Received: 16 August 2020 | Revised: 29 September 2020 | Accepted: 2 October 2020

DOI: 10.1002/jimd.12320

REVIEW ARTICLE

JIMD SSIEM WILEY

Seeking impact: Global perspectives on outcome measure selection for translational and clinical research for primary mitochondrial disorders

Amy Goldstein[1,2] | **Shamima Rahman**[3,4]

[1]Mitochondrial Medicine Frontier Program, Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

[2]Perelman School of Medicine, University of Pennsylvania, Philadelphia, Pennsylvania

[3]Metabolic Unit, Great Ormond Street Hospital for Children NHS Foundation Trust, London, UK

[4]Mitochondrial Research Group, UCL Great Ormond Street Institute of Child Health, London, UK

Correspondence
Shamima Rahman, Mitochondrial Research Group, Genetics and Genomic Medicine, UCL Great Ormond Street Institute of Child Health, London WC1N 1EH, UK.
Email: shamima.rahman@ucl.ac.uk

Funding information
Lily Foundation; Great Ormond Street Hospital Children's Charity; National Institute of Health Research Great Ormond Street Hospital Biomedical Research Centre; CHOP Mitochondrial Medicine Frontier Program

Communicating Editor: John Christodoulou

Abstract

Primary mitochondrial disorders (PMDs) are challenging due to overall poor outcomes, no proven treatments, and a history of failed clinical trials, leading to a critical need to design future trials that can prove efficacy of an intervention. Selection of outcome measures for PMDs is complicated by extreme clinical, biochemical and genetic heterogeneity; PMDs are effectively a collection of nearly 400 individually ultrarare diseases. In clinical trials, outcome measures aim to evaluate, and ideally quantitate, the efficacy of an intervention in ameliorating clinical phenotype(s). The heterogeneity and multisystemic nature of PMDs makes it unlikely that a universal outcome measure will be applicable to all PMDs. Instead, a composite score of the individual's most worrisome symptoms may be a preferable endpoint. A further challenge arises from the tension between finding outcomes suitable for use in clinical trials (able to produce a measurable change in a relatively short period of time, namely the duration of a clinical trial) vs measures that are clinically meaningful to individual patients. A number of clinical rating scales and proposed biomarkers have emerged to capture the features of PMDs for natural history and interventional trials. Here we review our collective experiences with clinical rating scales, patient-reported outcome measures, and physiological, imaging, biochemical and muscle phenotypes as outcome measures in paediatric and adult PMDs in natural history studies and recent clinical trials. There is a pressing need to agree on a set of validated, robust, clinically meaningful outcome measures internationally, to facilitate the multicentre international clinical trials needed for optimal evaluation of novel therapies for these ultrarare diseases.

KEYWORDS

biomarkers, clinical trials, common data elements, metabolic disorders, outcome measures, oxidative phosphorylation, primary endpoints, primary mitochondrial disorders (PMDs)

1 | INTRODUCTION

Primary mitochondrial disorders (PMDs) encompass hundreds of individually rare and ultrarare inherited neurometabolic and multisystem disorders. Together, they are a common cause of central and peripheral neurological symptoms, typically in combination with multisystemic symptoms including eye, heart, liver, gastrointestinal, kidney, endocrine, and auditory manifestations. Current management and treatment is mainly symptomatic and supportive, with no proven treatment for these progressive debilitating and often lethal diseases. Anecdotal therapies that have been investigated in previous and current clinical trials include vitamins, cofactors, repurposed medications, exercise and dietary management, all with unproven efficacy. Prior to 2012, very few clinical trials for PMDs had been conducted and comprehensive reviews of these trials have shown that improvement in clinical trial design, involving all stakeholders, is desperately needed.[1] PMDs are unique with respect to determining an effective trial design owing to the numerous individual genetic diseases, with poor genotype-phenotype correlation, uncertainty regarding which outcome measures are best to evaluate, long and unpredictable disease course with periods of relative stability and inactivity, difficulty in patients meeting inclusion criteria, statistical considerations, cost, travel, and data quality.

The field of mitochondrial medicine is actively participating in ongoing and planned clinical trials; however, there continues to be a paucity of prospectively collected, longitudinal natural history data, reliable biomarkers of disease, and validated outcome measures to establish efficacy of interventions. Over the past decade, we have seen an increased level of engagement between the patient community, clinicians, patient advocacy groups (PAGs), scientists, regulatory agencies, and industry to develop robust patient registries, natural history studies, and clinical trials for those affected by PMDs. During the Mitochondrial Medicine conference at the Wellcome Genome Campus, Hinxton, UK, December 11-13, 2019, clinicians, researchers, PAGs, and members of regulatory agencies and industry convened and collaborated on the current landscape of therapeutic opportunities. This article serves as a summary of a session dedicated to reviewing outcome measure selection for translational and clinical research on an international level. Key stakeholders gathered at this meeting to review disease mechanisms, latest science, and plan future projects with the ultimate goals of collaborating to run clinical trials and establish evidence-based therapies for patients affected by PMD. Prior to having an effective therapy, clinical trials need to be designed that can demonstrate clinical benefit by proving that the intervention affects how a patient survives, feels or functions. Obstacles to designing informative trials include the heterogeneous nature of PMDs, poor characterization of the onset and progression of most PMDs (with few published natural history studies), paucity of validated outcome measures, the fact that no single outcome measure will fit all PMDs (necessitating several options to account for the heterogeneity), and lack of funding opportunities for natural history studies.

