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International Workshop: Outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations. 16–18 November 2016, Rome, Italy

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1. Introduction

Twenty-six researchers from 10 different countries (USA, Spain, Italy, France, Germany, The Netherlands, United Kingdom, Japan, Norway and Canada) met in Rome, Italy, from 16–18 November 2016 to update current knowledge on clinical trial readiness and outcome measures for Primary Mitochondrial Myopathies (PMM). Patients' advocacy groups delegates also attended.

2. Background

Mitochondrial myopathy is a common manifestation of mitochondrial disease, the most frequent group of metabolic disorders in humans with an estimated prevalence of 1 in 4300 when all pathogenic mutations in mitochondrial DNA (mtDNA) and nuclear DNA (nDNA) are included [1]. Myopathy can be the only clinical feature of a mitochondrial disease, or, more commonly, may be associated with additional "mitochondrial red flag" manifestations such as diabetes, sensorineural hearing loss, optic atrophy, peripheral neuropathy, cardiomyopathy, nephropathy, hepatopathy, stroke-like episodes, seizures, ataxia, failure to thrive, developmental delay or regression, and dementia [1].

Primary mitochondrial myopathies (PMM), as defined by this consortium of international experts in mitochondrial disease, are genetically defined disorders leading to defects of

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oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle (see below for methodology). Thus, secondary involvement of mitochondria, frequently observed in multiple neuromuscular diseases (e.g. inclusion body myositis, Duchenne muscular dystrophy, Kennedy disease) is not considered PMM.

PMM may present at any age, patients with severe generalized muscle involvement typically present early in life, although individuals with milder forms of the disease, or symptoms confined to specific muscles tend to have later presentations. The most common presentation of PMM is chronic progressive external ophthalmoplegia (PEO). Chronic PEO is characterized by a slowly progressive, usually bilateral limitation of eye movements (ophthalmoplegia) in all directions of gaze so that patients turn their heads to see a target at the periphery of the visual field; patients sometimes report diplopia, especially when onset of ophthalmoplegia is asymmetric. Intrinsic ocular muscles are not involved. PEO is usually accompanied by bilateral eyelid ptosis, which is often the presenting symptom, associated with a compensatory frontalis muscle hyperactivity and, in severe cases, tilting of the head backwards. PEO is often associated with other signs of skeletal muscle involvement, typically a slowly progressive axial and proximal limb weakness affecting predominantly the hip and shoulder girdle as well as neck flexor muscles often with variable muscle wasting. Muscle weakness may also cause dysphagia and dysarthria due to oropharyngeal weakness, as well as respiratory failure. Distal myopathic weakness may be present but is rarely seen early in the disease.

From a genetic point of view, PEO may be autosomal dominant or recessive, sporadic (usually due to single large-scale deletions of mtDNA), or maternally inherited. Autosomal PEO can be associated with multiple deletions and/or depletion of mtDNA, caused by nuclear gene defects and subsequent impairment of mtDNA maintenance. PEO is also the most frequent phenotype associated with a single sporadic large-scale deletion of mtDNA. The “common deletion” is 4.9-kb and accounts for about one-third of all single large-scale deletions of mtDNA.

Myopathy can be the only clinical feature of a mitochondrial disease but may also be part of a component of other mitochondrial syndromes. For example, Kearns-Sayre syndrome is defined by the early onset of PEO before age 20 years in association with pigmentary retinopathy, and at least one of the following: cerebellar ataxia, cardiac conduction block, or cerebrospinal fluid protein levels >0.1 g/L.

Other manifestations of PMM are exercise intolerance often with myalgia, fatigue (defined as an overwhelming sense of tiredness, lack of energy, and feeling exhausted), muscle wasting, muscle cramps, and recurrent rhabdomyolysis with myoglobinuria triggered by exercise as seen in cytochrome *b* deficiency or in the myopathic form of CoQ_{10} deficiency. Exercise-induced symptoms are common in PMM and reflect lack of energy production due to mitochondrial dysfunction in skeletal muscle, increased lactate production and phosphocreatine depletion.

In early onset forms of PMM (i.e. the myopathic form of mitochondrial depletion syndrome typically due to *TK2* mutations), hypotonia, floppy infant syndrome, failure to thrive, respiratory insufficiency and reduced or absent deep tendon reflexes are common [2].

