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Results of a two-year pilot study of clinical outcome measures in collagen VI- and laminin alpha2-related congenital muscular dystrophies

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Abstract

Potential therapies are currently under development for two congenital muscular dystrophy (CMD) subtypes: collagen VI-related muscular dystrophy (COL6-RD) and laminin alpha 2-related dystrophy (LAMA2-RD). However, appropriate clinical outcome measures to be used in clinical trials have not been validated in CMDs. We conducted a two-year pilot study to evaluate feasibility, reliability, and validity of various outcome measures, particularly the Motor Function Measure 32, in 33 subjects with COL6-RD and LAMA2-RD. In the first year, outcome measures tested included: Motor Function Measure 32 (MFM32), forced vital capacity (FVC) percent predicted sitting, myometry, goniometry, 10-meter walk, Egen Klassification 2, and PedsQL™ Generic and Neuromuscular Cores. In the second year, we added the North Star Ambulatory Assessment (NSAA), Hammersmith Functional Motor Scale (HFMS), timed functional tests, Measure of Activity Limitations (ACTIVLIM), Quality of Upper Extremity Skills Test (QUEST), and Patient-Reported Outcomes Measurement Information System (PROMIS) fatigue subscale. The MFM32 showed strong inter-rater (0.92) and internal consistency (0.96) reliabilities. Concurrent validity for the MFM32 was supported by large correlations (range 0.623–0.936) with the following: FVC, NSAA, HFMS, timed functional tests, ACTIVLIM, and QUEST. Significant correlations of the MFM32 were also found with select myometry measurements, mainly of the proximal extremities and domains of the PedsQL™ scales focusing on physical health and neuromuscular disease. Goniometry measurements were less reliable. The Motor Function Measure is reliable and valid in the two specific

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subtypes of CMD evaluated, COL6-RD and LAMA2-RD. The NSAA is useful as a complementary outcome measure in ambulatory individuals. Preliminary concurrent validity of several other clinical outcome measures was also demonstrated for these subtypes.
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Keywords: Clinical outcome measures; Neuromuscular disease; Collagen VI related muscular dystrophy; Laminin alpha 2 related dystrophy; Motor function scales

1. Introduction

Congenital muscular dystrophy (CMD) comprises a clinically diverse and genetically heterogeneous group of early-onset muscle disorders with characteristic dystrophic features on muscle biopsy. Core groups within the CMDs include collagen VI-related muscular dystrophies (COL6-RD) (Ullrich congenital muscular dystrophy, intermediate collagen VI-related muscular dystrophy and Bethlem myopathy), laminin alpha 2-related muscular dystrophy (LAMA2-RD) (merosin deficiency), the α-dystroglycan-related muscular dystrophies (dystroglycanopathies), lamin A/C-related muscular dystrophy (L-CMD), and selenoprotein N 1-related myopathy (rigid spine CMD) [1]. COL6-RD and LAMA2-RD together are the most common subtypes, with some clinical similarities but also differences. Both are chronically progressive pediatric disorders that present with hypotonia at birth and lead to increasing muscle weakness, respiratory insufficiency, and joint contractures within the first two decades of life [1,2]. However, both types include early- and late-onset presentations, as well as a severity spectrum [1,2]. Given this broad phenotypic spectrum, the 173rd European Neuromuscular Centre (ENMC) International Workshop on CMD outcome measures recommended evaluating performance using a battery of outcomes such as forced vital capacity (FVC) percent predicted, motor scales, quality of life measures, caregiver assessments, goniometry, and myometry [3]. Because therapeutic interventions are currently under development for these two CMD subtypes, the establishment of validated clinical outcome measures becomes a clinical priority [3].

In COL6-RD, the phenotypic spectrum ranges from an early-onset, severe presentation with inability to achieve ambulation or loss of ambulation at a mean age of 10 years (Ullrich CMD) [4] to a milder form in which individuals can achieve and maintain ambulation through adulthood (Bethlem myopathy) [5]Intermediate COL6-RD individuals achieve ambulation, but do not run nor hop, lose ambulation at a mean age of 19 years, and may develop respiratory insufficiency while ambulant [6]. Individuals with complete deficiency of laminin alpha 2 (laminin alpha 2-related dystrophy [LAMA2-RD] or complete merosin deficiency) typically do not achieve ambulation [7–9]. Individuals with partial deficiency of LAMA2 have a more variable phenotype in regard to pattern of weakness and may achieve ambulation [10].

The lack of validated clinical outcome measures in these two CMD subtypes led us to implement a novel study design to validate several outcome measures simultaneously in preparation for clinical trials. The prospective cohort design involved administering 17 outcome measures, specified below, which have been validated in other neuromuscular diseases and were thus predicted to show validity in our population [11–18]. The battery of measures was administered in one weekend (two years in a row) to a cohort of 22 (year 1) and 32 (year 2) participants by 15 experts (neuromuscular physicians, physical therapists, and psychologists). The administration of outcome measures also served as the basis for an ongoing, 5-year, prospective, natural history study in these two CMD subtypes, which uses outcome measures shown to be feasible, reliable, and valid in this initial two-year pilot study.

We specifically chose assessments that would allow examination of changes within the domains of the international classification of functioning, disability, and health of the World Health Organization (WHO) (Table 1). Although the WHO international classification was originally developed as a tool to aid in the development of interventions, community programs, and public policy, it can be used as an appropriate framework to identify and understand outcome measures [19]. The WHO approach places an emphasis on quantifying impairments of body structure and function, activity limitations, and participation restrictions in the context of one's personal and environmental factors. This approach defines the factors that impact how people with a particular muscle disorder feel and function over time and the various influences that might come to bear on the measurement of disability in the context of a clinical trial. Defining outcome measures within this framework allows prioritization of outcomes that are important for affected individuals and caregivers and creates an awareness of potential intervening variables related to measurement of function that might not be immediately apparent. The ability of an outcome

Table 1
World Health Organization (WHO) domains. Health condition: collagen VI related myopathy and laminin alpha 2 related dystrophy.