2 | DEFINING OUTCOME MEASURES

In order to improve clinical trial design, and ultimately develop efficacious and approved treatments for PMDs, we must first address several barriers in the field of mitochondrial medicine. The first is a universal definition of PMDs, which are genetic diseases caused by pathogenic variants in more than 350 nuclear genes and 37 mitochondrial DNA (mtDNA) genes known to date.[2] Known disease mechanisms include mutations in genes encoding subunits and assembly factors of the mitochondrial oxidative phosphorylation enzymes, and disorders of mtDNA maintenance, protein synthesis, cofactor biosynthesis and lipid metabolism. The second issue is defining the outcome measures; these are elements, which should be broadly agreed upon, that measure change in health or quality of life. For clinical trials, these must be validated specifically for PMDs, dynamic, and reviewed frequently as we proceed in subsequent phases of trials in order to improve the quality of the trials. It is also important that the selected outcome measures are appropriate for use for their intended purpose, whether natural history studies, interventional clinical trials or to evaluate existing clinical services for overall improvements in patient care. Ideally, the same outcome measures would serve all of these purposes equally well. The United States Food and Drug Administration (FDA) has advised that a meaningful outcome measure must show impact on how the affected individual feels, functions, and/or survives, so that if an outcome measure is an objective laboratory test or a neuroimaging study, it must have a meaningful clinical correlate. In addition, outcome measures should match the pathophysiology and expected action of therapy; for example, if a drug is expected to increase mitochondrial biogenesis, then there is a need to include a measurement such as mtDNA copy number or citrate synthase or respiratory chain enzyme activities. Finally, the FDA recognizes that subjects can select their own most troublesome symptom in a clinical trial; this can be accomplished by engaging with the patient community in determining which outcomes are most important,

establishing a panel of all the major symptoms, and allowing each subject to score the symptom severity on a Likert or Visual Analog Scale. Similarly, the European Medicines Agency (EMA) provides guidance through several dedicated committees, including the Committee on Orphan Medicinal Products (COMP), allowing industries to apply for "orphan medicinal product designation" with the intention of developing products for the diagnosis, prevention or treatment of rare serious and life-threatening conditions. The ultimate approval is reviewed and granted by the European Commission. The FDA and the EMA have developed many resources for Clinical Trials and Drug Development; please see Box 1 for a list of resources available from the FDA, EMA and other regulatory agencies to aid in clinical trial design.

Historically and prospectively, it has been challenging to decide which outcome measures are most relevant for use in clinical trials. To date, no outcome measure has risen to the status of being universally applicable to assess all aspects of mitochondrial disease in all patients. Toolboxes of outcome measures exist, including some vetted specifically for mitochondrial disease using Delphi criteria: Common Data Elements (CDEs), collated through the National Institute of Neurological Disorders and Stroke,[3] and outcome measures for primary mitochondrial myopathy and for paediatric mitochondrial myopathies and encephalomyopathies.[4,5] However only three disease rating scales, the Newcastle Mitochondrial Disease Adult Scale (NMDAS),[6] the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)[7] and the International Paediatric Mitochondrial Disease Scale (IPMDS)[5] have been validated for use specifically in PMDs.

Obstacles encountered in clinical trial design include the tension between the inclusion of sufficient outcome measures, while accounting for patient limitations of time, travel, cost, and fatigue; site limitations of feasibility, cost, training and personnel; statistical limitations of controlling the number of variables so that overall power is not diluted; and the need to select clinically relevant outcomes that are important to patients and/or their caregivers. Several previous studies that included a large number of outcome measures were not able to meet their primary endpoints. For example, one early clinical trial included 37 patients with various mitochondrial disorders (biochemical or genetically defined) who were treated with sodium dichloroacetate (DCA), a compound thought to be helpful in reducing lactic acidosis.[8] The treatment period ranged from 3 weeks to 7 years (mean 3.25 years) with a wide range of both oral and intravenous dosing, in open label study. In addition to drug pharmacokinetics, the investigators evaluated biomarkers (blood and cerebrospinal fluid (CSF) lactate levels at two intervals), a "standard neurological inventory" to determine if any stabilization or improvement occurred over a 1-year period, subjective impression of overall disease course, number of stroke-like events prior to and during the study, and whether there was symptom resolution of severe headaches. Due to the variability of symptoms and limited understanding of the natural histories of multiple diseases, the efficacy of DCA was difficult to determine, but thought to provide some subjects with at least temporary symptomatic benefit. Another consideration is that people with PMDs can progress at different rates, and therefore trials in specific PMDs may need to be longer than they have been historically, which has been typically less than 12 months. The time needed to see a separation in effect between placebo and investigational drug may take several years (48 weeks has been proposed) in patients with a more slowly progressive disease course.

