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Meeting Report

Report of the third outcome measures in myotonic dystrophy type 1 (OMMYD-3) international workshop Paris, France, June 8, 2015

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Abstract.

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INTRODUCTION

In 2011, the Outcome Measure in Myotonic Dystrophy (OMMYD) working group was assembled, comprising clinicians and researchers, with the aim to select a core set of outcome measures with sound metrological properties to be used in clinical trials

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in myotonic dystrophy type 1 (DM1). OMMYD conference is based on the methodology developed by the OMERACT group in the rheumatology field for the development and selection of outcome measures [1]. The OMERACT process is data driven, and criteria for the endorsement of a measure by the workshop are based on the OMERACT Filter [2] and include truth, discrimination and feasibility. For this third workshop, a total of 68 attendees (clinicians and researchers working in DM1) from France, Canada, USA, the UK, Germany, Sweden, England, Hungary, the Netherlands and Italy met in Paris, France on June 8, 2015 (see list of participants at the end of the report). Seven Special Interest Groups (SIG) worked on the selection of outcome measures (OM) to be used in research and clinical trials based on metrological properties and experience of experts: Cognitive Functions; Patient-reported Outcome Measures; Functional Capacity Outcome Measures; Muscle Testing and Training; Disease Severity Index; Sleepiness/Fatigue/Apathy; and Respiratory. During the first two meetings, experts have reached consensus on the main domains to be assessed in each Special Interest Group and they made a preliminary selection of relevant outcome measures. This report summarizes the progress that has been made so far as well as the adopted group's research agenda.

SESSION 1. COGNITIVE FUNCTIONS SPECIAL INTEREST GROUP

The session was co-chaired by Dr. Giovanni Meola from the University of Milan, Italy and Dr. Louis Richer from Université du Québec á Chicoutimi, Canada.

Background discussion

During the OMMYD-2 meeting, the Cognitive Functions SIG has identified four relevant neuropsychological tests for use in clinical trials (see second report [3]) and also suggested to explore two batteries of tests in full or in part to establish their feasibility with patients: the Frontal Systems Behavior Scale [4] and the Cambridge Brain Sciences (CBS) computerized (online) tests [5]. Between the OMMYD-2 and 3 meetings, a trial of the CBS battery was conducted with patients to assess its feasibility. The SIG also previously highlighted the variability observed in the definition and classification of DM1 phenotypes. It was decided to and extend the mandate of the SIG to develop a common classification schema for use in future clinical trials and academic research. For that, a Delphi Process was conducted before the meeting to propose operational definitions of phenotypes. Thus, the OMMYD-3 focused on discussing the conclusions of both these projects and attempting to establish further consensus regarding parameters for clinical trials.

Resulting consensus

Use of the Cambridge Brain Sciences online tests

Prior to the meeting, a SIG member (LR) examined the feasibility of using part of a computerized battery of tests in order to assess cognitive and executive functions among a sample of 25 participants with adult-onset. The protocol was composed of four tests from the Cambridge Brain Science Web-based battery to evaluate visuospatial working memory (Monkey Ladder), attention and inhibition abilities (Double Trouble), planning (Hampshire Tree) and spatial memory (Spatial Search). These tests are game-like, easy to administer and require no special staff training. When necessary, test instructions are easy to translate and the tests involve no language component, except for three words used in the attention test. The protocol takes approximately 20 minutes to complete by patients and since no learning effect is involved, test-retest procedures are possible. The instructions' quality and understandability, and the ease of transition from instructions to tests were assessed. The participants were offered the option to use a mouse or a touch screen if they experienced difficulty manipulating a mouse. All results will be submitted for publication soon, but they are promising regarding the use of this cognitive test battery in the DM1 population.

Phenotype

A Delphi process took place in 2014-15 and mobilized 14 clinical and research experts. The process resulted in an array of suggested adjustments to existing definitions. During the OMMYD-3 meeting, a major focus of the participants was to seek consensus on phenotypes. The SIG discussions led to (1) the adoption of the criterion of "lumpers" instead of "splitters" for disease classification, and (2) a preliminary consensus on the five phenotype classification of DM1 considering the age of onset and most frequent presenting symptoms of each form: congenital, childhood, juvenile, adult, and late-onset. Frequent symptoms come from natural history studies and

from the analysis of the largest registries of the world. Concerning the size of CTG repeats, it was decided to not include it in the phenotype classification because it is not always determined accurately, consistently and can be confounding. It can be a useful tool in research but to ensure consistency between research centers, this item was abandoned from the classification. The SIG also highlighted the need to have more data on cognitive impairments according to each phenotype. The detailed classification will be published after having done a larger consultation and having the agreement of the whole OMMYD community. A session independent of OMMYD should take place to get there.

Conclusion and recommendations

The suggested phenotypic classification needs to receive a general consensus among other DM1 experts and the members and chairmen of the OMMYD-3 experts through a congress or a workshop devoted to this specific topic of phenotypic classification. Other recommendations for future studies include evaluation of cognitive impairment in late-onset form and its clinical relevance. Moreover, longitudinal studies that can deepen knowledge on the progression of subtle cognitive deficits from baseline could be very helpful. Another issue to cover will be the specificity of congenital group that can be split in "severe" or "mild" form. This could be helpful concerning prognosis, because the mild subgroup may not experience respiratory difficulties in comparison to the severe one which face greater challenge living with more impairing difficulties including respiratory problems.

SESSION 2. PATIENT-REPORTED OUTCOME MEASURE SPECIAL INTEREST GROUP

The session was chaired by Chad Heatwole, MD, MSCI from the University of Rochester, United States.

