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173rd ENMC international workshop: Congenital muscular dystrophy outcome measures 5–7 March 2010, Naarden, The Netherlands

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The 173rd ENMC/TREAT-NMD workshop on congenital muscular dystrophy (CMD) outcome measures is the 9th CMD workshop, beginning in 1993 with the establishment of a CMD consortium. The workshop brought together 22 clinicians and experts from five countries to advance the implementation of suitable clinical outcome measures and

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endpoints specific for the CMDs to advance CMD clinical trial readiness. The CMDs are a genetically diverse group of early onset disorders of muscle with dystrophic features in the muscle biopsy. The core genetic groups currently subsumed under the CMDs are the collagen VI related myopathies Ullrich and Bethlem, laminin alpha 2 deficient CMD, the alpha-dystroglycan related CMDs (dystroglycanopathies) and SEPN1 related myopathy (Rigid Spine CMD). Despite the genetic heterogeneity, the clinical problems posed by these conditions are sufficiently interrelated to justify developing an integrated diagnostic, management and therapeutic development approach across CMD forms. Such a unified approach for the CMDs has resulted recently in the launch of an international CMD registry (CMDIR) and a parallel effort to delineate CMD consensus care and diagnostic guidelines, as necessary steps towards the implementation of future CMD clinical trials.

The workshop focused on three specific goals: to identify clinically relevant functional classes within the individual CMD subtypes that could be combined for the purpose of clinical outcomes; to review currently available motor scales for their suitability for the functional classes and specific subtypes and to outline CMD common data elements to support the launch of a future international CMD longitudinal study.

The workshop highlighted the critical need to develop outcome measures, and determine the disease driven rate of change per endpoint (motor or pulmonary), the responsiveness of each motor scale to measure change within the time course of a clinical trial and the validity of the scale to the CMD context. Rating scales are increasingly used as primary or secondary outcome measures in neuromuscular clinical studies and have become key dependent variables upon which decisions are made that influence patient care and guide future research. The adequacy of these decisions depends directly on the scientific quality of the rating scales. Using motor scales as primary endpoints in clinical trials to assess therapeutic efficacy in chronic progressive diseases, such as CMD, has not been established. Despite limitations and concerns regarding commonly used scales in neurologic clinical trials, such as the Rankin scale in stroke research, the single item Ashworth scale, and the Alzheimer's Disease Assessment Scale cognitive behavior section (ADAS-cog) in dementia, their use remains widespread. Statistical adequacy does not automatically confirm clinical validity or interpretability. Identifying new approaches to define outcome measures, including patient reported outcomes and validating the scales in the disease specific context will improve their ability to effectively measure clinically significant endpoints that are meaningful to patients with a given disease. Scale evaluation needs to address two key requirements: satisfying the scientific definition for measurements and identifying the variables the scale is and is not measuring in a particular population. New psychometric methods, including Rasch analysis, provide a structured statistical approach to develop rigorous and transparent rating scales [1].

For the acquisition of adequate natural history data, established motor scales can either be adapted or used in their current form. Potential scale deficiencies in the CMDs can be analyzed using psychometric analysis, including Rasch analysis. To fully capture the CMD phenotypic and severity spectrum, age dependent motor functions in ambulatory and nonambulatory infants, children and young adults, need to be taken into account and underscore the importance of a functional phenotypic approach over a genotypic classification. Preliminary CMD functional cohorts for the purpose of outcome scale

development include: infants/children <2.5 years, ambulatory 2.5–5 years, ambulatory >5 years, nonambulatory 2.5–5 years and nonambulatory >5 years. Inclusion of quality of life measurements and assessment of meaningful age dependent activities of living from both the caregiver and affected individual perspective are critical to the design of a useful clinical trial toolbox.

1. Center specific CMD retrospective data analysis in the context of clinical endpoints

In order to define applicable outcomes and scales, clinician experts presented available retrospective CMD data with an emphasis on motor function, respiratory capacity, scoliosis and the progression of these parameters. This review, while addressing the variances between the individual subtypes also confirmed the significant overlap to justify addressing patients from different subtypes within common functional subclasses assessed by existing outcome scales. Differences in center specific retrospective data illustrate phenotypic ranges seen and reflect the different referral patterns as well as various approaches to medical management. Differences in medical approaches (bracing for scoliosis, use of polysomnography, placement of gastrostomy tubes with or without fundoplication) may impact the natural history of the disease and confound ability to determine therapeutic efficacy.