Despite the growing interest and an increasing amount of published literature and clinical data on mitochondrial disease and PMM, there are currently no available disease-modifying therapies for PMM [3]. Therefore, treatment of PMM focuses on symptomatic management often with a combination of vitamins and supplements (often referred to as “mito-cocktails”) for which there is no clear evidence base. An increasing number of therapeutic options are being considered [4,5], and with the development of large cohorts of patients and biomarkers, several clinical trials are already in progress (listed in https://clinicaltrials.gov). Many mitochondrial disease specialists use a set of internal guidelines based on theoretical concepts, as well as personal and anecdotal experience due to the lack of empiric data. As a consequence, there are inconsistencies in treatment and preventive care regimens.

In addition to this lack of care guidelines, there is no consensus on how to conduct randomized, controlled clinical trials (RCT) for mitochondrial disease in general, and PMM in particular. Given the necessity to reach consensus on clinical outcomes measures to quantify the impact of treatment, the following three actors are pivotal: patients who aim to have a better quality of life, clinical researchers, who need objective measures to assess treatment responses, and regulatory agencies (e.g. the U.S. Food and Drug Administration and the European Medicines Agency) who have emphasized preferences for functional outcome and patient-reported outcome (PRO) measures [6,7].

This paper reports the results generated by a Delphi consensus panel on some unanswered questions related to PMM. These questions covered three domains: (i) Identification of PMM functional outcome measures for clinical trials; (ii) Identification of selected quality of life and clinical outcome scales for mitochondrial diseases; and (iii) Identification of potential mitochondrial biomarkers to monitor the efficacy of future clinical trials.

2.1. The Delphi process

The Delphi method provides a systemic approach to collecting opinions from experts (the “Delphi panel”) and has been widely applied in various fields, including healthcare, to obtain consensus or to provide recommendations on a well-defined and specified topic [8]. Although often described as a ‘panel’, experts provide their opinions freely, individually and anonymously.

2.2. Phase I: pre-meeting

A survey designed to gauge the level of consensus among a group of experts from established centers of excellence in the diagnosis and management of mitochondrial disease, was created by four facilitators (MM, TK, RM and MH) and distributed online to participating clinicians; their responses were collected anonymously and analyzed prior to a face-to-face meeting.

Participants voted using a 5-point Likert scale to indicate their level of agreement on each statement (1 = absolutely disagree, 2 = disagree, 3 = no judgment, 4 = more than agree, 5 =

absolutely agree). A “strong consensus” for a statement was considered to have been reached when both more than 70% of scores were ≥ 4 and the mean score was >4. If only one of these two parameters was met then the consensus was considered as a “good consensus”. If both parameters were not met then the statement was considered to lack consensus agreement.

The facilitators evaluated the responses and identified statements for which there was no consensus.

2.3. Phase II – Delphi panel

Twenty-six researchers from 10 countries convened in Rome. Diversity of expertise and independence were guaranteed, by inviting neurologists, pediatric neurologist, geneticists, one neuroradiologist (DS), and an expert on biostatistics and clinical trials design (JLPT), all recognized experts on mitochondrial disease. Representatives from the MITOCON (Italy), United Mitochondrial Disease Foundation (UMDF, USA), International Mito-Patients (IMP), and Asociación de Enfermos de Patologías Mitochondriales (AEPMI, Spain) participated in the meeting as patient advocates, providing them with unique opportunities to meet and interact with clinicians working on mitochondrial disease, and allowing investigators to get input from the patients’ perspectives on clinical and research plans in PMM. The participants engaged in 3-days of face-to-face Delphi panel discussions, ensuring a multidisciplinary approach and allowing opinions and views from different perspectives to be expressed.

Mancuso opened the Delphi meeting with a discussion of the workshop aims. Hirano gave a brief overview of the current state of mitochondrial medicine and Schülke described the Human Phenotypic Ontology as a platform for international harmonization of mitochondrial patient registries. Mancuso presented the results from Phase I. Statements from Phase I without consensus were selected for discussion in the plenary session. Gorman and Koene updated the group on functional and clinical outcome measures; Turnbull and Bertini described current needs to be ready for clinical trials in PMM in adulthood and children. Moreover, Taivassalo presented recommendations for exercise physiology testing in mitochondrial myopathies, while Koga and Shungu reported on serum, tissues, and imaging biomarkers. Smeitink explained the many facets of the drug development process and its relation with outcome measures. After discussion, new statements from the Delphi panel discussions were generated; and, when required, statements were modified, and participants voted again on statements that previously lacked consensus using the same 5-point Likert scale. Statements were divided into seven main areas: 1) Clinical scales to be used in adults; 2) Clinical scales to be used in children; 3) Functional tests to be used in adults; 4) Functional tests to be used in children 5) Clinical trials performance outcome measures; 6) Patient-reported outcome measures; and 7) Biomarkers.