Background discussion

The SIG built upon the previous meeting's discussions and focused on the use of patient-reported outcome measures during DM1 clinical trials. Much of the discussion focused on the integral role of patient reported outcomes in clinical trials. This is underscored by the use of properly validated instruments for drug labeling claims and regulatory approval by the United States Food and Drug Administration (FDA) and other regulatory agencies. At this meeting, updates were provided on the Myotonic Dystrophy Health Index (MDHI), the congenital and childhood Myotonic Dystrophy Heath Indexes (CCMDHI), and the LIFE-H, ACTIVLIM, DM1-ACTIV, and SF-36.

Outcome measures

Myotonic Dystrophy Health Index

The Myotonic Dystrophy Health Index (MDHI) is a disease-specific patient reported outcome measure designed specifically for use in myotonic dystrophy clinical trials [6, 7]. It has been identified during OMMYD-2 [3] as potentially interesting and was translated into French and Italian at this time [8, 9]. Given the prior validation of this instrument, it has been identified by the NIH's Common Data Elements group as one of only four outcome measures that are highly recommended for use in DM1 studies and the only outcome measure that is highly recommended as an outcome/endpoint to measure multifactorial patient reported Burden of Disease. One limitation identified was the need to document responsiveness to change for this questionnaire.

Congenital and childhood Myotonic Dystrophy Health Index

The Congenital and Childhood Myotonic Dystrophy Health Index (CCMDHI) is a proxy reported outcome measure designed to measure the level of disease burden experienced by children with myotonic dystrophy. The instrument was derived from patient and parent qualitative interviews and later validated in a multinational survey. This instrument is completed by a parent or proxy on behalf of a congenital or childhood onset DM1 patients. As part of the CCMDHI initiative, additional age specific instruments were created to measure disease burden in children with DM1 directly using a child's perspective. These instruments were designed to be administered to specific age groups including patients ages 5–7, 8–11, and 12–17. Children complete questionnaires with assistance from a parent or proxy. For the 5–7 year-old age group, a picture based questionnaire is used. The instruments have been validated in a multinational disease progression study. Specific attention has been given to the weight of the proxy and pediatric responses in relation to other objective outcome measures.

ACTIVLIM

ACTIVLIM is a measure of activity limitation designed for children and adults with neuromuscular disorders [10]. The instrument was designed using Dutch and French neuromuscular patients. In the development process, 17 of the 369 patients (4.6%) had myotonic dystrophy and no children with myotonic dystrophy were included in the development of the instrument. The questionnaire was developed using Rasch methods and includes 14 base items, 4 child-specific and 4 adult-specific items. Intra-rater reliability was high among a neuromuscular population (ICC = 0.93).

LIFE-H

The short-version of Assessment of Life Habits questionnaire (LIFE-H 3.1) covers 12 generic domains of social participation with 77 questions including housing, responsibility and leisure. The total score has been reported to have an ICC of 0.86 for intra-rater reliability and 0.90 for inter-rater reliability among a DM1 population. Limitations of the LIFE-H include its completion time; it reportedly takes 20–60 minutes to complete. Additional versions of this instrument are being planned which may limit the amount of questions and the participant/examiner burden associated with this instrument.

DM1-Activ

The DM1-Activ is a disease-specific activity and participation scale developed for myotonic dystrophy type-1 using Rasch methods [11]. The questionnaire contains 20 items and was developed using DM1 patients recruited through the genetic register of the Maastricht University Medical Centre and through the Dutch neuromuscular patients' association. A strength of this instrument is that it was designed specifically using and for DM1 patients. The instrument has an excellent ICC of 0.93 for intra-rater reliability. The instrument is currently being utilized in the Optimistic trial as one of the clinical outcome measures. Limitations of this instrument's potential use for DM1 clinical trials were discussed and include the use of items that are seasonally and geographically tied (e.g. gardening), and the unknown relevance of some of the included items to the DM1 population (e.g. open toothpaste).

QoL-gNMD

The Qol-gNMD (formerly QoL-NMD) is a measure of health-related quality of life for adults with genetic neuromuscular disorders [12]. The instrument was designed using French patients with a variety of neuromuscular diseases; 44 of the 159 test sample had DM1. An English translation is available. The questionnaire was formed using item response theory (IRT) methods and includes 26 items and 3 domains. It showed adequate psychometric properties and met IRT assumptions. One limitation identified is the need to validate the questionnaire in on an independent sample of DM1 patients.

SF-36

The SF-36 is a generic health-related quality of life questionnaire. It was observed in previous studies that DM1 patients from Serbia had lower SF-36 scores compared to other countries showing the importance of transcultural studies utilizing patient-reported outcome measures. Analysis of quality of life changes in patients with DM1 during a five-year follow-up period, including assessment of responsiveness of the SF-36 questionnaire, was also presented. All mental subdomains, role physical and total SF-36 scores significantly improved after five years in 62 DM1 subjects. Unexpectedly, worsening of muscular weakness from mild to severe was in association with improvement of SF-36 scores.

Conclusion and recommendations

The SIG agreed that PRO should be properly validated in the myotonic dystrophy population prior to being considered for use in a DM1 clinical trial and research. Ideally, PROMs should meet the FDA's and EMA's rigorous requirements for validation. The SIG highlighted that translation of instruments should be performed using standard methodology including qualitative methods and direct patient input to support the cultural appropriateness of the translation. The SIG continued to affirm that PROs are an important and viable mechanism to include in DM1 clinical trials and research and have a unique capability to incorporate a patient centric view point into the evaluation of therapeutics.