The presentations emphasized the need to track respiratory complications, loss of ambulation status, onset of scoliosis and cardiac complications where pertinent and underscored the key elements of CMD longitudinal data collection with a need for standardization and development of CMD common data elements. Data presented supports conversion of respiratory data from FVC to % predicted FVC and obtaining FVC in both sitting and supine positions, allowing a more sensitive measurement of early respiratory insufficiency [2]. The data highlighted contractures as an integral feature for many with CMD, implicating motor assessment as well as height assessment required for standardized measurements of pulmonary function. Using ulna length as proxy for height has been validated in the neuromuscular population and may be necessary to calculate % predicted FVC %, representing the only standard height measurement obtainable consistently across all CMD patients [3,4].

The collagen VI retrospective data from five centers (Dubowitz Neuromuscular Center, Neuromuscular Centre Garches (GNMH), Children’s Hospital of Philadelphia, Newcastle Centre for Life and Gesu Bambino Hospital in Rome) emphasizes the range in phenotypic and functional severity, from patients who do not achieve the ability to walk (categorized: *severe or early onset Ullrich CMD*) to patients who achieve walking but lose the ability to walk during later childhood (categorized: *typical or moderate progressive Ullrich CMD*) to patients with ambulation into adulthood but considerable weakness with frequent use of part time assistive devices (categorized: *intermediate collagen 6 related myopathy or mild Ullrich CMD*) to patients with milder weakness who are able to ambulate without assistance into at least mid adulthood (categorized: *Bethlem*) (Table 1). For the purposes of data presentation in this review, the latter two categories were collapsed and classified as mild resulting in a

classification scheme defined as severe (never walked), moderate (lost walking) and mild (currently walking beyond childhood).

Additional center specific observations that require further analysis include the ability to use serial measurements of FVC to differentiate young ambulatory patients who will lose ambulation from those with a milder course who will remain ambulatory. Data presented from one center (Garches, Paris) suggests that % predicted FVC of 70% or more in the first decade of life is associated with a milder course, since it was found in patients who acquired walking and continued ambulating during childhood to early adulthood. An FVC under 70% predicted in the sitting position or under 60% in the supine position in the first decade of life was associated with the severe early onset or moderate-progressive course. Patients systematically showed a fall in FVC when measured in the sitting versus the supine positions indicative of purported diaphragmatic weakness. Comparative % predicted FVC measurements in sitting and supine positions, motor function measurements and progression of scoliosis provide useful clinical information for follow-up, treatment and possible clinical endpoints.

These observations are exemplified by three patients, part of the Italian cohort, in whom longitudinal measures of FVC with conversion to % predicted were obtained in both supine and sitting positions and reflect similar data from the additional centers. One patient at age 9.2 years had % predicted FVC of 39% in sitting position and 29% in supine position. Seven months later, the % predicted FVC worsened to 29% in the sitting position. The second patient who was still ambulant at the age of 8 years with a % predicted FVC of 68% demonstrated a decrease 8 months later to 59% in sitting and 44% in the supine position. The third patient with a % predicted FVC of 47% at the age of 9 years experienced a decrease to % predicted FVC of 20% at age 13 years with worsening scoliosis (Cobb angle of 40°). These patients demonstrate a decline in % predicted FVC in childhood with a difference between sitting and supine % predicted FVC of 10%, corroborated by data from similar cohorts at the other centers. Of note, there were at least two reports of children with collagen VI myopathy who required ventilation while still ambulatory, underscoring the need for early and serial pulmonary function tests in this patient cohort.

Motor disability in both collagen VI myopathies and in laminin alpha 2 deficient CMD may be influenced significantly by the often progressive contractures which impede both motor performance and its assessment with considerable impact on activities of daily living and quality of life [5,6]. Laminin alpha 2 deficient CMD patients often demonstrate severe weakness from an early age that is however seemingly only minimally progressive throughout the disease course. Nonetheless in these patients, progressive and severe respiratory and orthopedic complications requiring aggressive management develop in their teens. Nutritional deficiencies due to aspiration, feeding difficulties and prolonged meal times in MDC1A were highlighted in a small cohort study [7]. This constellation makes motor outcome measures difficult to address due to the slow rate of disease progression and the limited retrospective data available using motor function scales. Thus, pulmonary and perhaps nutritional data may serve as more appropriate clinical endpoints (Table 1).

In SEPN1 related myopathy (formerly rigid spine muscular dystrophy), motor impairment is also stable for many years despite respiratory impairment requiring ventilator support. The slow progression of motor involvement may hinder or preclude demonstration of a clinical benefit within a clinical trial timeframe (Table 1). Failure to demonstrate a short-term motor clinical benefit may lead to exclusion of therapies which are potentially beneficial in the long term. Predominant involvement of axial muscles and the lack of a consistent histopathological marker add to the difficulty and suggest that standard motor endpoints might be inappropriate for SEPN1-RM with the need to identify disease specific biomarkers validated in a longitudinal study. A recent international study, underscores consistent early pulmonary involvement while still ambulatory, emphasizing the usefulness of a primary pulmonary endpoint in an intervention trial [8]. Motor scale endpoints are less likely to demonstrate significant change over the time span of a clinical trial, de-emphasizing their role as a primary intervention end point. Motor scales may play a role in tracking change over greater spans of time, in longitudinal studies and clinical assessments.