Table 1 presents the results of all statements and responses. Those statements for which consensus was not achieved in the survey were discussed in the Delphi plenary session and a second votes were taken. Consensus was reached on all but five statements according to pre-defined criteria.

2.3.1. Definition of PMM—The definition of PMM, as presented in the Introduction, reached a strong consensus (Mean score: 4.88, number of experts voting 4 or above: 100%).

2.3.2. Mitochondrial registries harmonization—National clinical networks to recruit and standardize patient phenotyping have been established in multiple countries, and several national registries are available. These networks enable studies of mitochondrial disease natural history, overcome fragmentation of understanding individually rare entities, and establish national tissue biorepositories. For the majority of mitochondrial disease, development of successful treatments has proved to be extremely difficult. The main challenges are caused by the extreme genetic and phenotypic heterogeneity of these diseases, making it very difficult to collect sufficiently large groups of patients to conduct adequately powered, statistically valid, randomized, double-blinded, placebo-controlled clinical trials. Therefore, all the participants agreed that it would be ideal to establish a world-wide registry for mitochondrial disease, integrating existing prospectively collected data from the national networks registries, and providing access for all other countries. Moreover, we agreed to map each term from all registries to a standardized ontology term, likely Human Phenotype Ontology (HPO, http://human-phenotype-ontology.github.io).

2.3.3. Identification of elements to be monitored during a clinical trial—Protocols and outcome measures in mitochondrial disease clinical trials should be harmonized internationally. To assess changes over time in natural history studies and clinical trials the clinical manifestations should be graded using tangible and ‘fit for purpose’ outcome assessments that permit quantitation of clinical disease severity and patient-reported outcomes. While the choice of outcome(s) will primarily be determined by the aims and hypothesis of each study, judicious consideration of the validity, reliability, feasibility, practicality, and responsiveness of the outcome measure remains paramount. The group has therefore identified the following outcome measures and biomarkers for PMM studies.

2.3.4. Clinician-reported outcome measures

2.3.4.1. Clinical scales to be used in adults (see Table 1 for appropriate references): The Newcastle Mitochondrial Disease Adult Scale (NMDAS) is a validated clinical rating scale implemented in 2005, and is devised to capture the natural history of mitochondrial disease. NMDAS comprises both objective and subjective elements classified into three sections: current function, system specific involvement, and current clinical assessment. The Hammersmith Functional Motor Scale Expanded is a psychometrically robust clinical outcome assessment validated in SMA types 2 and 3, that has recently been revised to address discontinuity in its recorded performance, and its adoption in clinical trials may warrant consideration [12]. Health related quality of life (HRQoL) is increasingly recognized as a fundamental patient-centric outcome measure in both clinical intervention and research. The Short Form 36 version 2 (SF-36v2) Health Survey is a generic HRQoL measure that has been extensively validated in multiple, chronic disease states.

The Quantitative Myasthenia Gravis (QMG) test is a standardized quantitative strength scoring system developed specifically for Myasthenia Gravis. The QMG has been validated

and has been used by the investigators in several previous MG trials, and the workshop participants considered this scale very useful for PMM as well. Eyelid ptosis and ophthalmoparesis should also be monitored systematically including measurements of lid height, margin reflex distance, elevator function, and quantification of eye movements.

2.3.4.2. Clinical scales to be used in children (see Table 1 for appropriate references): Attempts to harmonize the selection of outcome measures in children with mitochondrial disease that can be used in clinical trials and natural history studies have been undertaken previously [99,100]. Experts at the workshop, endorsed the following outcome measures from a preselected list: Newcastle Pediatric Mitochondrial Disease Scale (NPMDS), PedsQL Neuromuscular Module (PedsQL-NMM), Gross Motor Function Measure (GMFM), Pediatric Evaluation of Disability Inventory, The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND), Hammersmith Functional Motor Scale Expanded, International Pediatric Mitochondrial Disease Scale (IPMDS), Childhood myositis assessment scale (CMAS), Quantitative Myasthenia Gravis (QMG) Test, eyelid ptosis and ophthalmoparesis.