Categories	Problem	Assessment
Body functions/body structures	Development of contractures	Goniometry
	Muscle weakness	Myometry
	Respiratory impairment	FVC % predicted sitting
Activity	Inability to walk and dependence with activities of daily living	QUEST Motor Function Measure 32 ACTIVLIM Hammersmith Timed/scored functional tests NorthStar Ambulatory Assessment ACTIVLIM EK2
Participation	Physical well-being affecting participation within the community	ACTIVLIM, PROMIS, PedsQL™

International Classification of Functioning, Disability and Health: ICF. Geneva, Switzerland: World Health Organization; 2001. Available at: http://www.who.int/classifications/icf/en. Accessed October 3, 2011.

measure to establish efficacy in clinical trials is established through the reliability of measurement and its ability to reflect the domain targeted for measurement [19].

In CMD, common tools for clinical evaluation and thus potential candidates for outcome measures include tests of: muscle power (Medical Research Council [MRC] scale, myometry), joint passive range of motion (goniometry), and motor performance (timed, 10-meter walk/run, rise from floor, ascend/descend 4 stairs) [13,20–22]. Although these domains can be measured over time, it is unclear as to whether better scores in impairment-based measurements (e.g., range of motion or strength) translate into an improvement in function and ultimately in the child's quality of life.

Motor function scales, such as the Hammersmith Functional Motor Scale (HFMS), the North Star Ambulatory Assessment (NSAA), and more recently, the Motor Function Measure (MFM32), which have been validated in other neuromuscular disorders, may provide information regarding the global ability of the child to perform common motor tasks. The HFMS is validated in children with spinal muscular atrophy (SMA) and functional impairments [12]; the NSAA is validated in ambulatory children with Duchenne muscular dystrophy (DMD) and SMA type III [14,23]. The MFM32, validated in individuals with various neuromuscular disorders, is a scale that spans the spectrum of abilities from non-ambulatory to ambulatory [11,24,25]. Other scales gather information about different aspects of function. For example, the Egen Klassification Scale Version 2 (EK2) provides a picture of overall function in non-ambulatory individuals with DMD and SMA [17], and ACTIVLIM is a self-reported questionnaire of limitations in daily activities in children and adults with various NM disorders [18,26]. The Quality of Upper Extremity Skills Test (QUEST) measures several domains of upper extremity function and has been validated in children with cerebral palsy [27]. The Pediatric Quality of Life Inventory (Generic and Neuromuscular modules) has been validated in healthy individuals and individuals with SMA [16,28,29]. Finally, FVC has been shown to be a reliable outcome measure in SMA [29] and, recently, in COL6-RD, with the latter showing predicted rates of decline specific to the severity of disease [6].

The main goal of this study was to validate the use of several of these measurements in these two subtypes of CMD given the urgent need to accurately test the efficacy of potential therapies, which are currently under development for clinical trials. To address the ENMC's recommendation, we implemented a 2-year pilot study in individuals with COL6-RD and LAMA2-MD to test the feasibility, reliability, and validity of several motor scales (primarily the MFM32), myometry and goniometry measurements, affected individual and caregiver assessments, and quality of life measurements. As mentioned above, the pilot study serves as the basis of an ongoing, 5-year, longitudinal study, which will evaluate the validated measures' sensitivity to change over the 5-year natural history of COL6-RD and LAMA2-RD in the enrolled individuals. FVC percent predicted has now been demonstrated to be a viable outcome measure [6] and was used as the initial standard in the current study.

2. Subjects and methods

We obtained approval from the National Institute of Neurological Disorders and Stroke (NINDS) Institutional Review Board for this study. Subjects (and/or parents) who agreed to participate provided informed consent (and assent if a minor under the age of 18 years). Parents or caregivers of minors, heretofore referred to as parents, signed informed consent forms.

2.1. Participants

A total of 33 participants between the ages of 4 and 21 years with a diagnosis of COL6-RD (n = 17) or LAMA2-RD (n = 15) were seen at the National Institutes of Health outpatient pediatric clinic. Diagnosis was made by prior clinical exam and medical history, and, in 31 cases (94%), diagnosis was confirmed by genetic testing. Of the 33, one individual had neither COL6-RD nor LAMA2-RD after further evaluation. In year 1, a total of 22 individuals participated. Please see Table 2 for patient demographics. Ambulatory status was defined by the ability to walk 10 meters without orthotics or assistive devices.

Table 2
Study participants by year.

	Number of patients		
	Year 1	Year 2*	Total (%)
Enrolled	22	32** (21)	33** (100%)
LAMA2-RD	8	15 (8)	15 (45%)
COL6-RD	14	16 (13)	17 (52%)
Age			
Median	10.1	9.7	
Range	5.8–21.2	4.8–22.2	N/A due to age change with time
Mean	11.8	11.4	
SD	4.54	5.18	
LAMA2-RD			
Median	8.7	7.9	
Range	5.8–16.8	5.0–19.3	
Mean	9.9	9.1#	
SD	4.1	4.5	
COL6-RD			
Median	12.2	12.6	
Range	6.4–21.2	4.8–22.2	
Mean	12.6	13.3#	
SD	4.7	5.1	
Male	11	13 (11)	13 (39%)
LAMA2-RD	3	5 (3)	5 (15%)
COL6-RD	8	8 (8)	8 (24%)
Ambulant	11	12 (11)	12 (36%)
LAMA2-RD	3	4 (3)	4 (12%)
COL6-RD	8	9 (8)	9 (27%)
Attrition/Screening Failure	1	3 (1)	4 (12%)

* Numbers in parentheses for categorical measures represent cases from year 1 participating in year 2.