A preliminary population based study from Italy in the alpha dystroglycanopathies provides new data on respiratory, cardiac and cognitive abilities in the alpha dystroglycanopathies. The retrospective analysis of cardiac and respiratory findings demonstrated that 13% (10/78) had respiratory failure and required overnight non invasive ventilation with a higher frequency in POMT1 and POMT2 mutations associated with the phenotype previously reported as ‘Italian MEB’ [9]. Patients were ventilated with or without tracheostomy in the first decade. Another group of patients had no mutations in the known alpha dystroglycanopathy genes but shared a distinctive phenotype with early and severe myoclonic epilepsy. These patients also had early and severe respiratory involvement and 4/5 died in the first decade. Only 1/78 patients had overt cardiac involvement. The small numbers of cardiac and respiratory impairment in this cohort may not accurately reflect disease progression as the majority of patients surveyed were under 15 years of age.

Systematic data collection on FVC and motor function has not yet been initiated in the alpha dystroglycanopathies. Identifying reliable outcome measures for a subset of alpha dystroglycanopathy patients may be challenging, given the broad phenotypic spectrum and possible cognitive involvement. For some of these patients, weakness is not the primary problem, at least not early on, while comorbidities such as seizures can dramatically affect function. Developing appropriate clinical tools to assess this patient population, including motor and cognitive testing, is necessary.

2. Motor scales and contractures in CMD

Available rating scales were reviewed for their applicability to the CMD functional classes as defined above with an overview of motor scales currently used in CMD patients at the Dubowitz Neuromuscular Centre in London. Infants and children with CMD are typically evaluated using the following set of clinical tools: muscle power (MRC, myometry), muscle function (Hammersmith Functional Motor Scale (HHFMS) and North Star, timed tests in ambulatory patients (10 m walk, rise from floor), joint passive ranges, neck and spine movement, mobility and gait and orthoses. MRC grading often did not correlate with functional scores, perhaps due to confounding involvement of joint contractures. Function

and speed improved following tibialis anterior release where appropriate in ambulant children, demonstrating a functional change after an appropriate intervention. Serial casting and orthotic intervention is frequently used in CMD for ambulant and non-ambulant children, although contractures, and patient compliance may significantly influence the outcome of this intervention.

Important floor effects in current scales have been alleviated in the stronger children by administering ambulant and nonambulant scales together. The greatest challenge to a scale based assessment of CMD motor function are the very weakest and in particular most contracted children (non-sitters) in whom contractures and limited mobility impede accurate assessment of motor strength. As an example, functional scales in non-ambulant laminin alpha 2 deficient CMD depends on degree of contractures and scoliosis with a maximal achievable score of 14/40 on the HHFMS, with loss of sitting dropping the maximal score possible to eight. In this setting, the HHFMS discerns a greater range of muscle strength/function and can be used for comparing individual children against themselves in a longitudinal fashion. Ceiling effect denotes high functional abilities, with a child who scores 40/40 on the HHFMS or achieves a full score on the more recently developed North Star, a very functional child. In this highly functional cohort, including Bethlem and ambulant CMD, timed tests are useful to grade functional abilities.

In SEPN1 related myopathies, in particular, RSMD, contracture development is dependent on functional level with ambulant children developing few contractures excluding spinal rigidity. Additional motor outcome scales reviewed included the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) and the Motor Function Measure (MFM). A small CHOP INTEND study in the infant neuromuscular population, including CMD, demonstrated excellent intra-rater reliability in a mixed cohort consisting of nine SMA type 1 infants, 10 infants with varied neuromuscular disease and eight typically developing infants. Validity data was presented that supported its use in SMA type I with significant correlations found between hours of BiPAP use, age at testing, and months since onset of disease. Revisiting this scale in comparison to Hammersmith scale in a genetically confirmed CMD infant cohort will be needed to determine validity and potential floor effects in the very weak.

The Motor Function Measure (MFM – www.mfm-nmd.org) is a scale designed to assess motor function and progression of weakness in a variety of neuromuscular disorders. It is applicable to both ambulant and non-ambulant patients with a wide range of severity. The scale exists in 2 versions, one validated in 303 patients with various neuromuscular diseases (including CMD) aged 6–60 years with 32 items (MFM-32), the other with 20 items (MFM-20) undergoing validation with 88 children aged 2–6 years (first phase completed, responsiveness ongoing). The total MFM score correlates with degree of severity, defined as severe (never walked), moderate (lost walking) and mild (currently walking). Discrimination between ambulant and nonambulant patients is observed with all sub scores. Sub-factor analysis identified three functional dimensions in the MFM32: D1 = standing position and transfers (13 items or eight items in the short version), D2 = axial and proximal motor function (12 items or eight items in the short version), and D3 = distal motor function (seven items or four items in the short version). The scale has been further analyzed in various

pathology types with different rates of disease progression, in particular in duchenne muscular dystrophy (DMD), spinal muscular atrophy (SMA), calpaïnopathy and late-onset Pompe disease with plans to evaluate international CMD data using this tool. Results of these studies demonstrate good correlation between MFM score and individual motor capacity, with additional correlations with age in DMD and SMA patients and with duration of symptoms in patients with calpaïnopathy or Pompe disease.