SESSION 3. FUNCTIONAL CAPACITY OUTCOME MEASURES SPECIAL INTEREST GROUP

The session was co-chaired by Professor Mario Leone from the Université du Québec á Chicoutimi, Canada and Marie Kierkegaard from the Karolinska University Hospital, and the Karolinska Institutet, Sweden.

Background discussion

The purpose of the SIG was to reach a consensus on the creation of a standardized test battery measuring the functional capacity of patients. Specific objective is to establish a procedure containing at least three tests which should be consistently utilized in all research projects related to functional capacity and/or clinical trials. Several functional capacity outcome measures were previously reviewed and four essential key tests were identified based on actual research and clinical evidences: 1) The Six-Minute Walk Test (6MWT) (walking capacity over longer distances); 2) The 10-meter Walk Test (10mWT) (walking speed over a short distance); 3) The 30-second chair-stand test (30s-CST) (lower limb strength and dynamic balance); and 4) The Nine-Hole Peg Test (9HPT) (upper extremity function, specifically fine dexterity and coordination. One "highly recommended" test was also identified: the Step Test (shifting the body's center of gravity – dynamic balance). In addition, a test using a modified Wii device to assess balance needed to be evaluated. The SIG also agreed on the need to seek a valid, reliable and sensitive balance test. During this meeting, experts have started a consultation on standardized procedures for the administration and scoring of the four key tests identified previously (6MWT, 10mWT, 30-s chair-stand, NHPT), addressed the issue of balance outcome measures, and initiated discussions on outcome measures for children.

Resulting consensus

Standardized administration procedures

The group discussed general recommendations when administrating tests. As fatigue is commonly present, the time of the day when tests are performed need to be considered. The group proposed that it would be preferable to perform tests between 10:00am and 4:00pm. Further, that fatigue/tiredness might be a confounding factor when capacity tests are performed, and that perceived fatigue/tiredness could be rated before and after a capacity test with the Borg category ratio scale with ratings from 0 to 10 (Borg CR10 scale®) or the Borg rating of perceived exertion scale (Borg-RPE-scale®) which ranges from 6 (no exertion at all) to 20 (maximal) [13]. When repeated tests are performed, in for example clinical trials or reliability studies, tests should be performed under the same conditions and at the same hour of the day. An important factor to take into consideration when administrating a capacity test, is the possible cognitive difficulties. This implies that the administrator of tests must make sure that the instructions are well understood, and the language should be adapted to the cognitive level of the persons to be tested. Short sentences and not too many instructions at the same time are recommended. As there is so far no consensus in the literature on how many trials to perform for each test, the suggestion from the group is that two trials are performed and that the best is used as the result.

Group members shared their experience of administering, scoring and interpreting results from various capacity tests. This led to a consensus on specific instructions for the administration of the 6MWT, 10mWT, 30s-CST, and 9HPT in adult DM1 patients. Complete administration guidelines are presented as supplementary file as well as development process.

Balance outcome measures

The group discussed different balance tests, such as the Berg balance scale, the mini-BESTest the walk in figure-of-eight test, stand on one leg test, and the step test. The Berg balance scale has been used in Canada and they found that it had major ceiling effects. The mini-BESTest will be used in a forthcoming longitudinal study, and for the next OMMYD meeting there will be research/clinical experience for this scale. The stand on one leg test and the walk in figure-of-eight test were considered to be of less value in DM1 as large within-subject variations and measurements errors have been reported for these tests. The step test has been recommended to be a reliable dynamic balance test, but members in the group had limited experience with this test and it was decided not to recommend this test as a "must" test at the moment.

Since OMMYD-2, new data were obtained regarding the use of a Wii balance-board to measure balance and was presented to the group. Further validation and development of the test and data on dynamic balance are necessary before taking a decision for this test.

Outcome measures for children

The SIG recommends that members who have expertise or experience on functional capacity outcome measures for children with DM1 be invited. A battery could thus be developed at the next meeting.

Conclusions and recommendations

When assessing people with DM1, the SIG recommends using the 6MWT, 10mWT, modified 30s-CST

and 9HPT with the standard operating procedures determined in this meeting (see Supplementary 1). Further research is needed to evaluate responsiveness and interpretability of scores and change scores in these outcome measures. In addition, research is needed to identify outcome measures for balance, other upper extremity functions and outcome measures suitable for children.

SESSION 4. MUSCLE TESTING AND TRAINING SPECIAL INTEREST GROUP

The session was co-chaired by Luc J. Hébert from the Université Laval, Canada, and Jean-Yves Hogrel from the Institut de Myologie, Paris, France.

Background discussion

The previous OMMYD meeting highlighted significant variations and shortcomings in study protocols and reporting of muscle testing. At the outset, OMMYD participants stressed the need for standardized protocols and evidence-based parameters to be used. During OMMYD-1 and OMMYD-2, the SIG discussed items and features they wished to find in a muscle testing protocol. Some consensus was reached on guidelines for the use of a standardized muscle strength assessment protocol (gold standard) (see OMMYD-2 report). The current literature on muscle testing illustrates the variability in muscle strength assessments in relation to DM1 characteristics and the questionable validity of the results with regard to undocumented metrological properties. Unfortunately, it seems that mainly reliability is reported [14].