** One new participant in year 2 was a screening failure (not LAMA2 or COL6-RD) after further evaluation, thus the sum of LAMA2-RD and COL6-RD subjects does not equal the total enrolled. Demographics in year 2 do not include this individual or the other 2 individuals lost to attrition early in year 2.

The mean age of COL6-RD participants was significantly higher than LAMA2-RD participants by a difference of 4.5 years ($p = 0.01$).

2.2. Outcome measures (year 1)

In year 1, pulmonary function tests (PFTs) were performed by handheld spirometry in the sitting position. In addition, FVC in liters was converted to FVC percent predicted using ulnar length as a proxy for height. Other outcome measures tested included: (a) MFM32, including three domains which represent different aspects of motor capacity (D1: standing and transfers; D2: axial and proximal motor capacity; D3: distal motor capacity); (b) right and left measurements of myometry (Microfet [www.hogganhealth.net]): *hip flexors, hip abductors, knee flexors, knee extensors, ankle dorsiflexors, cervical flexors, shoulder abductors, elbow flexors, elbow extensors* [30]; (c) right and left measurements of goniometry (standard 2 arm goniometer): *hip flexion, hip extension, knee flexion, knee extension, ankle dorsiflexion, plantarflexion, shoulder abduction, elbow flexion, elbow extension, wrist flexion, wrist extension*; (d)10-meter walk; (e) EK2; and (f) Pediatric Quality of Life (Peds QL™) (i.e., Generic Core Scales 4.0 [25] [PQL-GC] and Neuromuscular Module 3.0 [16] [PQL-NM]).

A single pediatric physical therapist completed all goniometry and myometry measurements using standard positions and instructions, and six pediatric physical therapists administered the MFM32. In addition, a single physician administered the EK2 interview of the participant and caregiver. The self-report measures for quality of life (PQL-GC and PQL-NM) were completed by parents and children independently; children were assisted by an evaluator as needed.

2.3. Statistical methods (year 1)

Descriptive statistics were generated for all measures. Intraclass correlation coefficients (ICC) were carried out to explore the inter-rater reliability among the six MFM32 raters [31]. Agreement for ICCs are described as poor to fair (≤0.40), moderate (0.41–0.60), good (0.61–0.80), and excellent (0.81–1.00) [31,32]. Scales with reliabilities of 0.70 or greater are recommended for comparing patient groups, while a reliability criterion of 0.90 is recommended for analyzing individual patient scores [33,34]. Spearman rank order correlations were performed to examine the concurrent validity between the three MFM32 domains and the total scale scores with percent predicted FVC, myometry measures, goniometry measures, EK2, 10 m run/walk, and PedsQL™ scales. Correlations are designated as small (.10–.29), medium (.30–.49), and large (>.50) [32,35].

2.4. Participants (year 2)

An additional 11 individuals were enrolled in year 2. One participant from year 1 was lost to attrition before year 2 and another discontinued participation upon arriving the second year. Also, one of the 11 new individuals was a screening failure, because she had neither COL6-RD nor LAMA2-RD. Thus, the total number of participants in year 2 was 32. (See Table 2 for information regarding new and returning subjects.)

2.5. Outcome measures (year 2)

A number of additions were made in the measurement of outcomes in the second year. The North Star Ambulatory Assessment (NSAA) and the Hammersmith Functional Motor Scales (HFMS) were added. We hypothesized that the HFMS and NSAA would expand the motor function assessment of the MFM32 at both extremes of functional limitation and disease severity (NSAA for higher functioning/less severe and HFMS for lower functioning/more severe). Timed tests were added (4 steps, 6-minute walk test [6MWT], Floor to Stand) to capture additional outcomes in ambulatory individuals. Eight physical therapists participated in a day-long training session to review the additional assessments. Two therapists each administered the MFM32, HFMS, the NSAA/Functional/Timed tests (4 steps up/down, 10-meter [10] run, floor to stand), and Myometry/Goniometry. There were four patients under the age of 6 in our study in year 2, who, over the course of the 5 year study, aged up into the MFM32 validated age range. Therefore, we started all patients with the MFM32. A single therapist administered the 6MWT.

An upper extremity scale (Quality of Upper Extremity Skills Test [QUEST]) was added because some individuals with CMD do not achieve ambulation and upper extremity function measurement is very important in this population [3]. Like the MFM32, it would allow assessment of both ambulatory and non-ambulatory individuals on a single scale. The QUEST was administered by a single occupational therapist (OT). Given the severity of many individuals in our study and the way QUEST scores are standardized to result in a lower score than the raw score, we used raw rather than standardized QUEST scores.

The ACTIVLIM was added to capture activities of daily living in addition to EK2 and was administered by the OT who administered the QUEST. The PROMIS fatigue subscale, which is a self-report questionnaire, was added to investigate a measure of fatigue, a common complaint of individuals with CMD. Finally, the PQL-GC was removed after year 1 to reduce participant burden; the PQL-NM was kept because it is specific to neuromuscular disorders.