3 | SYSTEMATIC REVIEWS OF PREVIOUS CLINICAL TRIALS

Historically, while there have been many published clinical trials for mitochondrial disease, there have been no proven therapies, at least in part due to inadequate trial design and lack of validated outcome measures. A Cochrane review of treatment for mitochondrial disorders, first published in 2006, sought to review critically whether there is objective evidence to support the use of current treatments (including vitamins and cofactors, dietary modification and exercise), preferably based on randomized controlled trials.[9] In this review, 678 abstracts were reviewed, but only six passed scrutiny and were considered to be formal clinical trials. An updated Cochrane clinical trials review in 2012 identified 1335 abstracts, with 21 meeting initial criteria and 12 meeting strict inclusion/exclusion criteria, including eight new studies since the 2006 review.[1] High risk studies and those with potential for bias were excluded. Included studies were reviewed for number of study participants, treatment, study design, study category, risk bias criteria, and characteristics of study participants. There were very few randomized controlled trials, and the published studies were hard to compare owing to heterogeneous study groups, different dosing of medications, different outcome measures used, and unknown natural history/clinical course of the disorders. Selected trials included a diagnosis of mitochondrial disease based on muscle histochemistry, respiratory chain enzymology, or genetic studies. The primary outcome measures used in these studies included change in muscle strength, change in endurance, or neurological clinical features. Secondary outcome measures included quality of life scales,

BOX 1 Resources for clinical trial design

***Resources available through the United States Food and Drug Administration (FDA)*:**

- Qualification Process for Drug Development Tools Guidance for Industry and FDA Staff; https://www.fda.gov/media/133511/download
- FDA's Patient-Reported Outcome (PRO) Guidance for Industry: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071975.pdf
- DDT Clinical Outcome Assessment Qualification Program webpage: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- FDA's DDT Qualification Program Guidance for Industry: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm230597.pdf
- "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry" (https://www.fda.gov/media/133660/download).
- ICH E10: Choice of Control Group and Related Issues in Clinical Trials (https://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_G ideline.pdf). FDA Draft Guidance for Industry Rare Diseases: Common Issues in Drug Development (https://www.fda.gov/media/119757/download). FDA Draft Guidance for Industry Rare Diseases: Natural History Studies for Drug Development (https://www.fda.gov/media/122425/download). FDA Draft Guidance for Industry: Adjusting for Covariates in Randomized Clinical Trials for Drugs and Biologics with Continuous Outcomes, April 2019 (https://www.fda.gov/media/123801/download).
- FDA COA Staff Website: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm349031.htm#Endpoints
- COA Qualification Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/ucm284077.htm
- COA Compendium Website: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm459231.htm
- PRO Guidance (2009): http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf
- Biomarker Qualification Program: https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugDevelopmentToolsQualificationProgram/BiomarkerQualificationProgram/ucm535383.htm https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-rare-diseases-pediatrics-urologic-and-reproductive-medicine-division-rare-diseases-and
- O'Brien, P. C.: "Procedures for comparing samples with multiple endpoints". Biometrics, Vol. 40, No. 4:1079-1087, 1984.
- Ristl R. et al: "Methods for the analysis of multiple endpoints in small populations: A review". Journal of Biopharmaceutical Statistics, 29:1, January 29, 2018.
- Morris M., Lee W., and Wang Y.: "Evaluation of Testing Methods for Multiple Endpoint in Small Sized Trials: Application to Rare Diseases" . CDER ORISE research project, 2019.

***Resources available through the European Medicines Agency (EMA)*:**

- Orphan designation: https://www.ema.europa.eu/en/human-regulatory/research-development/orphan-designation/applying-designation/orphans-regulatory-procedural-guidance-forms
- Pediatrics: https://www.ema.europa.eu/en/human-regulatory/research-development/paediatric-medicines-research-development
- Compassionate use: https://www.ema.europa.eu/en/human-regulatory/research-development/compassionate-use
- Clinical Trials: https://www.ema.europa.eu/en/human-regulatory/research-development/clinical-trials-human-medicines

biomarkers, lack of improvement in symptoms or adverse events, and survival. The overall conclusion was that there are no proven effective therapies for mitochondrial disease and that a critical review of previous clinical trials revealed weaknesses in study design; future trials testing novel agents should target homogeneous study populations and use clinically relevant primary endpoints.

A further review of new treatments for mitochondrial disease, published by an international group, re-emphasized standards to follow when designing clinical trials in order to develop successful treatments.[10] In a review of 1039 published studies over 47 years, only 35 studies included more than five patients. Jadad criteria were used to judge these studies and found the methodology to be generally suboptimal. Biomarkers without clinical significance were utilized in many of these studies, which were frequently not blinded or randomized. The standards proposed in this article called for: (a) a critical need to develop new biomarkers; (b) the mitochondrial clinical community to set an example by avoiding over-emphasis on recommending unproven therapies; (c) patient advocacy and support groups to educate the patient community about the clinical research process and encourage participation in high quality research; and (d) clinicians, support groups and patients to work in collaboration with industry to develop multicentreer randomized controlled trials.

The experience of previous failed trials for mitochondrial disease, as highlighted by the Cochrane systematic reviews, provide us with an opportunity to correct flaws in clinical trial design going forward, and avoid a situation where efficacy of a treatment is undetected because of poorly designed trials and/or suboptimal outcome measures.