In that context, the aim of the meeting was to determine the best outcome measures to characterize muscle impairments in clinic and/or research settings to eventually develop a universal protocol. More specifically, the SIG aimed to: 1) Revise/discuss/validate the final report that was adopted during OMMYD-2 taking into account the views of new experts on the subject matter; 2) Compare the previous OMMYD recommendations to the National Institute of Health report published in 2015; 3) With regards to the survey conducted prior to the meeting, briefly address any discrepancies between the consensus reached by the SIG and the protocol used by research groups in their DM1 studies.

Resulting consensus

Revision and discussion of the consensus adopted during OMMYD-2

SIG report from OMMYD-2 was revised and discussed, more specifically the desired features of the muscle impairments assessment protocol (see Table 1 of the second report). The first domain revised was the general statement, the assessment of muscle impairments. One issue in that domain that was discussed is the value of strength that should be retained for the final analyses according to the number of trials performed. After discussion, it was deemed appropriate to use, depending on the study, either the mean peak value of all trials or the highest peak value among all trials. However, it must be clearly understood the impact of each choice. With weaker patients, although it may be appropriate to use the peak force, caution is advised when using the peak force with a HHD with weak patients as it is easy to induce a break test and therefore not reporting the true isometric value. With regard to the assessment of both sides, as we cannot assume that both sides are equally affected, it remains the judgement of the clinician/researcher to decide but the assessment of both sides should be favoured as asymmetry of muscle impairments is often observed. And finally, the issue of assessing muscle endurance (defined as handling an isometric contraction between 50 to 70% of the maximal force for as long as possible) in this population was discussed. However, considering the negative past experience of some participants with this variable (presence of pain and difficulty to concentrate enough to maintain the targeted high level of contraction for a long period of time) and the subjectivity of this measure with DM1 patients in addition to the necessity to reach a state of exertion, it was agreed to not add this item to the main list of outcomes.

Also, a few clarifications were suggested. In the exclusion criteria, the terms congenital and infantile phenotypes should be well defined. It must be clear that this protocol focuses on adults. Also, the cognitive impairment as an exclusion criterion is determined by clinical judgment. Participants also mentioned that excessive daytime sleepiness should be better described by the SIG working on that issue.

With regard to the recommended muscle groups (see Table 2 of the second report), the overall consensus previously adopted remains but the long finger flexors were suggested as a valid indicator to detect early on the onset of the disease. However, as no specific protocol exists yet for measuring the muscle

Table 1
The 9 domains with their related items and the risk factors retained for the DSI-DM1

Items	Items
Central Nervous system	**Urinary system**
Executive functioning	Urinary incontinence
Apathy	**Metabolic/endocrine system**
Excessive daytime sleepiness	Diabetes
Fatigue	**Risk factors**
Visual system	Pain
Cataract	Smoking
Ptosis	Compliance to treatment
Respiratory system	Physical exercises
Pneumonia	Alcohol
Chronic respiratory insufficiency	Drugs
Assisted ventilation	Depression
Cardiovascular system	BMI
Conduction disorders	Dyslipidemia
Structural cardiomyopathy	**Excluded items**
Arrhythmia	Personality traits
Digestive system	Sleep apnea
Dysphagia	Male infertility
Abdominal pain	Dysmenorrhea/menstrual pain
Fecal incontinence	Constipation/Diarrhea
Gastro-intestinal tract issues	Waist circumference
Muscular system	Hypogonadism
Facial weakness	Hypotension
Myotonia	Erectile dysfunction
Muscular weakness	Gastroparesis
Motor function (assistive devices)	Gall-bladder stones
Motor function	Ptosis
Outdoor mobility	Hypothyroidism
Indoor mobility	
Stair climbing	
Hand function	

strength of this specific muscle group, the assessment process of this additional muscle group will need to be defined and validated. The consensus adopted on the number and distribution of muscle groups also remains but it was pointed out that in any study, at least one muscle group of each lower limb joint (hip, knee, ankle) should be assessed and additionally, the anti-gravity muscles should be favoured.

The previous consensus was maintained regarding the method to assess muscle strength (until the transition to QMT is completed, the use of MMT should favour the modified MRC scale/functional assessments graded from 0–10 in clinical research; however, QMT must be favored for muscle groups that have shown good to excellent psychometric qualities) but comments from representatives from the pharmaceutical industry reinforced the fact that quantitative measures may be favoured over manual muscle testing as the use of an ordinal scale may require a higher sample size to detect the effect of a therapeutic intervention.

The use of myotonia as a significant biomarker was also revisited. This variable seems to be perceived as an important one by the experts but the way myotonia is measured between centers seems to vary considerably. One suggestion was to gather the psychometric qualities of both measures and present the results to the next OMMYD. This may help to compare the methods and explore the possibility to keep both or recommend the use of one. It was also suggested that researchers who have data on myotonia further analyze their data to better understand the profiles of change, comparing isometric grip testing with isotonic testing and needle EMG testing. This will provide additional arguments in favour of using this variable or not.

Comparison of the OMMYD's consensus and the Common Data Element published by the NIH

The NIH held a meeting of the National Institute of Neurological Diseases and Stroke and suggested the creation of categories of neurologic diseases, with common elements that would enable benchmarking. The NIH report [15] that was recently posted and submitted for public consultation provides succinct recommendations but it is unclear how these recommendations were obtained and especially how the literature review that supports these recommendations was conducted. Specifically, several participants were very surprised by the recommendations on muscle testing as they look more like generic guidelines and some are even in opposition to what was recommended in the last OMMYD meeting. For example, from what was published in the past decade, there are no supportive arguments in favour of the use of break test. And in the same line of thoughts, while manual muscle testing is still used, there are several and strong arguments in the literature in favour on the use of quantitative muscle testing [14]. The bibliography used in the NIH report for the section on muscle strength seems incomplete and does not reflect the current level of knowledge on the assessment of muscle strength in DM1.