2.6. Statistical methods (year 2)

Descriptive statistics were generated for all measures performed in year 2. Analysis of the internal consistency reliability of all multiple-item scales was performed using Cronbach's alpha. The validity of the MFM32 was examined using Spearman rank order correlations with all other outcome measures as in year 1. Discriminant analysis of the MFM32 and HFMS for the trait of ambulation was performed using the two-sample Wilcoxon–Mann–Whitney test with a significance level of <0.05 to explore construct validity. We hypothesized that individuals with higher levels of ambulation would have higher scores on the MFM32 and HRMS. For the MFM32, HFMS, and NSAA, a ceiling effect was determined by >20% of

Table 3
Descriptive statistics (year 1).

Test	Measure	N	Mean	SD	Range
MFM32	D1: Standing and transfers	21	31.8	29.6	0–87.6
	D2: Axial and proximal motor capacity	21	71.5	23.2	21.9–98.2
	D3: Distal motor capacity	21	84.8	14.7	49.2–100.0
	Total score	21	58.9	21.4	25.1–93.9
Myometry	Elbow Flx R	21	6.8	2.7	1.6–11.9
	Elbow Flx L	21	6.9	2.4	1.6–10.9
	Elbow Ext R	21	4.1	2.2	1.2–8.0
	Elbow Ext L	21	4.6	2.6	1.0–10.1
	Knee Flx R	21	11.7	5.2	2.7–20.5
	Knee Flx L	21	12.2	5.9	1.4–22.9
	Knee Ext R	21	12.9	7.5	2.0–25.4
	Knee Ext L	21	12.1	8.1	1.6–30.6
Goniometry	Elbow Flx R	21	149.2	9.0	130–161
	Elbow Flx L	21	148.4	9.2	135–165
	Elbow Ext R	21	−39.8	41.3	−120 to 0
	Elbow Ext L	21	−34.7	36.0	−114 to 0
	Knee Ext R	21	−15.3	27.1	−95 to 12
	Knee Ext L	21	−15.6	27.3	−92 to 10
10 m walk		11	8.6	3.5	4.0–15.8
EK2	Total score	21	9.9	8.7	0–26
FVC sitting	% Predicted	21	60.1%	24.9%	16.7%–104.5%
PedsQL 4.0 Generic Core	Physical health	21	34.9	21.3	6–81
Parent Proxy-Report	Emotional functioning	21	70.9	20.1	40–100
	Social functioning	21	63.6	15.2	25–90
	School functioning	21	74.5	19.4	40–100
	Psychosocial health	21	69.6	14.8	40–95
	Total score	21	60.9	13.5	32–90
Test	Measure	N	Mean	SD	Range
PedsQL 4.0 Generic Core	Physical health	21	44.9	22.5	19–97
Child Self-Report	Emotional functioning	21	73.6	17.3	40–100
	Social functioning	21	65.7	17.4	10–95
	School functioning	21	77.1	18.9	40–100
	Psychosocial health	21	72.1	13.1	47–93
	Total score	21	65.3	12.2	49–94
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	20	61.8	18.4	25–93
Parent Proxy-Report	Communications	20	73.7	29.7	0–100
	Family resources	20	61.2	22.8	0–95
	Total scores	20	65.6	18.0	30–90
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	20	71.7	16.2	34–93
Child Self-Report	Communications	16	80.7	23.5	17–100
	Family resources	16	76.6	13.9	45–100
	Total scores	20	75.7	13.7	40–95

SD = standard deviation; D1 = domain 1; D2 = domain 2; D3 = domain 3; Flx = flexion; Ext = extension; R = right; L = left.

individuals scoring the maximum score on an item. Likewise, a floor effect was determined by >20% of individuals scoring the minimum score on an item. Greater than 20% of individuals were chosen based on previous research.

3. Results

3.1. Year 1

Descriptive statistics for all outcome measures performed in year 1 are provided in Table 3. Note that goniometry measurements display a wide range.

3.1.1. Reliability

MFM32: the inter-rater reliability was good to high for each of the three domains (standing and transfers [D1], axial and proximal motor capacity [D2], and distal motor capacity [D3]) and the total score, ranging from 0.78 to 0.94 (Table 4).

3.1.2. Concurrent validity

FVC: The associations of sitting FVC percent predicted with MFM32 domains and total score were large ($r = 0.51–0.84$) and significant ($p < 0.05–0.01$) (Table 5). Of note, Domain 1 (D1: Standing and Transfers), Domain 2 (D2: Axial and Proximal Motor Capacity), and the total score each had a stronger correlation with sitting FVC percent predicted than did Domain 3 (D3: Distal Motor Capacity).

Myometry and goniometry: Spearman rank order correlations of the measurements of myometry and goniometry with scores from each of the MFM domains and MFM total score are shown in Table 5. Myometry for the lower extremity muscle groups showed significant correlations ranging from

Table 4
Inter-rater Reliability for MFM32 based upon 6 raters (year 1).

Inter-rater reliability					
Statistic		MFM32 domain scores			
		D1: Standing and transfers	D2: Axial and proximal motor capacity	D3: Distal motor capacity	Total scores
Reliability measure	ICC	0.94	0.90	0.78	0.92

D1 = domain 1; D2 = domain 2; D3 = domain 3; ICC = intraclass correlation.

$r = 0.58$ to 0.87 and elbow and knee extension goniometry ranging from $r = 0.54$ to 0.83.

10-meter walk: Of the 22 individuals, 11 completed the 10 m walk. The associations between each of the MFM32 domains and total score with the 10 m walk were large and significant except for the Distal Motor Capacity Domain.

EK2: Large and significant correlations were found between the EK2 and the MFM32 in year 1 (Table 5).

Table 5
Validity – Spearman rank correlations of MFM with other measures (year 1).