Preliminary results of an MFM data review of 52 CMD patients comprising 41 patients age 6–72 years of age evaluated with theMFM32 and 11 children age 3–6 years evaluated with the MFM 20. Diagnosis was confirmed genetically in 56% of cases with UCMD subtype the most prevalent (50% of cohort) followed by patients with laminin alpha 2 deficient CMD, SEPN1 related myopathy (SEPN1), Lamin A/C CMD and dystroglycanopathy patients (FKRP and POMT2). Two patients had cognitive impairment. Ambulation was acquired by 75% of patients of whom 89% are currently ambulatory. Results confirm the scales general ability to describe motor capacities in CMD patients across the phenotypic spectrum. For CMD patients evaluated serially with the MFM (16 with MFM-32, 3 with MFM-20), individual curves show either a stable course or more often slow decline in score, depending on disease stage. Further retrospective analysis with a larger number of CMD patients is planned with subsequent need to validate in prospective longitudinal fashion. Experience with the 32 item MFM in 11 patients with Ullrich congenital muscular dystrophy and Bethlem myopathy at the Children’s Hospital of Philadelphia highlighted potential difficulties in assessing motor strength in the setting of contractures (see below) and led to the suggestion to test strength at the midpoint of the available range as has been done in patients with Charcot Marie Tooth disease.

3. Additional motor scales: upper limb motor scales

Ambulation in CMD is frequently not attained or lost in childhood, underscoring the need to develop and validate upper limb motor scales as a clinical endpoint. Performing comparative analysis of a dedicated upper limb scale, a functional scale assessing impact of disease progression on ADL’s involving the upper extremities and longitudinal myometry and goniometry may assist in identifying most sensitive measurement approach to quantitate disease progression involving both weakness in contractures in the upper extremities. Functional upper extremity tests that may be applicable, include the Jebsen timed tests, the Brooke scale, the nine hole peg test and a recently developed Upper Limb Scale (ULS) which will require validation in the CMD population. Measurement of strength by manual muscle testing, hand held myometry or quantitative muscle testing may not reflect changes in strength in CMD subtypes with contractures and confound efforts to standardize and obtain consistent upper extremity strength measurements, reducing enthusiasm for their use in clinical trials while still relevant in a descriptive longitudinal study.

A novel upper extremity strength and functional measurement, called the Motriplate (also referred to as the French Piano) is composed of two circular targets that the patient must alternatively hit. The primary outcome is the number of contact couple in 30 s, but the strength and the rhythm of the hits are also recorded. A multicenter study has been established to evaluate this device in 100 non-ambulant neuromuscular disease patients and

60 age-matched controls. Four different strength measures (handgrip, pinch, wrist flexion and extension), two functional tests (taping and motriplate), and two scales (MFM and functional hand scale) are completed over four visits. Preliminary data analysis is available for 11 patients demonstrating that motriplate, handgrip and pinch are very reproducible measures, without floor and ceiling effects. A recently presented poster, further validates the motriplate scores compared against traditional upper limb measures, including pinch, handgrip and MFM 32 total score.

For nonambulant patients development of robust upper limb functional assessment is mandatory to demonstrate therapeutic effects on muscle strength. An exploratory approach, actimetry by accelerometry was presented which must overcome inherent difficulties including effect of wrist rotation on gravity projection, integration of wheelchair and other passive movements as standard reference, stability of signal/noise ratio over time and effect on data of intra and inter-individual inconsistent activity level over time. Recent preliminary data demonstrates improvements in overcoming gravity projection and establishing passive movement reference points with mean acceleration strongly (r^2 from 0.92 to 0.98) correlated with the efficiency of predefined and quantified task, such as Minnesota test, motriplate, computer writing or drinking with a spoon with reproducibility for a given defined task.

The Egen Classification Scale (EK) was developed in Denmark to evaluate the motor function and quality of life specifically in non-ambulant individuals with Duchenne Muscular Dystrophy (DMD) and Spinal Muscular Atrophy (SMA). It has recently been extended to include items more relevant to SMA such as bulbar function. To begin the process of determining whether the EK scale might be useful in non-ambulant patients with CMD, a small CMD cohort in Newcastle, UK was assessed (eight patients with CMD aged between 7 and 22). Preliminary analysis demonstrates the majority of category items were relevant, although additional analysis has begun to probe individual items for their applicability in the context of nonambulant collagen VI and laminin alpha 2 deficient CMD.