Discrepancies between protocols used by research groups in their DM1 studies

A general discussion took place around the possibility to develop/use the equivalent of an ISO norm to assess muscle function. Some tools/protocols used to assess muscle function are very responsive but require

Table 2
Final RESPICHECK questionnaire

1 - Orthopnea	
	Do you feel short of breath when you lie down?
	Do you need to sleep with more than 1 pillow because you feel short of breath?
	Do you sleep sitting in a chair or arm-chair because you feel short of breath?
2 - Dyspnea when performing activities of daily living	
	Do you feel short of breath when you move around the house?
	Do you feel short of breath when you wash or dress?
	Do you feel short of breath when you talk?
3 - Apneas	
	Do you usually wake up short of breath during the night?
	Are you told your breathing usually pauses while you sleep?
	Are you told you usually stop snoring suddenly start again while you sleep?
4 - Poor sleep	
	Do you feel tired when you wake up in the morning?
	Do you wake up more than once during the night other than to go to the toilet?
	Are you usually sleepy during the day?
5 - Morning headaches	
	Do you usually wake up with a headache in the morning?
	Do you feel like your head was heavier in the morning than it used to be in the last 3 months?
	Do you usually feel a pressure in your head when you wake up in the morning?
6 - Decreased concentration and attention	
	Do you feel like your concentration has worsened than usual in the last 3 months?
	Do you find your thinking has been slower than usual in the last 3 months?
	Do you think your attention has worsened than usual in the last 3 months?
7 - Daytime sleepiness	
	Do you usually fall asleep while you are sitting inactive in a public place?
	Do you usually tend to fall asleep while you are sitting in a car for more than 1 hour as a passenger without stopping?
	Do you usually take more than 1 nap a day?
8 - Fatigue	
	Have you felt more tired than usual in the last 3 months?
	Have you felt that fatigue was amongst the most disabling symptoms in the last 3 months?
	Do you feel that fatigue has prevented sustained physical functioning in the last 3 months?
9 - Treated chest infections	
	Have you had a chest infection that required treatment with antibiotics, steroids or other medication in the last 3 months?
	Did you have to use antibiotics, steroids or other medication for a bad cough in the last 3 months?
	Have you been admitted to hospital because of a chest infection or because you were short of breath in the last 3 months?

specific knowledge and skill sets. Thus, evaluator training is of utmost importance. While there is no ISO norm per se yet to measure muscle function, four basic parameters were identified: evaluators should be well-educated regarding muscle function; the best available equipment should be used; evaluators should receive high quality, standardized training; and training should involve a certification process.

The SIG also discussed the use of normative values that is a term that should be used with caution. The use of normative data to compare results may at some point have to struggle with regional differences within countries. The use of the word '*Reference values*' was suggested as it implies the limitations associated with the use of such data. Reference values should be collected from various geographical areas and each population or group of patients must be clearly described to ensure reproducibility of studies.

Conclusion and recommendations

Some concerns about the slow progress since OMMYD 1 were expressed, which highlighted the importance for the group to identify the list of facilitators and obstacles to this progress. Moreover, additional items such as muscle endurance, muscle strength of the long finger flexors, and myotonia should be considered as significant biomarkers to the standard list of outcome measures in the near future. The SIG has expressed its desire to pursue a few specific goals until the next OMMYD meeting such as making a list of all measures available in each of our lab/clinic and how we administer them. Also, it was deemed important until the next meeting to assess and document the metrological properties of these outcome measures in order to present this data to the next OMMYD meeting. It was also deemed relevant

to explore the possibility to share the data with the SIG functional group in order to demonstrate the relationship between the measures of impairments and physical limitations (functional level). It was suggested to organize, for the next OMMYD meeting, a small session between the muscle testing and training and the functional SIGs for sharing ideas and discussing outcomes together.

SESSION 5. DSI-DM1ISEASE SEVERITY INDEX SPECIAL INTEREST GROUP

The session was chaired by Professor Cynthia Gagnon from the Université de Sherbrooke, Canada.

Based on Merkel et al.'s desirable properties for a disease severity index [16] and from OMMYD-1 onwards, the SIG agreed that the index should have some core properties. It should: (1) quantify disease severity on a continuous scale; (2) quantify changes in severity over long periods of time; (3) discriminate clinically relevant disease subsets with unique characteristics (e.g. patients with a congenital phenotype should have a higher DSI than a patient with a late phenotype); (4) provide prognostic information relative to morbidity and mortality; (5) be easily used in clinical trials but also in clinical practice; and (6) be as short as possible and simple to use in the context of clinical practice.

A first draft of the DSI-DM1 was presented at OMMYD-1 and included a total of 11 domains reflecting organ-based systems and 39 individual items. This nomenclature was revised during and after the session and again during the OMMYD-2 session (October 16, 2013) where it was downscaled to 8 domains and 19 items, plus 6 risk factors, scored separately. A Delphi process was conducted in 2014 to validate the remaining items and develop the scoring system. The objectives of the OMMYD-3 meeting (June 8, 2015) were to revise the list of items and their scoring and make the scale suitable for a pretest. The scale was further revised during and after the session and its final iteration expanded to 9 domains, 26 items and 9 risk factors. The DSI is intended to be administered by a health care provider.