Test	Measure	Spearman rank order correlations			
		MFM D1: Standing and transfers	MFM D2: Axial and proximal motor capacity	MFM D3: Distal motor capacity	MFM total scores
FVC sitting	% Predicted	.793**	.836**	.510*	.819**
Myometry	Elbow Flx R	.271	.229	.452*	.295
	Elbow Flx L	.416	.365	.535*	.419
	Elbow Ext R	.541*	.458*	.575**	.525*
	Elbow Ext L	.545*	.472*	.534*	.541*
	Knee Flx R	.731**	.701**	.871**	.762**
	Knee Flx L	.632**	.583**	.819**	.673**
	Knee Ext R	.738**	.687**	.709**	.729**
	Knee Ext L	.685**	.630**	.767**	.688**
Goniometry	Elbow Flx R	−.021	−.040	−.225	−.053
	Elbow Flx L	.081	.138	−.210	.033
	Elbow Ext R	.759**	.826**	.624**	.777**
	Elbow Ext L	.774**	.812**	.584**	.765**
	Knee Ext R	.748**	.675**	.542*	.663**
	Knee Ext L	.784**	.724**	.594**	.716**
10 m walk		−.780**	−.734*	−.299	−.743**
EK2 (year 1)	Total score	−.582**	−.500*	−.611**	−.550**
PedsQL 4.0 Generic Core Parent Proxy-Report	Physical health	.602**	.472*	.444*	.482*
	Emotional functioning	.356	.167	.155	.284
	Social functioning	.065	−.017	.093	.059
	School functioning	.140	.037	.146	.136
	Psychosocial health	.268	.120	.149	.234
	Total score	.367	.178	.229	.293
PedsQL 4.0 Generic Core Child Self-Report	Physical health	.584**	.510*	.163	.495*
	Emotional functioning	.155	−.031	−.055	.066
	Social functioning	−.317	−.409	−.198	−.337
	School functioning	.114	−.019	.144	.118
	Psychosocial health	−.053	−.233	−.093	−.094
	Total score	.212	.036	−.037	.150
PedsQL 3.0 Neuromuscular Module Parent Proxy-Report	Neuromuscular disease	.500*	.376	.336	.400
	Communications	.116	.117	.278	.146
	Family resources	.484*	.389	.478*	.463*
	Total scores	.415	.342	.496*	.420
PedsQL 3.0 Neuromuscular Module Child Self-Report	Neuromuscular disease	.403	.291	.356	.309
	Communications	.186	.126	.017	.142
	Family resources	.330	.176	.333	.243
	Total scores	.434	.340	.415	.391

D1 = domain 1; D2 = domain 2; D3 = domain 3; Flx = flexion; Ext = extension; R = right; L = left.
*p ≤ 0.05, **p ≤ 0.01.
Correlations are designated as small (.10–.29), medium (.30–.49), and large (>.50) [35].

Table 6
Descriptive statistics (year 2).

Test	Measure	N	Mean	SD	Range
MFM32	D1: Standing and transfers	29	31.17	30.40	0–100
	D2: Axial and proximal motor capacity	29	72.69	26.38	11.1–100
	D3: Distal motor capacity	29	83.40	14.09	47.6–100
	Total score	29	58.21	22.89	19.8–100
Myometry	Elbow Flx R	27	5.23	4.64	0–23.8
	Elbow Flx L	27	5.46	4.07	0–19.9
	Elbow Ext R	26	3.13	4.22	0–20.1
	Elbow Ext L	27	3.42	3.71	0–18.6
	Knee Flx R	27	9.42	7.32	2.3–36.3
	Knee Flx L	27	9.60	6.49	2.3–30.4
	Knee Ext R	26	10.80	9.34	2.0–43.6
	Knee Ext L	27	10.14	9.63	0–46.9
Goniometry	Elbow Flx R	23	149.52	5.04	140–160
	Elbow Flx L	23	148.04	5.74	138–160
	Elbow Ext R	23	−38.09	37.10	−115 to 10
	Elbow Ext L	23	−37.00	39.42	−120 to 8
	Knee Ext R	22	−19.77	27.83	−86 to 16
	Knee Ext L	22	−19.73	29.45	−105 to 10
FVC sitting	% Predicted	29	62.38%	26.50%	10–105%
EK2	Total score	29	9.62	7.96	0–21
Stand_Time		11	30.67	56.46	2.5–197.4
Run10m_Time		13	7.70	3.22	3.0–14.7
Ascend4Steps		29	1.83	1.36	1–6
Descend4Steps		29	2.24	1.79	1–6
Meters6MinWlk		11	338.27	126.65	144–600
Minutes6MinWlk		11	5.62	1.05	2.51–6.0
QUEST		29	77.68	24.28	28.24–100
ACTIVLIM Logit score		24	0.56	2.99	6.26 to −0.32
NSAA (NorthStar)		29	7.52	10.21	0–34
Hammersmith		29	22.24	14.48	0–40
PROMIS		29	50.28	9.28	34–72
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	26	54.73	16.92	31–94
Parent Proxy-Report	Communications	26	74.04	22.62	17–100
	Family resources	26	55.77	19.06	10–95
	Total scores	26	61.58	14.78	40–95
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	26	71.65	13.58	50–96
Child Self-Report	Communications	17	76.00	24.47	25–100
	Family resources	17	78.24	18.02	45–100
	Total scores	26	73.58	14.67	49–99

SD = standard deviation; D1 = domain 1; D2 = domain 2; D3 = domain 3; Flx = flexion; Ext = extension; R = right; L = left.