4 | THE IMPORTANCE OF NATURAL HISTORY STUDIES IN DETERMINING CLINICALLY RELEVANT OUTCOME MEASURES

Because mitochondrial diseases are progressive disorders, which lead to significant morbidity and mortality, one of the key outcome measures is overall survival. We continue to have limited understanding of the natural history of PMDs, which not only limits our ability to help a patient understand their own prognosis, but also makes it difficult to ascertain whether an intervention is altering the path of the natural history by either slowing progression or improving symptoms. Through understanding the natural history, we will be able to identify outcome measures that can be utilized in interventional clinical trials as well as improving clinical care.

In common diseases, it is not difficult to generate data through prospective natural history studies and interventional clinical trials in large cohorts. However, in rare and ultrarare disorders it is exceedingly difficult due to a paucity of available subjects, lack of a wide body of natural history data and unknowns regarding optimal outcome measures. Natural history data may already exist in patient registries and databases, yet this information has been collected in different ways, sometimes retrospectively (prospective data collection is preferable), without harmonization of endpoints and may be difficult to compare between different sources. Understanding what data are already available longitudinally is important to guide and design efficient natural history studies that can capture a wide array of patients spanning the phenotypic and genotypic spectrum of PMDs. Natural history data should inform optimal outcome measures in future interventional trials by identifying demographic, genetic, environmental, and additional variables that correlate with disease progression and outcomes. The data obtained from a natural history study, especially a prospective longitudinal study, can inform decisions about inclusion criteria, stage of disease to treat, duration of the trial, frequency of data collection, and other specific endpoints. In regards to the duration of the trial, the treatment should be long enough to impact a clinical outcome measure. Several prospective natural history studies are ongoing. For example, current studies through the North American Mitochondrial Disease Consortium (NAMDC) include the natural history of Alpers-Huttenlocher Syndrome, Mitochondrial NeuroGastroIntestinal Encephalomyopathy (MNGIE), Pyruvate dehydrogenase complex (PDHC) deficiency, and Pearson syndrome (https://www.rarediseasesnetwork.org/cms/namdc/Get-Involved/Studies).

A recent systematic review of published natural history studies analyzed studies reporting at least 20 subjects and the common phenotypes described in at least 30% of those subjects. Thirty-seven natural history studies were identified, representing 29 PMDs, most with multisystem involvement, and 81% had onset before 18 years of age. The publication reviewed organ involvement, biomarkers, and mortality rates, and concluded that natural history studies can help us redefine diagnostic criteria in addition to establishing a historical baseline for clinical trials.[11] Another lesson learned from reviewing available natural history data for PMDs is that in some cases the specific genotype of the disorder can impact the overall natural history for that phenotype. For example, in Leigh syndrome, one of the most common causes is SURF1 deficiency, and while overall the mortality rate for Leigh syndrome is high, *SURF1*-associated Leigh syndrome has a *relatively* better prognosis compared to other aetiologies

of Leigh syndrome, many of which are associated with mortality in early childhood, especially those associated with metabolic decompensation.[12] In addition, the natural history study confirmed relatively homogeneous clinical and biochemical features of SURF1 deficiency. While a more favourable prognosis is helpful for families, this can complicate the results of clinical trials for Leigh syndrome if the different survivals are not accounted for a priori in the overall study design.

The age of onset of symptoms can significantly impact the phenotype, survival and potential response to therapy. For example, in thymidine kinase 2 (TK2) deficiency, a wide spectrum of age of onset and severity of myopathy are seen, which affects the rate of progression of weakness to nonambulatory status, in addition to long-term post-onset survival. A natural history study conducted by 42 investigators across 31 academic medical centres described the clinical course of 92 patients with TK2 deficiency, and identified three categories based on age of onset: infantile, childhood, and late-onset, with a clear difference in survival probability. The infantile-onset group showed worse prognosis compared to the older presentations, demonstrating a need for comparison to age-matched controls in clinical trials going forwards.[13] The natural history study of this ultrarare disorder revealed the need for multicentre involvement and collaboration, especially if a potential therapy is available for clinical trial. Elucidating the natural history of TK2 deficiency has been pivotal in planning the clinical trial "Treatment of TK2 Deficiency with Thymidine and Deoxycytidine" (ClinicalTrials.gov Identifier: NCT03639701).

For PMDs, which have been recognized as having poor genotype-phenotype correlations, the specific phenotype can also impact the natural history and needs to be taken into consideration when planning future clinical trials. For example, single, large-scale mtDNA deletion syndromes are associated with a continuum of clinical phenotypes; some patients have a classical syndromic presentation such as Pearson or Kearns-Sayre syndrome, while others have atypical clinical presentations, and long-term survival varies according to the particular phenotype. Prognosis in a retrospective study of 34 patients in three centres correlated mainly with the clinical phenotype and less to the size and location of the deletions as previously reported.[14] In addition, a review of all symptoms shed light on the renal involvement in 85%, much higher than previously recognized, which informs clinical management as well as being a potential endpoint for clinical trials.

The most common single-gene cause of mitochondrial disease is pathogenic variants in *POLG*, encoding the catalytic subunit of DNA polymerase gamma, which historically has six clinically defined phenotypes with significant clinical overlap and heterogeneity. A multicentre genotype-phenotype review of paediatric patients helped provide a clinically useful comprehensive description of *POLG*-related disorders and expanded the classically described phenotypes.[15] Paediatric onset disease was much different than later onset disease, and this review helped establish that a clinical trial of *POLG*-related disorders should not compare paediatric to adult patients together in one study as the natural history and therefore outcome measures used to follow response to therapies would be too different for easy comparison.