Serious adverse events should also be reported for good clinical practice.

The group did not consider the number of hospitalizations as a reliable outcome measure due to differences in health care practices across countries.

2.3.4.3. Functional tests to be used in adults (see Table 1 for appropriate references): To date, validation of commonly used clinician reported functional outcomes in patients with mitochondrial disease, remains limited. The following assessments have undergone preliminary evaluation in PMM: 6-Minute Walk Test (6MWT), Timed Up and Go (TUGx3), and Five Times Sit to Stand (5XSTS). Each of these outcome measures has been shown to be valid and able to definitively discern patients from control subjects; while 5XSTS exhibits greatest responsiveness to change.

A clinical or bedside swallow assessment is the first step in identifying whether dysphagia is present. The workshop participants have considered that clinical assessment can be improved, if considered safe, by using a 100 ml water swallow test (WST) and the Test of masticating and swallowing solids (TOMASS). Such information may improve the predictive value of clinical assessment and provides a simple way of monitoring change over time in patients with dysphagia of different origin.

Academic and pharmaceutical industry researchers designing clinical studies should be cognizant that many outcome measures require further longitudinal testing to assess their validity and reliability. Furthermore, variability due to motivation, fatigue or learning effects needs to be considered. For example, a recent consensus statement from the chronic respiratory disease field recommends two repetitions of the 6MWT at baseline due to the well-known familiarization effect [46]. To this end, we strongly advise adoption of standardized operating procedures as 'good practice' to aid standardization and ultimately improved measurements of clinical outcome measures.

2.3.4.4. Functional tests to be used in children (see Table 1 for appropriate references): Regarding selection of functional tests in PMM children, the group reached consensus on the following points: (a) the proposed test must be reliable and sensitive, with normative data available; (b) the test should be able to measure changes over time; and (c) it must be simple to administer (understandable, total time, cost, etc.). On the basis of these criteria as well as those described above, experts preselected a list of three tests that are most relevant for assessing PMM children: 6MWT, TUGx3 and 5xSTS. Noticeably, 6MWT is reliably used in children at age 5 years and beyond. Moreover, TOMASS and Timed water swallow may be useful tools, if considered safe, to evaluate and monitor dysphagia also in children.

2.3.4.5. Performance outcome measures (see Table 1 for references): Although no official consensus for exercise physiology testing has been established to date, experts from this workshop endorsed the value of aerobic exercise testing for PMM patients 14 years of age and older, due to its ability to stress the aerobic energy pathway and reveal abnormalities in oxygen delivery and utilization as has been previously described. Such testing, using a metabolic cart to measure the rate of oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation during incremental cycle ergometer exercise is available in most hospital cardiopulmonary testing laboratories. While standardized measurement of resting blood lactate may be useful, end-exercise blood lactate normalized to peak power in combination with a low peak oxygen consumption and high respiratory exchange ratio (VCO_2/VO_2) are highly suggestive of PMM [42,44]. Additionally, simultaneous measurement of cardiac output during exercise, when available, increases the diagnostic value of aerobic exercise testing by revealing a disproportionately high cardiovascular response to exercise and a blunted muscle oxygen extraction capacity (low systemic arteriovenous oxygen difference) [44]. Pulmonary function testing at rest using standardized measurements of spirometry may be used. However measurement of ventilation relative to workload and metabolic rate during exercise is also helpful in revealing a distinctive pattern in PMM [45]. Testing by experienced evaluators and standardization of aerobic exercise testing protocols are strongly advised with collection of normative data in healthy and disease controls. Furthermore, the Common Data Element Project initiated by the National Institute of Neurological Disorders and Stroke (NINDS) considered maximal and submaximal exercise testing, along with the Borg Scale of Perceived Exertion, as supplemental-highly recommended tools for clinical research in mitochondrial disease [101].

Given the wide use of the 6MWT as a functional measure in clinical research, combined with the utility of the physiological measures mentioned above in reflecting disease severity in PMM, the use of mobile telemetric cardiopulmonary monitoring during a 6MWT as has recently been reported in cardiovascular and pulmonary diseases [48,49] was also put forth by this group as a potentially useful performance outcome measure. Moreover the 6MWT can also be used as a measure of fatigability being sensitive to fatigue-related changes [102].