4. The impact of contractures on motor assessment and quality of life

Contracture development may act as a confounder in accurate motor power assessment in several CMD subtypes (collagen VI myopathy spectrum, laminin alpha 2 deficient CMD, SEPN1 related myopathies, L-CMD) and challenge motor outcome scales as clinical endpoints. In the Dubowitz Neuromuscular Centre experience, Bethlem patients rarely demonstrate hip flexion contractures but tend to hyperextend the knees to compensate for tibialis anterior and hamstring tightness. Approximately 50% of patients, have elbow contractures though supination is only minimally affected and 2/3 have long finger flexor tightness. The tibialis anterior tightness affects the ability to rise from floor, walk slopes and get up stairs or rise from a low seat, thus affecting several items on the motor scales. In contrast, in non-ambulant UCMD many have hip flexion contractures with some losing ambulation due to hip tightness. UCMD patients also demonstrate marked hamstring tightness and reduced plantar flexion, with knee contractures in particular in the non-ambulant children. 50% have elbow flexion contractures with loss of supination. Neck rigidity is present in 50% and spinal rigidity is universal.

In nonambulant laminin alpha 2 deficient CMD, contractures present as early as first year of life with neck and spine rigidity. Early onset (by age 3 years) hip flexion contractures and iliotibial band tightness have been seen in all children, with the exception of 1 case. Significant knee contractures are present in 50% along with tibialis anterior tightness with knee extended. Elbow flexion contractures are quite severe and limit function in most with loss of supination. Shoulder abduction contractures have been seen in a limited number of patients.

5. Pulmonary outcome measures in the CMDs

While motor function assessments may qualify gradual loss of strength over time, appropriate for longitudinal studies, pulmonary outcome measures may take precedence as the primary endpoint in intervention trials. Preliminary data provided by reference centres demonstrate CMD subtype specific quantifiable force vital capacity consistent annual rates of decline. The progressive nature of respiratory involvement due to declining respiratory muscle strength, chest wall compromise and presumed diaphragmatic weakness effects quality of life and measurable outcomes, such as rate of chest infection and hospitalization and supports the use of pulmonary outcome measures as a primary CMD trial endpoint.

Pulmonary outcome measures under consideration for the CMDs fall into three distinct categories: measurements of pulmonary function, muscle strength and nocturnal hypoventilation. Pulmonary function by spirometry includes: slow vital capacity (sVC), forced expiratory volume in one second (FEV1) and forced vital capacity (FVC). FVC is the measurement of choice in the neuromuscular cohort due to ease of performance, consistent current use during pulmonary neuromuscular visits and test reliability in children who demonstrate compliance and ability to generate a good seal around mouthpiece. sVC may be useful in children who have difficulty understanding forced exhalation. Testing in upright and supine positions, can establish the presence of early respiratory insufficiency thought to be due to significant diaphragmatic weakness, a common finding in CMD subtypes with rigid spine morphology with a 10% decrease in FVC associated with position change. This is particularly observed in the forms due to SEPN1 and COL6 gene mutations and likely in alpha dystroglycanopathies, but not in LAMA2-related CMD. Retrospective CMD FVC data will need to be validated in a prospective longitudinal CMD study to determine subtype specific annual rate of decline.

Muscle strength can be measured by assessing inspiratory muscle strength (MIP) which has been shown to predict onset of nocturnal hypoventilation and daytime hypercapnia though not as sensitive as vital capacity [10,11]. Indeed, a prospective study found a high prevalence of impaired respiration during sleep in children with CMD who were referred for a sleep study with 52% with either nocturnal or diurnal hypoventilation [12]. A recent report indicates sniff nasal inspiratory pressure (SNIP) may be easier to obtain than MIP to measure respiratory muscle strength [13]. To assess expiratory muscle strength, one can evaluate both expiratory muscle strength (MEP) and peak cough flow (PCF). A MEP >60 cm H_2O will provide an effective cough and PCF can be measured serially to look at cough efficacy. Threshold values for an ineffective cough and the requirement of mechanical insufflations/exsufflations are defined solely for the adult population. Available normal

pediatric values for FVC, MIP, MEP, SNIP and PCF facilitate comparison with the neuromuscular cohort.

Sleep studies constitute another possible pulmonary outcome measure. The study may consist of simple overnight oximetry or of oximetry coupled with transcutaneous or end-tidal carbon dioxide (CO_2) monitoring with abnormal values defined as a pulse oximetry value <95% and a transcutaneous carbon dioxide >6.5 kPa for more than 1/3 of the night. An arterial or capillary blood gas is essential to confirm trans-cutaneous measures of CO_2. To diagnose nocturnal hypoventilation a full night measurement of CO_2 is essential unless the child already has daytime hypercapnea. Institution specific practices differ in the use of detailed polygraphy (respiratory channels only) and full polysomnography use to evaluate the neuromuscular cohort.