PQL-GC and PQL-NM: The physical health domain of the PQL-GC (parent and child) showed medium and significant correlations with the MFM total score. The PedsQL™ neuromuscular module neuromuscular domain and family resources domain (parent only) showed medium to strong correlations with the MFM32's D1 score (Table 5).

3.2. Year 2

Descriptive statistics for all outcome measures performed in year 2 are shown in Table 6. Similar to year 1, goniometry results display a wide range.

3.2.1. Reliability

Internal consistency, as assessed by Cronbach's α reliability coefficients, for year 2 measures was above 0.86 for the total scores of all scales, including MFM32, NSAA, HFMS, QUEST, ACTIVLIM, PROMIS fatigue subscale and PQL-NM (parent and child). Cronbach's alpha for domains within scales ranged from .73 to .96 (Table 7).

3.2.2. Concurrent validity

Spearman rank order correlations of all year 2 outcome measures including myometry, goniometry, NSAA, HFMS, timed tests, EK2, QUEST, ACTIVLIM, and PQL-NM (parent) with MFM32 total scores are shown in Table 8. With few exceptions, correlations were statistically significant and showed medium to large associations. Exceptions included several goniometry measures, the PROMIS fatigue subscale, the PQL-NM child scale, and one domain of the PQL-NM parent scale.

We subdivided the entire cohort by mean age (11 years) and the only major difference in the correlations was between MFM32 total score and FVC% predicted (<11 years = .470 vs. > 11 years = 0.905; group = 0.623). Although COL6-RD individuals were older by a mean difference of 4.4 years

Table 7
Reliability – Cronbach's coefficient α for measures in year 2.

Measure	Cronbach's α
MFM	
D1: Standing and transfers	.96
D2: Axial and proximal motor capacity	.93
D3: Distal motor capacity	.73
Total	.96
QUEST	.88
ACTIVLIM (items 1–14)	.97
NSAA	.98
Hammersmith	.96
PROMIS	.87
PedsQL Neuromuscular (Child)	
Disease	.73
Communication	.63
Family resources	.73
Total	.87
PedsQL Neuromuscular (Parent)	
Disease	.86
Communication	.78
Family resources	.74
Total	.88

D1 = domain 1; D2 = domain 2; D3 = domain 3.

($p = 0.02$), analyses by disease subtype did not differ dramatically. The only major difference was in the correlation of Peds QoL parent scores to the MFM32 total score (COL6-RD = 0.744 vs. LAMA2-RD = 0.076; group = 0.489). The timed motor measurement correlations (floor to stand and 10 m run) were also different by subtype, but this can be attributed to the small number of ambulatory LAMA2-RD patients (n = 4).

3.2.3. Discriminant analysis

The MFM32 total score showed a significant difference between non-ambulatory individuals, median score 44.8 (range: 19.8–80.2), and ambulatory individuals, median score 82.3 (range: 59.4–100.0), with a $p < 0.0001$. All of the MFM32 domains showed a significant difference in median scores: D1 non-ambulatory median score 3.8 (range: 0.0–56.4) and ambulatory median score 61.5 (range: 25.6–100) with a $p < 0.0001$; D2 non-ambulatory median score of 61.1 (range: 11.1–97.2) and ambulatory median score 94.4 (range: 75.0–100.0) with a $p = 0.0009$; D3 non-ambulatory median score 71.4 (range: 47.6–100.0) and ambulatory median score 95.2 (range: 81.0–100.0) with a $p = 0.0038$. Likewise, the HFMS showed a significant difference with a non-ambulatory median score 9.5 (range: 0.0–38.0) and an ambulatory median score 36.0 (range: 22–40) with a $p = 0.0002$.

3.2.4. Ceiling and floor effect

In the MFM32 (32 items total), 23 items (72%) had >20% of participants with a maximum score of 3 (Appendix S1: Supplementary Table S1). Of these items, 5 were from D1, 11 from D2, and 7 from D3. In addition, 14 items (44%) had >20% of participants with a minimum score of 0, of which 12 were from Domain 1. The HFMS (20 items total) had 2 items (10%) with >20% of participants with a maximum score of 2 and 17 items (85%) with >20% of participants with minimal score of 0 (Appendix S1: Supplementary Table S2). The NSAA (17 items total) had 2 items (12%) with >20% of participants with maximum score of 2 and all 17 items (100%) had >20% of participants with minimum score of 0 (Appendix S1: Supplementary Table S3).

4. Discussion

Until recently, natural history studies in CMD have been limited to small, retrospective studies of key medical care issues [10]. A universal finding highlighted in these previous studies is that the rate of change in FVC percent predicted was indicative of the progressive respiratory insufficiency in CMD [4,10]. A more recent, larger, retrospective study of pulmonary function in 145 individuals with COL6-RD confirmed this finding, and showed predicted rates of decline based on disease severity in COL6-RD [6].

Thus, although progress has been made in characterizing the annual rate of change in pulmonary function, this has not been studied prospectively. Furthermore, challenges remain in identifying a sensitive measure of skeletal muscle function and ascertaining the strength of the association between respiratory and muscle function and functional impairment [21]. Because FVC is not a global measure of motor function, we used FVC percent predicted as an initial standard in our study and compared it to the total score and the three domains of the MFM32. As would be expected because distal motor capacity does not involve the thorax or abdomen, which directly affect respiration, the MFM32 total score and domains reflecting standing/transfers and axial/proximal motor function were associated more strongly with FVC than the distal motor capacity domain. In a separate study, we will report the differences in pulmonary function between individuals with COL6-RD and LAMA2-RD, which is beyond the scope of this manuscript.