The use of quantitative muscle dynamometry to measure peak isometric strength was not strongly endorsed because fewer PMM patients present with overt muscle weakness relative to those with reduced aerobic capacity. Measurement of muscle endurance/fatigue was

thought to be a more biologically relevant outcome measure although standardized testing protocols for PMM are lacking. Specialized dynamometers for upper and lower limb, as well as handgrip, can be found in most institutional physiotherapy centers. Standardization of evaluator training on the proper use of dynamometers and performance of quantitative muscle testing is also important [103].

Physical activity monitors (3D accelerometry) are increasingly being used in clinical research as an outcome measure and provide information on time spent in sedentary, light to vigorous activity, daily step counts, sleep monitoring, and energy expenditure. Feasibility and face validity of 3D accelerometry has recently been established in children with mitochondrial disease, of which some had PMM [58]. For certain PMM patients with gait abnormalities, the use of the GAITRite computerized system was endorsed as an objective assessment of gait. The GAITRite has proven feasible, reliable and valid in adult carriers of the m.3243A>G mutation [104]. The nine-hole PEG test and the maximal sniff nasal inspiratory pressure (SNIP) are used in other neuromuscular disorders and may be relevant for certain patients with PMM. .A ‘6-minute mastication test (6MMT)’ was also suggested as a Pilot outcome measure. The 6MMT was developed to measure mastication endurance and participants are asked to chew on a chewing tube during 6 minutes [55]. The total amount of chewing cycles, as well as a qualitative rating are determined.

2.3.4.6. Patient-reported outcome measures (measurements of patient functions or feelings): NMDAS and NPMDS Section IV, Quality of Life questionnaires: Patient-Reported Outcomes Measurement Information System (PROMIS) and The World Health Organization Quality of Life (WHOQOL); fatigue scales: Checklist individual strength (CIS), Fatigue Severity Scale (FSS), Multidimensional Fatigue Inventory (MFI), Patients’ Global Impression of Change (PGIC) scale, Pediatric quality of life inventory (PedsQL), West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Mitochondrial disease-specific patient questionnaires should also be developed.

2.3.4.7. Biomarkers to be monitored during a clinical trial: The role of serum biomarkers was also discussed. The group reached a consensus on the following biomarkers: GDF15, FGF21, basal venous blood lactate and pyruvate, resting CK, metabolomic studies (including serum amino acids (AA) and acyl-carnitine profiles, and urine organic acids (OA)). Promising approaches such as proton or ^{31}P-MRS of muscle at baseline should be explored in research settings, as well as creatine levels in PMM. ^{31}P-MRS of muscle at baseline, during exercise (pedal depressing) and during recovery may also be useful biomarkers (good, but not strong, consensus).

3. Conclusions

The working group has defined PMM with a strong consensus. There was an agreement that registries and natural history studies are key to becoming trial ready, and that each term from all registries should be mapped to a standardized ontology term, likely HPO. The group has then identified, through a Delphi method, a set of recommended outcome measures to be implemented in PMM clinical studies. Strengths of the identified outcome measures include the comprehensiveness of the measures, prior validation studies, practicality for use in

clinics, and applicability to adults and children with PMM. Patient-reported quality of life, fatigue, and pain questionnaires were also considered to be important. These outcome measures may also be combined in a composite endpoint that can measure minimal, moderate, and major improvement on a continuous scale, provide differential weights to each of the core set measures, and do not require large degrees of improvement in all of the measures to meet the criteria for clinical improvement.

We therefore propose a set of clinical scales, functional tests, performance and patient-reported outcome measures, and biomarkers to be applied to both adults (Table 2) and children (Table 3) affected by PMM.

4. Participants

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Table 1

Items of the Delphi working group.