Understanding the overall natural history of PMD helps to identify demographic, genetic, environmental and other variables that correlate with the disease development and outcomes (ie, key prognostic variables) and may help identify which patients may benefit most from a given treatment. All studies of rare disease should try to include as much clinical and biomarker information about each subject as possible before the actual baseline visit, especially in studies where the patients acts as their own control (PAOC). For PAOC studies, it is important to examine the placebo group subjects to determine if they are behaving the same as prior to randomization, and the treatment group to see if they are behaving differently (ie, an inflection point or divergence) compared to prior to randomization. When using natural history data as a control for a study, both the placebo and treatment groups can be compared to matched controls, specifically if there is concordance between the natural history and those randomized to placebo and divergence for those randomized to treatment. Natural history data can be collected prospectively or retrospectively as historical controls; the FDA has a regulatory statement about utilizing historical controls in an adequate and well-controlled study (21 CFR 314.126(b)(2)(v)) "Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products: Guidance for Industry" (https://www.fda.gov/media/133660/download). The FDA Office of New Drugs (OND) has also approved use of external controls in clinical trials to obtain both natural history and PAOC data. A recent example of a new drug approval using retrospective natural history data is the approval of Brineura (cerliponase alfa) for CLN2 Batten disease.[16]

One of the largest prospective natural history studies was recently published, examining a cohort of 151 subjects from 61 families with the common pathogenic m.3243A>G variant in *MT-TL1* over 6 years.[17] Disease progression and quality of life were measured by the NMDAS and SF-36 scores, respectively. Changes in the percentage of mutation load did not correlate with disease severity due to large intrapatient day-to-day

variability, as this group had found previously.[18] In this cohort, the physical quality of life declined with age and the NMDAS score rose yearly, indicating disease progression. Symptoms that determined overall quality of life scoring included hearing loss, speech issues, exercise intolerance, gait difficulties, psychiatric comorbidities and gastrointestinal problems. The authors suggested that a delay in disease progression would be a favourable outcome measure in this cohort based on their prospective study, as has been suggested in previous literature.[10]

Survival is an optimal outcome measure, but can be unpredictable in mitochondrial disease as it is influenced by many factors, as discussed above. Therefore, development of additional outcome measures is essential, and these need to be selected based on the situational context (eg, acute deterioration leading to hospitalization vs chronic progressive course vs clinically stable), age of onset/age of patient currently, and by the specific disorder (taking into consideration both the genotype and the phenotype). The following are examples of best outcome measures selected for a particular preclinical or clinical study.

5 | CLASSIFICATION OF OUTCOME MEASURES

Primary endpoints for use in clinical trials need to provide a primary assessment of the treatment effect, and may consist of multiple components in rare disease trials. A composite endpoint may address specific events (eg, cardiac event, renal event, death) and a multicomponent endpoint is a within-patient combination of multiple components, such as a total strength or movement disorder score for different parts of the body. Multiple primary endpoints may be needed in rare diseases due to the genetic and phenotypic heterogeneity and uncertainty of therapeutic effect; examples include using a 6 minute walk test combined with a PROM. However, challenges are demonstrating statistical significance and low power, owing to small sample size or small treatment effect. In addition, the use of multiple outcomes or a composite score may complicate the interpretation of results, especially if an intervention helps one symptom, but not others in multisystemic disease. One possibility is that the patient could select the most important outcome measure they wish to follow, but then a clinically important benefit may be overlooked. Ideally, outcome measures should be tailored to address the expected benefit of the experimental treatment.

To overcome these challenges, the FDA supports innovative trial designs and analyses in designing and conducting adequate and well-controlled rare disease trials (Box 1 summarizes available FDA resources). Given the unknown disease course, the clinical trial must be able to distinguish therapeutic effects from natural history, placebo effects, or bias.

Developing outcome measures for PMDS has been challenging due to the lack of a single universally applicable outcome measure for use as a primary endpoint. Outcome measures may include patient-focused Clinical Outcome Assessments (COAs), PROMs, clinician-reported outcomes (CROs), observer-reported outcomes (ObsROs), and performance based outcomes (PerfOs). Figure 1 outlines selected outcome measures arranged categorically. Clinical outcomes can demonstrate how one feels (symptom diary), functions (physiological measure such as Cardiopulmonary Exercise Testing [CPET]), or survives. Additional endpoints include biomarkers, which are objective measurements and include imaging studies, muscle biopsy, metabolic studies, and genetic or epigenetic factors. Recently transcriptomic, proteomic, and metabolomic data are emerging as potential novel biomarkers.[19] Table 1 lists a selection of outcome measures utilized in past and ongoing clinical trials.