Retrospective CMD pulmonary data from the Royal Brompton Hospital where CMD represents the 3rd most prevalent neuromuscular disease treated with non-invasive ventilation (NIV) after DMD and SMA provides the largest volume of CMD longitudinal data. Greater than 100 patients electronic patient records were cross-referenced with a confirmed genetic list provided by the Dubowitz Muscle Centre, 43 CMD charts followed longitudinally into adulthood were identified (Table 2). The data is based on the presumption that this cohort represents a more severe end of the CMD spectrum with a high requirement for NIV and may therefore demonstrate inclusion bias. Preliminary data analysis demonstrates that MIP and MEP correlate with FVC and supports MIP as sensitive at predicting sleep disordered breathing but was not sensitive enough to distinguish two patients with nocturnal hypercapnea without hypoventilation on sleep study. Ambulant patients had higher FVC than non-ambulant patients of the same age. While FVC correlated with daytime PaO_2 ($r = 0.76$, $p = <0.01$) and between FVC and daytime $PaCO_2$ ($r = -0.44$, $p = <0.03$) there was no correlation between FVC and overnight room air oxygen saturation or overnight transcutaneous carbon dioxide level.

Although cardiac involvement is relevant to only a subgroup of CMD, very few systematic series are available. Limited individual cardiac data collected on CMD patients from the Royal Brompton hospital demonstrate an overall low incidence of cardiac dysfunction, though not followed rigorously (Table 3).

6. Cognitive assessment in the CMDs

Defining and evaluating neurocognitive impairment in CMD as an outcome measure will present challenges given the broad phenotypic spectrum precluding the use of available development scales and ability to obtain accurate patient or proxy reported outcomes. Data presented on cognitive impairment in CMD was obtained from a population study performed in Italy from the 11 tertiary care centres responsible for pediatric patients with neuromuscular disorders [14,15]. Cognitive function was always normal in Ullrich CMD and the SEPN1 related myopathies. Cognitive impairment was most frequent in the alpha-dystroglycanopathies and equal prevalence in cases with a mutations in one of the six known genes and in those in whom no mutation was detected [16,17]. In general, the severity of cognitive impairment was correlated with the severity of brain MRI structural changes.

Patients with cortical structural brain changes had higher incidence of epilepsy. Patients with normal brain MRI or with minimal structural brain changes tended to have mild cognitive impairment. These trends held true in the majority of CMD alpha dystroglycanopathy cases, irrespective of the gene involved and with no clear phenotype-genotype correlation.

As previously reported, cognitive impairment was also found in some patients with merosin deficient CMD and was more often associated with cortical dysplasia even though not all patients with cortical dysplasia had cognitive impairment. At variance with previous reports, however, cognitive impairment was also found in patients with the typical white matter changes only, with and without epilepsy.

Cognitive impairment was also found in 13 patients (17% of the whole group with cognitive impairment) in whom alpha dystroglycan and merosin muscle immunohistochemistry was normal. These patients were screened for all known genes without molecular confirmation. Two of the 13 patients had adducted thumbs and cataracts while others had clear signs of cerebellar atrophy and have also been previously reported without gene identified [18,19].

7. Quality of life assessments

Both the Food and Drug Administration and World Health Organization support health related quality of life (HRQOL) tools to support patient reported outcome of therapeutic benefit with an emphasis on collection of a minimum of three dimensions, physical, psychological and social health. An existing well validated HRQOL scales include the PedsQL™ System which provides both generic and neuromuscular health related quality of life instrument modules for pediatric patients and parent proxy reports, neither validated in the CMD population.

The psychometric properties of the Neuromuscular Module have been demonstrated in two pediatric patient populations with muscular disease, spinal muscular atrophy (SMA) and Duchenne muscular dystrophy (DMD). The results of these two studies demonstrated high internal consistency and test–retest reliability as well as good validity noted by high associations between the Neuromuscular Module and generic core of the PedsQL™ for all child and parent proxy reports, and disease specific measures and total scores on the parent-proxy report and the DIS domain for child report [20,21] suggesting that these instruments could be applicable in the CMD population as well. An additional study has provided evidence of reliability and validity for the telephone administration of the Neuromuscular Module for patients with SMA. To assess current CMD quality of life from the caregiver and affected individual perspectives, Cure CMD, a nonprofit advocacy, presented data from an on line survey that asked five open ended survey questions focused on meaningful functional changes, in both the positive and negative direction, in the lives of caregivers and affected individuals. The survey was distributed to 82 affected individuals and their caregivers December 2009. Caregivers were defined as those parents or guardians living with children or adults with CMD and affected individuals as those with CMD. Caregivers were asked to assist affected individuals between the ages of 2–14 with the survey. Each response was qualitatively analyzed, categorized and subsumed under a domain with caregiver and affected individual responses collected and evaluated separately. Thirty unique domains

were identified. The analysis demonstrated that for caregivers both positive and negative changes in an affected individual's *activities of daily living* and *strength* have the greatest impact on caregiver "burden".