Definition	Consensus		References
	Percentuage of sum 4 + 5	Mean score	
DEFINITION OF PRIMARY MITOCHONDRIAL MYOPATHIES			
PMM are genetically defined disorders leading to defects of oxidative phosphorylation affecting predominantly, but not exclusively, skeletal muscle. Secondary involvement of mitochondria, frequently observed in multiple neuromuscular diseases (i.e. inclusion body myositis, Duchenne muscular dystrophy, Kennedy disease) are not considered PMM.	100%	4.88	
MITOCHONDRIAL REGISTRIES HARMONIZATION			
The clinical phenotype should be recorded in a “computer readable” format, which enables automatic comparisons between patients, e.g. through an ontology	92%	4.52	
To assess changes in natural history studied and therapeutic clinical trials, the manifestations should be “graded” using consensus and user-friendly outcome measures	100%	4.72	
Should protocols for mitochondrial disease trials be harmonized?	88%	4.28	
Should data elements collected in different registries and natural history studies be harmonized between groups internationally?	96%	4.52	
The interrater-reliability of clinical manifestation quality and quantity should be established during the study by the independent rating of the patients’ manifestations by two raters who are blind to the rating of their counterpart	80%	4.12	
Should outcome measures be harmonized between different studies?	80%	4.24	
Clinician-reported outcome measures: Clinical scales to be used in adulthoods			
Newcastle Mitochondrial Disease Adult Scale	76%	4.24	Schaefer, 2006 [9]
Hammersmith Functional Motor Scale, Expanded	84%	4.2	O’Hagen, 2007 [10] Glanzman, 2011 [11] Ramsey,2017 [12]
Short Form 36 Health Survey (SF-36) score	76%	3.8	Pfeffer, 2012 [3] Lins, 2016 [13]
Myasthenia gravis tests	72%	3.96	Sharshar, 2000 [14] Bedlack, 2005 [15]
EOM/ptosis	88%	4.4	Richardson, 2005 [16] Fahnehjelm, 2012 [17]
Clinician-reported outcome measures: Clinical scales to be used in childhood			
Newcastle Pediatric Mitochondrial Disease Scale (3 age range)	80%	4.16	Phoenix, 2006 [18]
International Pediatric Mitochondrial Disease Scale	84%	4.14	Koene, 2016 [19]
PedsQL Neuromuscular Module (PedsQL)	92%	4.5	Varni, 2009 [20] Varni, 2011 [21] Davis, 2010 [22]
Gross Motor Function Measure (GMFM)	92%	4.4	Russell, 1989 [23] Alotaibi, 2014 [24]
Pediatric Evaluation of Disability Inventory (PEDI-CAT)	96%	4.44	Haley, 1992 [25] Haley, 2010 [26] Dumas, 2016 [27] Pasternak, 2016 [28]
The Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)	92%	4.36	Glanzman, 2010 [29] Glanzman, 2011 [30]
Hammersmith Functional Motor Scale, Expanded	96%	4.52	O’Hagen, 2007 [10]

Definition	Consensus		References
	Percentuage of sum 4 + 5	Mean score	
			Glanzman, 2011 [11] Ramsey, 2017 [12]
Childhood Myositis Assessment Scale	76%	3.96	Huber, 2004 [31]
Myasthenia gravis tests	72%	3.96	Sharshar, 2000 [14] Bedlack, 2005 [15]
Serious Adverse Events	88%	4.48	Pfeffer, 2012 [3]
Number of Hospitalization	44%	3.32	Pfeffer, 2012 [3]
IDENTIFICATION OF ELEMENTS TO BE MONITORED DURING A CLINICAL TRIAL			
Functional Tests: ADULTHOOD			
6-Minute Walk Test	84%	4.24	Guyatt, 1985 [32] McDonald, 2013a and b [33,34] Tveter, 2014 [35] Dunaway Young, 2016 [36]
Timed Up-and-Go test (x3)	76%	4	Dunaway, 2014 [37] Newman, 2015 [38]
Five times Sit-To-Stand test	96%	4.52	Newman, 2015 [38]
Timed water swallow	72%	3.8	Hughes and Wiles, 1996 [39] Nathadwarawala,1992 [40] Patterson, 2011 [41]
Test of masticating and swallowing solids (TOMASS)	80%	4.16	Hughes and Wiles, 1996 [39]
IDENTIFICATION OF ELEMENTS TO BE MONITORED DURING A CLINICAL TRIAL			
Functional Tests: CHILDHOOD			
6-Minute Walk Test	84%	4.2	McDonald, 2013 [33,34] Tveter, 2014 [35] Dunaway Young, 2016 [36]
Timed Up-and-Go test (x3)	92%	4.4	Dunaway, 2014 [37] Newman, 2015 [38]
Five times Sit-To-Stand test	92%	4.4	Newman, 2015 [38]
Test of masticating and swallowing solids (TOMASS)	83%	4.16	Hughes and Wiles, 1996 [39]
IDENTIFICATION OF ELEMENTS TO BE MONITORED DURING A CLINICAL TRIAL			
Performance outcome measures			
Aerobic exercise testing: Cardiopulmonary cycle ergometry (above 14 years of age)	96%	4.6	Tarnopolsky, 2004 [42] Tarnopolsky, 2012 [43] Taivassalo, 2003 [44] Heinicke, 2011 [45] Puente-Maestu, 2016 [46]
Systemic arteriovenous oxygen difference (calculated from measurement of cardiac output and rate of oxygen utilization during exercise)	100%	4.56	Connes, 2009 [47]
6MWT with mobile telemetric cardiopulmonary monitoring	96%	4.44	Kern, 2014 [48] Van Gestel,2014 [49]
Standardized Lactate pre and post-exercise	88%	4.4	Tarnopolsky, 2003 [50] Taivassalo, 2003 [44]
Quantitative dynamometry for muscle strength and endurance.	88%	4.16	Barden, 2012 [51] Tveter, 2014 [35] Tarnopolsky, 2004 [42] Taivassalo, 2002 [52]
30 Second Sit-To-Stand test	92%	4.36	Tveter, 2014 [35]
Nine hole peg test	84%	4.04	Kellor, 1971 [53] Mathiowetz, 1985 [54]