Discussions were conducted to better define the central nervous system domain, resulting in all previously agreed items being maintained, with the exclusion of personality traits. The involvement of a cardiologist with the group led to the inclusion of an item to grade arrhythmia under cardiac systems. Discussions over digestive systems resulted in the inclusion of items grading abdominal pain, fecal incontinence and gastro-intestinal tract issues and the exclusion of gastroparesis, gall bladder stones and waist circumference, although the latter will be noted (not scored) along with the BMI under metabolic and endocrine systems, where only diabetes will be graded. Finally, discussions led to the inclusion of motor function as a new domain, involving 4 items (outdoor mobility, indoor mobility, stair climbing and hand function). Depression, BMI and dyslipidemia were included as additional risk factors. Since the first proposition of the index, a total of 13 items were rejected by the SIG as it does not reflect the severity of the disease (see Table 1).

All domains and their related items reviewed during the three meetings are presented in Table 2. During the OMMYD-3, discussion was started concerning the scoring of all items. However, the final scoring system was not completed and the SIG agreed to work on it after the meeting. The objective is to create a preliminary version of the DSI-DM1 to conduct a pilot testing with a small sample of DM1 patient in order to be able to propose some modifications (if needed) for the next OMMYD in 2017.

SESSION 6. SLEEPINESS/FATIGUE/ APATHY SPECIAL INTEREST GROUP

The session was chaired by Dr. Luc Laberge from ÉCOBES – Recherche et transfert, Cégep de Jonquière, Canada.

Background discussion

In addition to define a core set of outcome measures, the overall goal of the Sleepiness/Fatigue/ Apathy SIG is to have a unified definition and a conceptual operationalization of sleepiness, fatigue, and apathy. Indeed, without gold standards for defining and measuring these symptoms in DM1, the availability of empirically sound measures is imperative. More particularly, specific objectives were: 1) to present preliminary results on the use of the Fatigue and Daytime Sleepiness Scale (FDSS) by the Clinique des maladies neuromusculaires (Jonquière) and the MRC Neuromuscular Centre (Newcastle); 2) to present clinical experience and preliminary results of Marin's Apathy Evaluation Scale (AES) and Lille Apathy Rating Scale (LARS) by the Clinique des maladies neuromusculaires (Jonquière), and; 3) to present preliminary results on predictors of change in fatigue levels

using the Fatigue Severity Scale (FSS). Also, commonly used fatigue rating scales were assessed by the members.

Outcome measures

Fatigue and Daytime Sleepiness Scale (FDSS)

Some concerns were raised about FDSS [17] items 9, 10, and 11 which were derived from the Epworth Sleepiness Scale and slightly modified (see supplementary material). It relates mainly to the necessity of providing examples to patients. The SIG advises to talk to the authors of the FDSS to debate these issues and help reach an agreement. For the meantime, the SIG reached a consensus to simply deliver rating scales to patients without giving examples, so not to bias the results and ensure better comparability between neuromuscular clinics. However, the SIG acknowledges the relevance of developing a guide with standardized examples to be given to patients whose verbal abstract reasoning skills have been previously raised.

A sample of 143 patients from MRC Neuromuscular Centre (Newcastle) filled out the FDSS. Mean $\pm$ SD score was 44.8 ± 16.4 and female patients exhibited higher FDSS scores than male ($p < 0.05$). Also, FDSS scores were significantly associated with body mass index ($p < 0.05$), Muscular Impairment Rating Scale (MIRS) score ($p < 0.001$), QT interval ($p < 0.05$), and sitting forced vital capacity (FVC) ($p < 0.05$). On the other hand, FDSS scores did not vary with age, walking distance, lying FVC, blood pressure, heart rate, PR interval, and QS duration. Moreover, reliability of the FDSS was documented on 20 patients (7 from the Newcastle neuromuscular center and 13 from the Clinique des maladies neuromusculaires, Jonquière). Internal consistency and intra-rater reliability were good (Cronbach's alpha = 0.82; ICC = 0.82, $p < 0.001$).

Multiple Sleep Latency Test and Maintenance of Wakefulness Test

Some SIG members suggested that the Multiple Sleep Latency Test (MSLT) characterizes the intensity of DM1 patients' sleepiness while the Maintenance of Wakefulness Test (MWT), by asking them to stay awake, both tracks sleepiness as well as capacity/motivation to stay awake. Hence, if the MWT is improved, both sleepiness and motivation may be improved whereas improvement regarding the MSLT may solely reflect improved sleepiness per se. Results yielded by these two polysomnographic techniques should be compared in patients in order to clarify their relationship and increase our understanding of the reportedly various excessive daytime sleepiness (EDS) phenotypes noted. Also, studies should explore whether some personality features influence MSLT results. SIG members feel that an important issue is to better characterize the habitual sleep/wake cycle of DM1 patients. Are they all long sleepers? What is their napping behavior? Is their habitual sleep/wake cycle irregular? Does it vary with employment status or activity level? Actigraphic studies could namely help clarifying these issues.

Apathy Evaluation Scale (AES)

The three versions of the AES (self (AES-S), clinician (AES-C), and informant (AES-I) (significant other, e.g. personal or professional caregiver)) [18] were administered at the Clinique des maladies neuromusculaires (Jonquière). It was noted that patients had difficulty understanding some AES items. The advantages of the AES are that it can be rapidly administered (about 10 min for the clinician version and 3 min for the self and informant versions) and that there is no significant difference in the median score obtained from the clinician, self, and informant versions ($n = 20$). Preliminary results regarding test-retest reliability of the AES in patients ($n = 13$) and caregivers ($n = 9$) suggest good to excellent reliability ($0.70 < \text{ICC} < 0.85$).