Ideal outcomes would measure patient-prioritized symptoms with validated PROMs. PROMs should directly relate to how one feels, functions, and/or survives, as required by the FDA, and measures quality of life. Outcomes must be flexible, correlate with the clinical course, and allow for the variable presentation and progression of mitochondrial disease, even within the same genotype and/or phenotype. Ideally, the same outcomes can be used for natural history studies and intervention trials in the same patient cohort. Specific outcomes likely responsive to therapy should be selected for interventional trials, in addition to assessing the full burden of disease of a patient, with an average of 16 symptoms per patient affected by PMD.[20]

6 | CLINICAL RATING SCALES TO MEASURE MITOCHONDRIAL DISEASE

Mitochondrial disease rating scales aim to capture the history, physical examination findings, and quality of life for patients with PMDs. Separate scales have been developed for adults and children and different rating scales have been compared to one another in several studies. For example, the Japanese Mitochondrial Disease Rating Scale (JMDRS)[21] has been compared to the NMDAS and the IPMDS to the NPMDS. Overall disease burden can be measured by these disease rating scales, which are a composite of symptoms and testing results in addition to clinically relevant measurement tools, some with specific

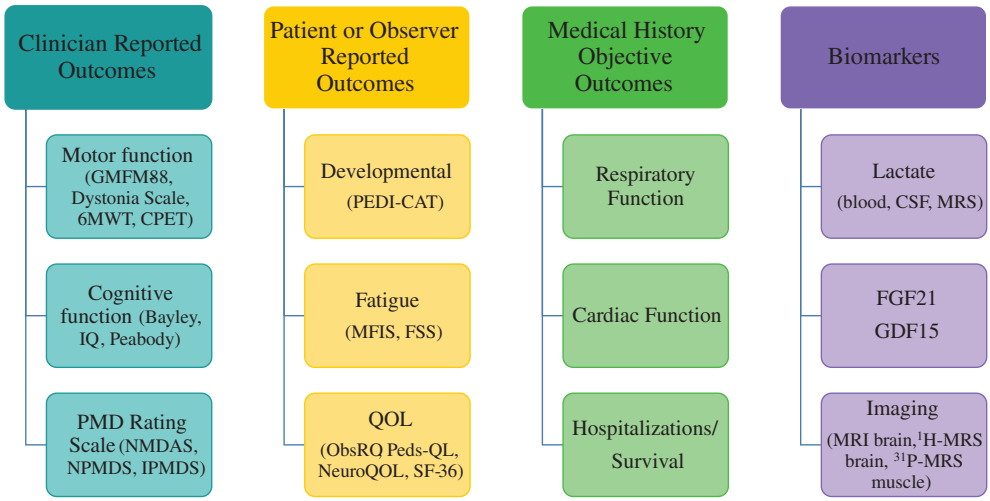

FIGURE 1 Some potential clinical outcome assessments and biomarkers for primary mitochondrial diseases. Clinical outcome assessments may be clinician-reported (including the validated mitochondrial disease rating scales), patient or observer-reported (such as quality of life questionnaires), or objective outcomes derived from the medical history (such as respiratory or cardiac function or number of hospitalized days). Biomarkers constitute another category of outcomes and may be measured in blood, CSF, invasive biopsy samples or by imaging methods

focus on patient prioritized symptoms of fatigue and quality of life. Given the heterogeneity of symptoms among the hundreds of PMDs, a list of best outcome measures or a composite scale, prioritizing the patients' most worrisome symptoms, is needed.[20] An international call to action to improve clinical trial design recommended the use of CDEs, such as those developed in partnership with the NINDS,[3] Human Phenotype Ontology terminology (HPO),[22] and international collaboration.[10]

As mentioned above, regulatory agencies including the FDA have emphasized that new drugs considered for approval must improve how a patient feels, functions, and/or survives. The available rating scales have attempted to incorporate these important outcome measures and are increasingly used in clinical trials. The NMDAS and NPMDS have been utilized in a number of interventional trials, despite being originally designed for prospective long-term natural history studies and not for interventional trials, especially those of short duration. Novel observer-reported outcome tools have emerged for specific trials, such as the Observer-Reported Outcome survey instrument (ObsRo) developed for a randomized controlled trial of DCA in children with PDHC deficiency, which aims to capture in-home daily functioning.[23] Another example of a novel outcome measure is the Primary Mitochondrial Myopathy Symptom Assessment (PMMSA), a patient-reported outcome questionnaire capturing the most common and relevant patient symptoms, developed by Stealth Biotherapeutics (with FDA guidance) for a randomized placebo controlled trial of elamipretide for primary mitochondrial myopathy.[24]

The IPMDS was designed for natural history studies, by adapting the NPMDS using a Delphi-based process with key stakeholders (selected international clinician collaborators, patients and carers), and then piloted among five international mitochondrial medicine centres for feasibility, reliability and validity. The main focus of the IPMDS is to establish validated outcome measures for paediatric clinical trials and to define the minimal clinically important difference for future trials.[5] The IPMDS is serving as the primary outcome measure in a current clinical trial (Table 1). A subsequent international workshop discussed outcome measures and consensus recommendations for clinical trials involving children with mitochondrial disease for both myopathy and encephalopathy symptoms, for either natural history study or for validation of outcomes, and stressed the need for sensitive and valid endpoints to measure efficacy of potential treatments.[25] A similar workshop was held to develop outcome measures for adults and children with primary mitochondrial myopathies.[4]

7 | BIOMARKERS

Ideal biomarkers are diagnostic of mitochondrial disease (high sensitivity and specificity), account for the heterogeneous nature of these diseases, evaluate disease severity and progression, measure treatment efficacy, and ideally have an automated high-throughput assay for