After finding empirical support for the concurrent validity of the MFM32 against FVC percent predicted and discussions with experts, we tested other motor function scales against the MFM32. The HFMS (strongly) and NSAA (moderately) correlated significantly with FVC percent predicted (data not shown), and both had high and significant correlations with all domains of the MFM32 and its total score, which provided support for concurrent validity. Furthermore, a discriminant analysis showed that the HFMS score, each MFM32 domain, and the MFM32 total score differed significantly between ambulatory and non-ambulatory individuals.

Although both of these motor function scales had a floor effect in many items, the floor effect in the MFM32 was limited primarily to the domain evaluating standing and transfers. This enables the scale to remain useful in severely affected individuals as the other two domains can still be evaluated. Although individuals who were non-ambulatory had a floor effect in the standing/transfers domain of the MFM, contrary to our hypothesis, the HFMS did not test any lower functioning skills and thus would not be advantageous to administer in the same study. Therefore, to reduce participant burden the use of one of these two scales is likely sufficient in a study as their association was very high, many of the tasks were redundant, and the time to administer each is

Table 8
Validity – Spearman rank order correlations of MFM32 total with other outcome measures (year 2).

Test	Measure	Spearman rank order correlations			
		MFM D1: Standing and transfers	MFM D2: Axial and proximal motor capacity	MFM D3: Distal motor capacity	MFM total scores
Myometry	Elbow Flx R	.632**	.544**	.776**	.650**
	Elbow Flx L	.539**	.420*	.718**	.540**
	Elbow Ext R	.722**	.699**	.750**	.745**
	Elbow Ext L	.599**	.547**	.669**	.600**
	Knee Flx R	.709**	.554**	.850**	.716**
	Knee Flx L	.677**	.494**	.786**	.674**
	Knee Ext R	.728**	.618**	.715**	.720**
	Knee Ext L	.712**	.637**	.706**	.715**
Goniometry	Elbow Flx R	.081	.140	.052	.117
	Elbow Flx L	.078	.064	.009	.069
	Elbow Ext R	.738**	.812**	.487*	.772**
	Elbow Ext L	.795**	.852**	.502*	.820**
	Knee Ext R	.784**	.882**	.456*	.819**
	Knee Ext L	.799**	.875**	.477*	.833**
FVC sitting	% predicted	.619**	.691**	.143	.623**
EK2	Total score	−.796**	−.716**	−.743**	−.794**
Stand_Time		−.648*	−.742**	−.617*	−.774**
Run10m_Time		−.779**	−.709**	−.347	−.801**
Ascend4Steps		.881**	.812**	.722**	.888**
Descend4Steps		.893**	.794**	.713**	.895**
Meters6MinWlk		.848**	.727*	.457	.831**
Minutes6MinWlk		.273	.370	.546	.392
QUEST		.871**	.832**	.505**	.849**
ACTIVLIM (items 1–14)		.855**	.852**	.739**	.871**
NSAA (NorthStar)		.921**	.846**	.693**	.929**
Hammersmith		.936**	.907**	.672**	.936**
PROMIS		.285	.200	.080	.237
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	.487*	.421*	.422*	.467*
Parent Proxy-Report	Communications	.112	.220	.085	.186
	Family resources	.427*	.299	.323	.392*
	Total scores	.447*	.444*	.421*	.489*
PedsQL 3.0 Neuromuscular Module	Neuromuscular disease	.169	.135	.263	.225
Child Self-Report	Communications	−.261	−.134	.149	−.198
	Family resources	.084	−.014	.472	.098
	Total scores	−.026	−.036	.280	.055

D1 = domain 1; D2 = domain 2; D3 = domain 3; Flx = flexion; Ext = extension; R = right; L = left.
*p ≤ 0.05, **p ≤ 0.01.
Correlations are designated as small (.10–.29), medium (.30–.49), and large (>.50) [35].

approximately equivalent. The MFM32 provides more information than the HFMS: its floor effect is limited to the standing/transfers domain, and the MFM32's classifies items into three differing domains of motor performance. It is also validated in children and adults who are both ambulatory and non-ambulatory. However, Mazzone and colleagues recently noted that the HFMS and the MFM20, which are validated through a younger age group than the MFM32, may provide different information at the extreme levels of the spectrum of motor performance [36].

Although the MFM32 was originally designed for individuals with various forms of neuromuscular disease, individuals with CMD in this study had difficulty with specific tasks because of their prominent joint contractures. Many could not achieve the required starting positions and were limited in their ability to complete other tasks because of their restricted joint range of motion. A formal Rasch analysis of the MFM32 in congenital muscle disorders is currently underway to identify specific tasks on the scale that may not be appropriate in CMD in order to eliminate the problematic items and further develop its use in this sub-population of neuromuscular disease.

As a pure ambulatory assessment, the NSAA has some higher functioning skills such as climbing, jumping, and hopping (bilaterally tested) that are not included on the MFM32. Because of the phenotypic spectrum of CMD, some of the higher functioning individuals displayed a ceiling effect on the MFM32. These individuals could be assessed using the NSAA, which did complement the MFM32 in individuals who were ambulatory as we had hypothesized. In keeping with the NSAA's original intent for use only in ambulatory individuals [14], all items on the NSAA had a floor effect, and many non-ambulatory individuals could not complete the items because they could not stand.

Selected domains of the MFM32 and its total score were associated with certain myometry measures, in particular elbow flexors, knee flexors, and knee extensors. We find in the ongoing study that measurements of these muscle groups have relatively high inter-rater reliability and thus lend themselves to consistent use across clinical sites. In year 2, the ACTIVLIM, EK2 and timed tests generally showed associations with all three domains of the MFM32 and its total score. This finding is encouraging as ACTIVLIM and EK2 address activities of daily living whereas timed tests and MFM32 capture performance in a clinical setting, suggesting the two concepts are related and complementary.