Lille Apathy Rating Scale (LARS)

Results concerning the use of the Lille Apathy Rating scale [19] to measure apathy in 87 patients with classic adult and late-onset phenotypes were presented. It was found that the 4 dimensions of apathy tracked by the LARS (intellectual curiosity, emotion, action initiation, self-awareness) were significantly higher in DM1 patients with the classic adult phenotype than in those with the late-onset phenotype ($p < 0.01$). Of note is that about 1 of 4 patients (24%) with the classic adult phenotype met the criterion for apathy while none of the late-onset patients did.

Face validity of commonly-used fatigue rating scales

SIG members first examined the subjective fatigue experience dimension of the Checklist Individual Strength (CIS20-R) [20], a well validated and widely used multidimensional self-report measure that aims to assess subjective experience of fatigue, concentration, motivation, and physical activity. Some SIG

members expressed the view that the 8 items of the fatigue subscale seemed to evaluate peripheral or muscle fatigue consecutive to physical activity rather than central fatigue per se. Others were of the opinion that the subjective fatigue items appeared to have been devised for healthy people rather than for individuals with chronic neuromuscular conditions. In addition, SIG members expressed some concerns regarding the content validity of the fatigue subscale, most items seemingly focusing on physical fatigue and not sufficiently documenting aspects of mental fatigue or weariness that many patients typically feel upon morning awakening. Moreover, many items are not plausible for DM1. For example, no clinician would ask DM1 patients whether they "feel fit" (item 3). Similarly, it may not be relevant to ask a patient whether s/he feels, physically, in an excellent condition. Also, the timeframe "in the last two weeks" is not relevant for DM1 patients. Results from the OPTIMISTIC study on fatigue and exercise therapy shall permit to further document the validity of this rating scale, namely the convergent validity.

The 9-item Fatigue Severity Scale (FSS) [21] was originally developed for patients with multiple sclerosis and systemic lupus erythematosus. Its reliability was previously determined in DM1. As regards item 5 "Fatigue causes frequent problems for me", it was noted that patients often ask to which problems this refers to. In order not to bias patients' answers, SIG members advise to say "any kind of problem that you may think of". On the other hand, it has been generally easy for patients to fill out this scale. Finally, SIG members particularly appreciated the fact that the FSS addresses fatigue's effects on daily functioning and that patients can easily refer to their daily life situations.

The Chalder Fatigue scale [22] was designed to measure the severity of fatigue in adults. Its 14 items examine symptoms of both physical and mental fatigue. This scale has been shown to be reliable in DM1 patients. It can be administered both by interview and through the use of a pencil-and-paper test. SIG members believe that the response options are not adapted to such a chronic condition as DM1, patients oftentimes having been drowsy or fatigued for decades. SIG members do not routinely use that scale because they hold the view that the content validity remains questionable. For example, items 7 and 8 "Do you have less strength in your muscles?" and "Do you feel weak?" respectively appear unsuitable for DM1.

The Brief Fatigue Inventory [23] was devised to assess the severity of fatigue in cancer patients. It is based on the same principle as a visual analog scale for fatigue. SIG members believe that it may not be relevant to inquire about fatigue and its effects during the past 24 hours in the context of a chronic, progressive neuromuscular disease. Moreover, this rating scale does not evaluate symptoms of fatigue and their repercussions on patients' lives. Even if there may be a bit of fluctuation in the daily levels of fatigue that patients experience, it is not of particular interest to document peaks and troughs from day to day. On the other hand, circadian variation of fatigue levels may be worth studying, but other scales such as the Stanford Sleepiness Scale and the Karolinska Sleepiness Scale should preferably be used.

The Piper Fatigue Scale (PFS) [24] is a self-reported instrument measuring cancer-related fatigue. The scale has well established reliability and validity in American women with breast cancer. SIG members first consider that the 27-item PFS is a bit long and that the answer choices are too numerous (1 to 10). Almost half of the scale's items ask patients to which degree they are "now" feeling strong, refreshed, relaxed, lively, etc. Other items deal with the degree to which fatigue experienced "now" interferes with various aspects of patients' lives (eg. work and school sexual activity, social relationships, etc.). Some SIG members have the impression that some items tap sleepiness more than fatigue. In all, this fatigue rating scale does not seem applicable to DM1.

The Fatigue Symptom Inventory (FSI) [25] was developed with women undergoing treatment for breast cancer and aims to assess the severity, frequency, and diurnal variation of fatigue, as well as its perceived interference with quality of life. Also, the Multidimensional Fatigue Symptom Inventory – Short Form (MFSI-SF) [26] was developed to capture the full spectrum of the fatigue symptom profile in cancer patients. SIG members consider that those scales are too broad and unspecific as regards DM1.

Conclusions and research agenda

Although the FDSS shows promising results, SIG members emphasize that FDSS results should take into account occupational activity (employment status) of DM1 patients. Therefore, more works need to be done before the SIG makes a final selection of outcome to measure the three components sleepiness, fatigue and apathy.

SESSION 7. PULMONARY SPECIAL INTEREST GROUP

The session was chaired by Valeria Sansone from the NEMO Clinical Center, University of Milan.

Background discussion

The respiratory SIG was formed to explore which respiratory parameters, tests, or findings in general could be considered to be useful outcome measures to be used in clinical settings and in clinical trials. Specific objectives were to discuss: 1) the utility and validity of the respiratory symptom checklist (RESPICHECK questionnaire) for patients with DM1; 2) the NINDS Common Data Elements on respiratory screening and monitoring; and 3) the existing respiratory parameters used in clinical trials for other respiratory diseases including compliance as hints/helpful suggestions to design trials addressing respiratory function in DM1.