TABLE 1 Classification of outcome measures and use in clinical trials

Type of outcome measure	Examples proposed for mitochondrial disease	Validated for mitochondrial disease	Primary outcome measure in mitochondrial disease clinical trials[a]	Secondary outcome measure in mitochondrial disease clinical trials[a]
Mitochondrial Disease Rating Scales	Newcastle Mitochondrial Disease Adult Scale (NMDAS)	Yes		KHENERGY (KH176) study in PMD (NCT02909400) Bezafibrate in PMM (NCT02398201)
	Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)	Yes	EPI-743 for Leigh syndrome (NCT01721733) EPI-743 for Leigh syndrome: long term (NCT02352896) Cysteamine (RP103) (NCT02023866)	EPI-743 for Leigh syndrome (NCT01370447)
	International Paediatric Mitochondrial Disease Scale (IPMDS)	Yes	CD34+ cells enriched with MNV-BLD for Pearson syndrome (NCT03384420)	
Patient reported outcome measures	Observer-reported outcome (ObsRO)	Yes (PDH)	Dichloroacetate (NCT02616484)	
	Primary Mitochondrial Myopathy Symptom Assessment (PMMSA) Total Fatigue Score	Not yet published		Elamipretide for PMM (MMPOWER-2) (NCT02805790)
	Fatigue Severity Scale (FSS)	No		Idebenone for MELAS (NCT00887562)
	Fatigue Impact Scale score	No		Bezafibrate in PMM (NCT02398201)
	Quality of Life in Neurological Disorders (Neuro-QOL)	No		Elamipretide for PMM (MMPOWER-2) (NCT02805790)
	Pediatric Quality of Life Scale (PedsQL)	No	Phase III Trial of Coenzyme Q_{10} in Mitochondrial Disease (NCT00432744)	
	RAND-SF36 score	No		KHENERGY (KH176) study in PMD (NCT02909400) Gene Therapy for LHON (rAAV2-ND4) (GS010) (NCT03293524)
	Patient Global Assessment (PGA) Score	No		Elamipretide for PMM (MMPOWER-2) (NCT02805790)
Developmental scales	Bayley Scales of Infant Development-III Score	No		EPI-743 for Leigh syndrome (NCT02352896)
	Wechsler Scale of Intelligence and Movement Assessment Battery Score for Children	No		EPI-743 for Leigh syndrome (NCT02352896)
Neurological/ Performance based Scales	Barry-Albright Dystonia Scale Score	No		EPI-743 for Leigh syndrome (NCT01721733)

(Continues)

TABLE 1 (Continued)

Type of outcome measure	Examples proposed for mitochondrial disease	Validated for mitochondrial disease	Primary outcome measure in mitochondrial disease clinical trials[a]	Secondary outcome measure in mitochondrial disease clinical trials[a]
				EPI-743 for Leigh syndrome: long term (NCT02352896)
				Cysteamine (RP103) (NCT02023866)
	Gross Motor Function Measure (McMaster GMFM-88)	No	Phase III Trial of Coenzyme Q_{10} in Mitochondrial Disease (NCT00432744)	EPI-743 for Leigh syndrome (NCT01721733)
			ABI-009 (Nab-sirolimus) in Patients With Genetically-confirmed Leigh or Leigh-like Syndrome (NCT03747328)	Cysteamine (RP103) (NCT02023866)
	6 minute walk test (6MWT)	No	Elamipretide for PMM (MMPOWER) (NCT02367014)	KHENERGY (KH176) study in PMD (NCT0290940)
			Elamipretide for PMM (MMPOWER-2) (NCT02805790)	Omaveloxolone (RTA408) for PMM (MOTOR) (NCT02255422)
				Cysteamine (RP103) (NCT02023866)
	Cardiopulmonary exercise test (CPET), change in peak workload)	No	Omaveloxolone (RTA408) for PMM (MOTOR) (NCT02255422)	Elamipretide for PMM (MMPOWER) (NCT02367014)
Physiological measures	Near infrared spectroscopy (NIRS)	No	Diagnostic of CPEO and paediatric PMD	
			PMD as control group in SMA study (NCT02895789)	
	Muscle Electron Transport Chain Activities	Yes	Bezafibrate in PMM (NCT02398201)	
Biomarkers	FGF21	No		KHENERGY (KH176) study in PMD (NCT02909400)
				Bezafibrate in PMM (NCT02398201)
				TEETPIM (MNGIE) (NCT03866954)
	GDF15	No		KHENERGY (KH176) study in PMD (NCT02909400)
				TEETPIM (MNGIE) (NCT03866954)
	Lactate	No	Sodium phenylbutyrate (NCT03734263)	Idebenone for MELAS (NCT00887562)
				Elamipretide for PMM (MMPOWER) (NCT02367014)

TABLE 1 (Continued)

Type of outcome measure	Examples proposed for mitochondrial disease	Validated for mitochondrial disease	Primary outcome measure in mitochondrial disease clinical trials[a]	Secondary outcome measure in mitochondrial disease clinical trials[a]
				Cysteamine (RP103) (NCT02023866)
	Thymidine and deoxyuridine	Yes (MNGIE)	TEETPIM in MNGIE (NCT03866954)	
Imaging	MRI	No		TEETPIM in MNGIE (NCT03866954)
	^{31}P-MRS (muscle)	No	Nicotinamide riboside (NCT03432871)	Bezafibrate in PMM (NCT02398201)
	MRS (brain)	No	Idebenone for MELAS (NCT00887562)	CD34+ cells enriched with MNV-BLD for Pearson syndrome (NCT03384420)
Specific affected organ measure	Best Corrected Visual Acuity	No	Idebenone for LHON (NCT02774005)	Elamipretide for LHON (NCT02693119)
			Gene Therapy for LHON (rAAV2-ND4)(GS010) (NCT03293524)	
Composite measure	Global Assessment of Treatment Efficacy (GATE)	No	Dichloroacetate for Congenital Lactic Acidosis (NCT00004490)	

[a]Some examples are provided, not an exhaustive list.