Regarding upper extremity function, the QUEST unexpectedly showed associations with the MFM32 total score and its standing/transfers and axial/proximal domains but had a lower correlation with the distal motor capacity domain. Of note, given the severity of many individuals in our study and the way QUEST scores are standardized to result in a lower score than the raw score, we used raw rather than standardized QUEST scores. In another ongoing analysis, we are evaluating the QUEST by domain rather than by its total score, which was ultimately recommended in the validation of the QUEST in cerebral palsy [27]. Hopefully this ongoing study will elucidate the reason for the lower correlations between the MFM32 distal motor capacity domain and the QUEST domains. As part of the 5 year study, additional upper extremity function measures are also being validated in this population, including the Jebsen Hand Function Test, Myogrip, Myopinch, and Moviplate.

For the concurrent validity of the PROMIS Fatigue subscale and the PQL-GC and PQL-NM, lower correlations with the MFM32 were somewhat expected. These findings reflect that the construct of fatigue differs from that of motor function. In addition, the significant correlation with the MFMF32 of the PQL-NM in the neuromuscular and family resources domains (parent, year 2) suggests that motor function may be only one of several factors that influences quality of life in individuals with CMD. Future research is needed to better understand the factors that might mediate the relationship between motor function and changes in quality of life given that quality of life is an important clinically meaningful factor that the FDA considers in clinical trials [37], and children may underreport decreased quality of life [38].

In regard to feasibility and reliability, we found that the majority of the measures were both feasible and reliable for use in individuals with CMD. All domains and the total score of the MFM32 showed both very high inter-rater and internal consistency reliability, with the exception of the distal domain showing slightly lower internal consistency. A number of other scales also displayed high internal consistency, which shows that the items on each scale reflect a consistent construct in these two subtypes of CMD.

Goniometry was the main measure that was unreliable in select joints. Based on the literature and our findings, we recommend that repeated goniometry measures in clinical trials be limited to joint measurements with reliable bony landmarks [13,19–21,39]. In fact, a limitation of the study was that goniometry was reproducible only in certain joints over 2 years (hip extension, knee extension, elbow extension), and inconsistent measurements as evidenced by large standard deviations were found in other joints (shoulder abduction, hip flexion, ankle dorsiflexion, cervical flexion). This inconsistency may have resulted from the challenges in obtaining a standard point of reference to assess these joints. Although contractures in these joints play a significant role in activity limitation, assessment tools, even with well-defined protocols, are lacking.

To identify whether age and diagnosis affected the results of our study, we subdivided the cohort by mean age and by disease subtype and found no major differences overall. The few exceptions included a major difference based on age between MFM32 total score and FVC% predicted; younger children had lower association between MFM and FVC% predicted as they may not understand how to properly perform the maneuver. The two major differences by subtype were 1) Peds QoL parent scores, where LAMA2-RD parent scores showed a lower association with MFM32 and 2) timed motor measurements (floor to stand and 10 m run) associations differed, which can be attributed to the small number of ambulatory LAMA2-RD patients (n = 3). The 5 year study will allow us to explore these differences further.

In summary, a 2-year pilot study in individuals with COL6-RD and LAMA2-MD was completed to test the feasibility, reliability, and validity of selected motor scales, myometry and goniometry measurements, caregiver assessments, and quality of life measurements in this population. Assessment tools were selected to reflect the WHO domains of body function, activity, and participation. We particularly focused on the MFM32 because of its coverage of three different domains of motor function affected in CMD: standing and transfers, proximal and axial, and distal. The ultimate goal was to validate these measures for future clinical trials. We found that the MFM32 total score correlated very strongly with FVC percent predicted sitting, which is arguably the best currently available standard for disease status, particularly in COL6-RD. MFM32 also discriminated between ambulatory and non-ambulatory status, but had a floor effect assessing standing and transfers in this population. A ceiling effect was also noted, and we thus recommend supplementing the MFM32 with the NSAA in ambulatory individuals. An ongoing Rasch analysis of MFM32 will be used to identify items that are not feasible in these conditions because of prominent contractures, which make attaining certain starting positions very difficult.

In the final three years of the 5-year study, we will carry forward the MFM32 rather than the Hammersmith because the two were redundant and the Hammersmith did not add any information for individuals who had a floor effect on the MFM32. The NSAA will be used in ambulatory individuals only to complement the MFM32. We will also continue to test FVC percent predicted prospectively. Although all timed tests will be carried forward, only certain myometry and goniometry measures, namely elbow flexors, knee flexors, and knee extensors, will be assessed in the final three years based on the results of this study and previous goniometry literature.

Measures related to activities of daily living (EK2 and ACTIVLIM), upper extremity capacity (QUEST), which had good reliability and concurrent validity, will continue to be used to complement the motor function measures. The PQL-NM will also be kept because of the importance of capturing quality of life in clinical trials.

We hypothesize that meaningful and significant changes in function and quality of life can be captured by the above battery of preliminarily validated outcome measures over a minimum of three years, the final three years of the ongoing study, and up to five years for those participating since this pilot phase. Because the magnitude of change may be associated with individuals' CMD subtype, ambulatory status, and respiratory support level, we will explore the rate of change in the outcome measures and their association with these contributing factors. This sensitivity to change will be studied at the individual and cohort levels and will provide novel insight into progression of disease as well as the outcome measures best suited for clinical trials.

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Appendix: Supplementary material

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