Outcome measures

Respiratory Symptom Checklist questionnaire

The RESPICHECK questionnaire was drafted during the 207th ENMC workshop on the diagnosis and management of chronic respiratory insufficiency in myotonic dystrophies. It includes 9 domains: orthopnea, dyspnea, sleep, headaches, apnea, cognitive performance, excessive daytime sleepiness, fatigue, and chest infection. Data was presented from the experience at the NEMO Center and at the Neurological Institute Besta in Milan. The initial questionnaire was administered twice within a 4-week interval to 25 patients to assess test-retest reliability (correlation coefficient 0.02; $r = 0.82$; $p = 0.65$; ANOVA = 0.25). The RESPICHECK questionnaire was then correlated with the Epworth Sleepiness scale (ESS) and other respiratory parameters. It showed to have a good convergent validity with the ESS ($r = 0.52$, $p = 0.02$) and, after adjusting for age and sex, showed to have a direct correlation with the pC02 level ($p < 0.05$), and an indirect correlation with the sitting forced vital capacity and the forced expiratory volume ($p < 0.05$).

This checklist was reviewed item by item first with the respiratory SIG and then with the Sleepiness/Fatigue/Apathy SIG. Wording was reviewed and questions related to excessive daytime sleepiness and fatigue were modified by the respiratory SIG. A new version of the questionnaire was agreed upon (see Table 2) and validation of this version is currently ongoing.

Existing respiratory parameters used in clinical trials

An overview of respiratory outcome measures used in other trials in pulmonary diseases was given as well as programmes to improve adherence and compliance in other pulmonary diseases. The SIG ultimately concluded that a multidisciplinary approach is needed to ensure the best compliance. Experience from other trials seems to show that preliminary psychological interviews on motivation and educational training sessions on the importance of non-invasive ventilation and respiratory involvement in general may be a good option to improve compliance and adherence to prescriptions in this population. There is a lack of standardized respiratory outcome measures which is known to be sensitive to change in this population group and this needs further investigation.

Conclusion and recommendations

The RESPICHECK questionnaire will need validation before its recommendation by the SIG in clinical trials. It was agreed upon that motor function tests would have to be combined to respiratory function tests to better assess the efficacy of any intervention. It was also suggested that researchers should start thinking about mice models of respiratory involvement. It was anticipated that this may be important because, unexpectedly, nuclear foci are found in respiratory parenchyma and not only in respiratory muscles and it would be expected. It was agreed that studies of lung parenchyma should be considered to better address respiratory involvement in selected DM1 patients.

RESEARCH AGENDA FOR THE OMMYD WORKING GROUPS

As discuss above, SIGs pointed out the lack of metrological properties concerning some specific instruments, methods or protocols. They agreed together to accomplish some small projects prior to OMMYD-4. For the majority of the SIGs, there is an important need to obtain more data on reliability, validity, and responsiveness of the protocols used by each research group.

Cognitive-SIG

The next expected steps will be to: 1) conduct more longitudinal studies in homogeneous cohorts of patients based the phenotypic classification; 2) finalize identification of outcome central nervous system measures for future clinical trials; 3) include complementary family members/partners/caregivers context reports; and 4) review studies comparing neuropsychological and neuroimaging data.

PROM-SIG

Studies on the reliability and of the LIFE-H (measurement of life habits), DM1-Activ, the MDHI, and the use of an actigraph to capture information on physical activity and sleep/wake should be performed.

FCOM-SIG

Studies on responsiveness or sensitivity to change for the four selected outcome measures in the DM1 population (6MWT, 10mWT, 30s-CST, 9HPT) should be performed. Detailed standardized instructions and instructional videos in at least English should be also developed before the next meeting.

Muscle-SIG

Studies of the intra- and interrater reliability of the published protocol of Hébert et al. to measure muscle strength of the muscle groups selected by the SIG should be performed. Also, more data on the measurement of myotonia will be essential for the pursue of the discussion.

DSI SIG

The SIG will elaborate a DSI administration guidelines and will conduct a pilot study to assess the feasibility of the DSI in clinical practice and to insure patients and clinicians understanding of the index.

Sleepiness/Fatigue/Apathy

The convergent validity of the FDSS should be assessed against the Epworth Sleepiness Scale which is the most commonly used daytime sleepiness rating scale. Moreover, factorial validity should be evaluated in order to verify whether FDSS items assess a single construct or multiple constructs. Most importantly, there is a need to determine a score and cutoff point that would identify DM1 patients with fatigue and sleepiness, using namely ROC curves and running separate analysis for sex. The relationship between the reportedly peculiar personality profile of patients with DM1 and various outcome measures of apathy, fatigue, and sleepiness, including MSLT and MWT, should be documented. In addition, the effects of interventions devised to alleviate these latter symptoms should be assessed, in conjunction with a prospective assessment of sleep with sleep-wake logs and/or actigraphy.

Pulmonary SIG

It was agreed that the validation process of the RESPICHECK questionnaire modified by the SIG would take place in Italy with a larger cohort of DM1 patients and that, once this was completed, the questionnaire would be translated and tried in other countries. Candidate countries are France, the United Kingdom, Germany, Canada and Serbia. It was agreed that respiratory symptoms assessed in the RESPICHECK questionnaire would be compared and validated with the Borg scale. Luc Laberge suggested validating the RESPICHECK questionnaire with the Profil Multidimensionnel de la dyspnée (MDP).

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SUPPLEMENTARY MATERIAL

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