For affected individuals, changes in *strength* and *ambulation* abilities scored the highest both as positive and negative meaningful change. 65% of participating affected individuals were ambulatory, demonstrating that retaining and achieving ambulation are major priorities for this population.

8. Pharmaceutical industry perspective on rare disease clinical trial readiness paradigms

Industry representatives provided their perspective about steps in clinical development of drug candidates in rare neuromuscular disorders, highlighting the importance of reliable natural history data for clinical study design, selection of clinically relevant endpoints, baseline determination, duration of intervention expected to result in detectable change in endpoints, inclusion and exclusion criteria and sample size calculation.

Experience accumulated at Genzyme in orphan drug development and neuromuscular treatment stems largely from development of Myzozyme for Pompe's disease and illustrates the importance of test validation and establishment of natural history longitudinal data to provide a baseline and expectation of progression. Additional perspectives provided by Santhera Pharmaceuticals provided an overview of the FDA and pharmaceutical industry perspective based upon the company's prior experience in the rare disease arena, including Friedreich's ataxia and DMD and a current focus on developing Omigapil in CMD. Key barriers to drug development in the CMDs includes the number and accessibility of patients, the heterogeneity of clinical presentation and disease progression, dearth of natural history data, lack of previous clinical trial experience in CMD, and consequently, lack of validated endpoints in which change represent clinically relevant outcomes and established regulatory pathway to registration. All these aspects constitute uncertainties which impact clinical trial protocol design and possible study outcome.

Considerations in selecting appropriate outcome measure tests emphasized by the industry representatives include a minimization of unnecessary data collection, restricting the number of tests performed to maintain feasibility in study conduct, minimizing patient discomfort and fatigue, reducing invasiveness and maximizing information obtained while ensuring study endpoints and change in them will satisfy regulators that the treatment is safe and effective in children. Outcome measure scales need to be validated for the specific purposes and tests should be reproducible, with acceptable test–retest reliability. Ideally, tests should be applicable to a broad age group and cultural bias and "voluntary effort" should be minimised. Most importantly, endpoints should reflect a medically relevant outcome or benefit.

Clear guidance on how to carry out efficacy assessments and tests should be provided and strictly followed by the study investigators using standardized and calibrated equipment to reduce variability.

In summary, the industry perspective pointed out that planning of a controlled clinical intervention trial in the CMDs should consider:

- Availability of natural history data to inform about study design, allow determination of effect size and calculate sample sizes.
- Collection of common and core data elements within natural history should be conducted in a standardized manner allowing inter centre and rater comparison.

9. Summary

The awareness among caregivers and affected individuals of the underlying muscle pathology and desire for treatments to target strength, ambulation and activities of daily living need to be taken into consideration when planning outcome measure scales for clinical trial interventions. Treatments which slow disease progression may fail to register a clinically significant effect on a given motor scale endpoint. There is a clear need for analysis of existing and newly amended motor scales in CMD patients as part of a natural history longitudinal study in close correlation with other scales that assess function in the context of activities of daily living to ensure meaningful data capture across the CMD cohort, including children and adults on both ends of the weakness severity spectrum and in the context of contractures and possible cognitive involvement (alpha-dystroglycanopathy subtype). The ENMC panel concluded that a natural history study on the major CMD subtypes remains critical to the future success of clinical trials for these diseases. One strategy is to design a single study across subtypes that would leverage financial resources and clinician time.

The meeting successfully provided a preliminary CMD retrospective data analysis across subtypes and centers, identifying prognosis, subtype specific disease course and highlighting potential clinical endpoints and need for prospective analysis. Planned Rasch analysis on retrospective CMD data will clarify motor scale range in the CMD population in the setting of contractures and potential cognitive delay. A focused and data driven revision of outcome measure scales with an emphasis on development of CMD specific global motor and upper extremity assessments, quality of life scales and patient reported outcomes will assist in evaluating clinical endpoints for CMD studies. Appropriate scale selection followed by an international multicenter natural history study to test scale validity, reliability and reproducibility combined with the biomarker exploration is the necessary next step in pursuit of clinical trials readiness.