Definition	Consensus		References
	Percentuage of sum 4 + 5	Mean score	
6 Minutes Mastication Test (PILOT)	84%	3.88	vd Engel-Hoek, 2017 [55]
GAITRite	96%	4.4	McDonough, 2001 [56] Bilney, 2003 [57]
Physical Activity meters (including sleep monitoring)	96%	4.4	Koene S, 2017 [58] McDonald, 2013 [33,34] Stehling, 2016 [59] Georges, 2016 [60]
Spirometry	92%	4.52	Paschoal, 2007 [61] Fauroux, 2014 [62]
SNIP (Sniff nasal pressures)	96%	4.44	Fauroux, 2007 [63] Barnes, 2014 [64] Fauroux, 2014 [62]
IDENTIFICATION OF ELEMENTS TO BE MONITORED DURING A CLINICAL TRIAL			
Biomarkers			
31P MRS of muscle at baseline	52%	3.08	Chance, 1981 [65] Kemp, 1994 [66] Prompers, 2006 [67]
31P MRS of muscle at baseline - then during exercise (pedal depressing) – and then during recovery	72%	3.56	Kemp, 1994 [66] Taylor, 1994 [68] Argov, 2000 [69] Valkovič, 2016 [70]
Proton MRS of muscle (research only)	40%	3.04	
GDF15	88%	4.4	Yatsuga, 2015 [71] Koene, 2015 [72] Fujita, 2015 [73] Fujita, 2016 [74] Montero, 2016 [75]
FGF21	92%	4.24	Suomalainen, 2011 [76] Suomalainen, 2013 [77] Davis, 2013 [78] Lehtonen, 2016 [79]
Basal venous blood lactate and pyruvate	80%	4.2	Debray, 2007 [80] Patel, 2012 [81] Tarnopolsky, 2012 [43] Sperl, 2015 [82] Parikh, 2015 [83]
Resting blood CK	92%	4.36	Marsden, 2001 [84] Chanprasert, 2013 [85] Parikh, 2015 [83]
Metabolomic studies (including AA, urine OA, acyl-carnitine profiles)	96%	4.4	Barshop, 2000 [86] Barshop, 2004 [87] Wortmann, 2009 [88] Sakamoto, 2011 [89] Su, 2014 [90] Parikh, 2015 [83]
Metabolomic studies: creatine (exploratory only)	64%	3.64	
ICF-CY and other methods to classify and search for outcome measures			
Should we develop outcome measures that are applicable to a large majority of patients?	92%	4.16	
Should we focus on one domain of mitochondrial disease (e.g. eye) to prove the effectiveness of a compound in all mitochondrial diseases?	32%	2.72	
Should we target the development of outcome measures per syndrome/mutation individually?	64%	3.6	

