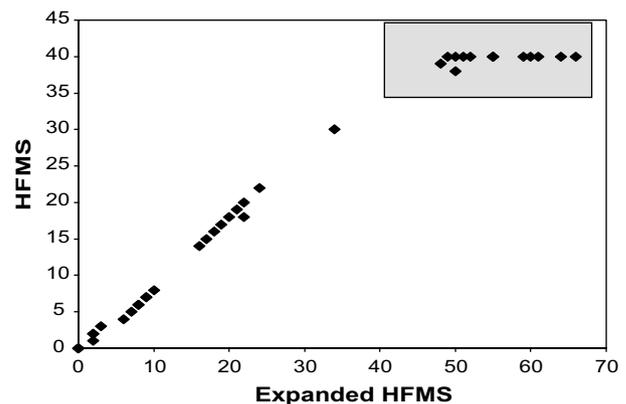


Fig. 3. Relationship of the HFMSE to the HFMS. Highlighted in gray are subjects at the ceiling of the original scale, but differentiated by the expanded instrument, the HFMSE.

( $\rho = 0.97$ , Fig. 2). Clinical presentation, as measured by the independent functional rating score, was also highly correlated with the HFMSE ( $\rho = 0.90$ ). The HFMSE was able to capture differences among type III patients who scored at the ceiling (40) of the HFMS (Fig. 3).

In the subgroup of 17 patients with SMA type III the mean HFMS score was  $36.8 \pm 7.0$  out of a maximum total score of 40. The mean GMFM score was  $78.1 \pm 24.3$  out of a maximum total score of 100. The mean HFMSE score was  $50.1 \pm 13.0$  out of a maximum total score of 66. The correlations between the HFMSE and the GMFM, GMFM-75, and the functional rating score remained very high in this subgroup (Table 3).

The intra-rater reliability of each of the three outcome measures (GMFM, HFMS, and HFMSE) was excellent. For the combined group of patients with SMA type II or type III, the ICCs were 0.99 for the GMFM, 0.98 for the HFMS, and 0.99 for the HFMSE. For the subgroup of patients with SMA type III, the ICCs were 0.99 for the GMFM, 0.97 for the HFMS, and 0.99 for the HFMSE.

## 7. Discussion

The HFMS provides an excellent tool for evaluation of motor function in pediatric patients with SMA type II. It is

responsive to change [15] and reliable [10,14] but it is limited by design to non-ambulatory patients with SMA. The items are designed to look at skills that are typically demonstrated by this population and that are a part of their unique developmental sequence. This allows an economy of effort on the patient's part while still producing valid data. However, clinical trials in this rare disease need to accommodate a broad spectrum of function to allow inclusion of as many patients with SMA as possible. Our analysis of the HFMS shows there is little concern for a floor effect since only 8% of our sample of type II and III SMA patients scored a 0 on the HFMS. However, as expected, the HFMS was not able to distinguish among high functioning patients with type II SMA and ambulatory patients with SMA III as it was not designed for ambulatory patients. Items needed to expand the HFMS into a scale applicable to a wider group of patients with SMA type II and III would need to include ambulation skills that were more advanced than "taking 4 steps independently".

The add-on items were chosen from the GMFM because it has been validated and shown to be reliable in patients with SMA [9,11]. We have shown that the HFMSE measures motor function in high functioning patients with SMA II and III. It captures the advantageous properties of the HFMS and the GMFM. Like the HFMS, it is administered in a short period of time and is less fatiguing to patients. It requires a minimal amount of equipment to perform the evaluation. Similar to the GMFM, the HFMSE has the ability to distinguish among ambulatory SMA III patients, and it allows for inclusion of a wider range of intermediate and mild SMA patients. The HFMSE is highly correlated with other clinical assessments and shows good test–retest reliability. These preliminary findings are encouraging and suggest that the HFMSE will be a valuable outcome measure in phase II and III clinical trials involving a broader range of patients with SMA II and III. Further research is needed to fully evaluate the reliability and validity of the HFMSE and to firmly establish its usefulness as a standardized outcome measure for SMA trials.

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