As a tangible first meeting outcome there will be additional efforts at CMD retrospective chart review focused upon motor scales and functional vital capacity. An NIH CMD Comparative Outcome Measure study (June, 2010) will evaluate various clinical endpoints, including FVC, quality of life, caregiver assessment, goniometry and myometry in two CMD subtypes: collagen VI CMD and laminin alpha 2 deficient CMD, demonstrating the ability to run cross subtype studies with particular objectives. A subsequent meeting in October 2010 will prioritize strength as key outcome measure and evaluate data generated to identify elements with existing motor scale (s) for future CMD motor data collection,

including a CMD natural history study. Data analysis and a future natural history study are required to determine to what degree motor endpoints assessed by motor scales are able to demonstrate % change in motor function over the time course of a clinical trial. Depending on the CMD subtype, using pulmonary endpoints against a presumed (still requiring validation) annual subtype specific FVC rate of decline may provide the strongest evidence of motor improvement and function. CMD natural history studies will highlight the ability of various endpoints to discern significant changes in quality of life, caregiver assessments, respiratory function and motor strength.

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Table 1

CMD subtype specific data per center.

CMD subtype	Center	Type of center	Location	Total # patients	Mean age loss of ambulation	% ventilation total (NIV, trcheostomy)	Mean age at start of NIV
Collagen VI	GNMH	National referral for severe neuromuscular patients	Garches, France	28	14 years	50% (46%, 21%	NIV: 9.5 years +/−4 yr Trch 10.5
Collagen VI	DNC	National referral center for CMD	London, UK	33	11.1 years +/− 4.8 years for Ullrich	69.20% for Ullrich	14.3 years +/− 5 years for Ullrich
Collagen VI	GBH	1 of 13 neuromuscular centers in Italy	Rome, Italy	12	10 years	33%	11 years
Collagen VI	CHOP	Pediatric tertiary care hospital	Philadelphia, USA	50	10.5 years +/−5.5 yrs	26%	11.68 years +/− 5.25 years
Laminin alpha 2 deficient CMD	GNMH	National referral for severe neuromuscular patients	Garches, France	32	90% never achieved ambulation	53%	11.5 yrs +/− 9 years
Laminin alpha 2 deficient CMD	DNC	National referral center for CMD	London, UK	51	<age 10 years 96% never achieved ambulation	25%	
SEPN1 related Myopathy	DNC	National referral center for CMD	London, UK	40		57.50%	13 years

GNMH: Centre de Reference Maladies Neuromusculaires; DNC: Dubowitz Neuromuscular Center, GBH: Gesu Bambino Hospital; CHOP: Children's Hospital of Philadelphia.

Table 2

Respiratory data in CMD (Royal Brompton Hospital, UK).

CMD subtype	Collagen VI	Laminin alpha 2 deficient CMD	SEPN1
Total # of patients	14 (6 M/8F)	19 (9 M/10F)	5 (3 M/3F)
% Emergent indication for NIV on referral	42%	21%	0%
Median referral age	15 years	11 years	14 years
Age initiation of NIV	15 years	13 years	14 years
Current mean age	24.5 years	17 years	23 years
Survival	86%	79%	100%
% Feeding tube	42%	63%	20%
% Ambulant	17%	0%	100%
% NIV for median yrs	93% for 11 years	79% for 5 years	100% for 10 years
Mean referral FVC	0.59 (0.24) L	0.47 (0.2) L (9 unable to perform)	1.0 (0.38) L
Mean current FVC	0.56 (0.34) L	0.49 (0.5) L	1.2 (0.5) L
Mean ABG PaO_2	10.34 (1.3)	11.15 (1.6)	12.89 (1.1)
Mean ABG $PaCO_2$	6.71(0.81)	5.97 (1.36)	5.43 (0.6)
Mean sleep study room air O_2 sat	90(8)%.	93(5)%.	92(4)%.
Mean sleep study transcutaneous Co_2	10.04(3.2) kPa	7.09(1.6) kPa	8.2(1.3) kPa

Table 3

Cardiac data in CMD (Royal Brompton Hospital, UK).

CMD subtype	Total patients evaluated	Evaluated with	Indication for evaluation	Finding	Mortality secondary to cardiac etiology
Collagen VI	(2/14)	Echo, event monitor	Surgery, tachycardia	Normal	Not reported
Laminin alpha 2 deficient CMD	(7/19)	Event monitor, echo	Scoliosis surgery, tachycardia	1 patient with SVT on event monitor with 65% LVEF, 1 document tachycardia, 1 abnormal Holter	Not reported
SEPN1	(3/5)	Pregnancy, high pulmonary artery pressure	Echo	Not reported	Not reported
FKRP		(dystroglycanopathy)	(2/2)	Echo	Scoliosis surgery
1/2 mild left hypokinetic left ventricle	Not reported				
Lamin A/C	(2/2)	Holter	Tachycardia	1 patient had AICD placed for VT, 1 patient currently monitored	50%