Definition	Consensus		References
	Percentuage of sum 4 + 5	Mean score	
Should we develop outcome measures for subjects who are not able to follow instructions?	92%	4.32	
Identification of PMM outcome measures			
Patient-reported outcome measures Measurements of patient function or feeling			
NMDAS/NPMDS Section IV	96%	4.56	Schaefer, 2006 [9] Phoenix, 2006 [18]
Quality of Life: Patient-Reported Outcomes Measurement Information System (PROMIS)	88%	4.28	Fries, 2005 [91] Cella, 2007 [92]
Quality of Life: The World Health Organization Quality of Life (WHOQOL)	92%	4.36	WHOQOL Group, 1995 [93]
Fatigue scale: Checklist individual strength (CIS)	80%	4.04	Chalder, 1993 [94] Koopman, 2014 [4]
Fatigue scale: Fatigue Severity Scale (FSS)	80%	4.24	Hewlett, 2011 [95]
Fatigue scale: Multidimensional Fatigue Inventory (MFI)	80%	4.2	Smets, 1995 [96]
Patients' Global Impression of Change (PGIC) scale	64%	4.44	Arnold, 2011 [97]
Mitochondrial disease-specific patient questionnaires? (to be developed)	92%	4.52	
PEDS QL (Pediatric quality of life inventory)	88%	4.48	Varni, 2009 [20] Varni, 2011 [21] Davis, 2010 [22]
Pain to be monitored in PMM	100%	4.3	
West Haven-Yale Multidimensional Pain Inventory (WHYMPI) in adulthood	82%	4.1	Kerns, 1985 [98]
West Haven-Yale Multidimensional Pain Inventory (WHYMPI) in children	50%	3.4	Kerns, 1985 [98]

Table 2

Consensus of measures suitabole to assess adulthood PMM Patients in clinical studies.

Clinician-reported outcome measures: Clinical scales to
Newscastle Mitochondrial Disease Adult Scale (NMDAS)
Hammersmith Functional Motor Scale Expanded
Short Form 36 Health Survey (SF-36) score
Myasthenia gravis test QMG?
Functional tests
6MWT
Timed Up and Go (x 3)
Five times Sit-To-Stand test
Timed water swallow
TOMASS
Performance outcome measures
Exercise physiology testing
Systemic arteriovenous oxygen difference (calculated from measurement of cardiac output and rate of oxygen utilization during incremental exercise)
6MWT with cardiorespiratory measurement
Standardized lactate pre- post- exercise
Quantitative muscle dynamometry
30 Second Sit-To-Stand
Nine Hole Peg Test
6 Minutes Mastication Test (Pilot)
GAITRite
Activity meters (including sleep monitoring)
Spirometry
SNIP
Patient-reported outcome measures Measurements of patient function or feeling
NMDAS/NPMDS Section IV
Quality of Life: PROMIS
Quality of Life: WHOQOL
Fatigue scale: CIS
Fatigue scale: FSS
Fatigue scale: MFI
PGIC
WHYMPI
Biomarkers
GDF15

FGF21
Basal Venous Blood Lactate And Pyruvate
Resting Blood Ck
Metabolomic Studies (including AA, urine OA, acyl-carnitine profiles)
31P MRS of muscle at baseline - then during exercise (pedal depressing) – and then during recovery

Table 3

Consensus of measures suitable to assess childhood PMM Patients in clinical studies.

Clinician-reported outcome measures: Clinical scales to
Newcastle Pediatric Mitochondrial Disease scale (NPMDS)
International Pediatric Mitochondrial Diseases Scale (IPMDS)
Quantitative Myasthenia Gravis test (QMG)?
Gross Motor Function Measure (GMFM)
PedsQL
Pediatric Evaluation of Disability Inventory (PEDI-CAT)
The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND)
Hammersmith Functional Motor Scale, Expanded
Childhood Myositis Assessment Scale
Functional tests
6M-WT
Timed Up and Go (x 3)
Five times Sit-To-Stand test
Test of masticating and swallowing solids (TOMASS)
Timed water swallow
Performance outcome measures
Exercise physiology testing (above 14-years of age)
Systemic arterio-venous oxygen difference (calculated from measurement of cardiac output and rate of oxygen utilization during incremental exercise)
6MWT with cardiorespiratory monitoring?
Standardized lactate pre- post-exercise
Dynamometer
30 Second Sit-To-Stand
Nine Hole Peg Test
Functional Muscle Test
6 Minutes Mastication Test (Pilot)
GAITRite
Activity meters (including sleep monitoring)
Spirometry
SNIP
Patient-reported outcome measures Measurements of patient function or feeling
NPMDS/NPMDS Section IV
Quality of Life: PROMIS
Quality of Life: WHOQOL
PedsQL (Pediatric quality of life inventory)
Fatigue scale: CIS

Fatigue scale: FSS
Fatigue scale: MFI
Patients' Global Impression of Change
Biomarkers
GDF15
FGF21
Basal venous blood lactate and pyruvate
Resting blood CK
Metabolomic studies (including AA, urine OA, acyl-carnitine profiles)
31P MRS of muscle at baseline - then during exercise (pedal depressing) – and then during recovery