Abbreviations: CPEO, chronic progressive external ophthalmoplegia; LHON, Leber hereditary optic neuropathy; MELAS, mitochondrial encephalopathy, lactic acidosis and stroke-like episodes; MNGIE, mitochondrial neurogastrointestinal encephalomyopathy; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; PDH, pyruvate dehydrogenase deficiency; PMD, primary mitochondrial disease; PMM, primary mitochondrial myopathy; SMA, spinal muscular atrophy.

maximum usefulness. Biomarkers should correlate with disease progression and therapeutic effect and be able to predict the disease course and treatment response, and therefore guide patient selection and dose selection in drug development programs. Current potential biomarkers include: metabolites, serum growth factors, exercise physiology testing, and imaging studies.[19] The source of the biomarker and potential effect from treatment need to be considered; for example, biomarkers can be measured in blood, urine, CSF or an invasive tissue biopsy sample.

Biomarkers continue to be explored and compared to those already in use, with growth differentiation factor 15 (GDF15) one of the latest to be evaluated for diagnostic and therapeutic sensitivity and specificity.[26] Given the complexity of establishing a diagnosis of PMD vs another paediatric neurogenetic condition, screening tests such as near-infrared spectroscopy with vascular occlusion (NIRS) have been proposed to help discriminate those with a neurogenetic disease from healthy controls.[27]

Neuroimaging biomarkers have been underutilized for clinical research purposes, perhaps because the natural history of these disorders via neuroimaging is also largely unknown. Since some neuroradiological patterns are sufficiently specific for diagnostic utility, imaging provides a potential primary endpoint for mitochondrial disorders that involve the central nervous system (CNS).[28] Using another CNS disease as an example, a meta-analysis of randomized trials demonstrated that the effect of treatment on preventing relapses in multiple sclerosis can be predicted by MRI lesions.[29] This meta-analysis also demonstrated that MRI can provide primary endpoints in clinical trials of potential treatments, especially those with a well-known mechanism of action expected to change brain structure or chemistry, or to trial drugs approved for another disease. Neuroimaging biomarkers are important to consider as outcome measures for clinical trials, especially for individuals with progressive CNS symptoms. Both structural as well as biochemical features may serve as endpoints, and may include MRI brain, ^{1}H-magnetic resonance spectroscopy (MRS) of brain, and ^{31}P-MRS of muscle (Table 1). ^{1}H-MRS can measure brain lactate noninvasively, and has been reported to correlate with clinical response to

treatment with L-arginine in MELAS, suggesting its usefulness as a biomarker.[30] While neuroimaging has been described in small case series as well as larger cohorts, the natural history of mitochondrial disease has infrequently been studied through neuroimaging. A recent large series of paediatric Leigh syndrome explored correlations between genotype, clinical phenotype, and unique neuroimaging findings.[31] Once there is a deeper understanding of genotype-phenotype correlations via neuroimaging, imaging studies may serve as outcome measures in clinical trials to show either improvement or lack of expected progression.

Currently there are no biomarkers that are predictive of clinical outcome in PMDs and therefore, no biomarkers can be used as primary outcome measures in clinical trials. Instead, biomarkers need to be assessed in natural history studies and as secondary outcome measures in clinical trials in order to determine whether they may be surrogate endpoints in the future.

8 | SELECTION OF OPTIMAL OUTCOME MEASURES

Collectively, we are making strides toward developing robust outcome measures for clinical trials that are specific and sensitive to PMDs, especially those that can measure improvements through patient-reported rating scales. All patients affected by mitochondrial disease should be enrolled in a patient registry (ideally entered by clinicians to ensure accuracy) and their data captured in a prospective natural history study. Sites participating in clinical trials should have the ability to review the medical history retrospectively to determine the individual subjects' natural history and disease course, and engage in data integration efforts to allow for better visualization of outcomes and produce data driven improvements in care.

No single outcome measure will fit all PMDs, demonstrating the need for multiple or composite scores, using the simplest trial design possible. Biomarkers can be used if they are reasonably likely to predict clinical benefit. While invasive studies should be avoided, there may be a need to use them in initial small studies to demonstrate large effect size. For example, lumbar puncture may be needed to measure levels of a drug crossing the blood brain barrier, or muscle biopsy to assess changes in heteroplasmy of mtDNA variants. CSF studies may also be indicated to monitor toxicity and pharmacokinetics in case of breech of blood brain barrier causing higher levels in the CNS. Selecting optimal outcome measures in the context of designing an ideal clinical trial needs to be based on preclinical studies, genotype, available natural history studies, and management strategies based on known pathomechanisms of disease. A plethora of emerging therapeutic trials are exploring pharmacological and genetic therapies for PMDs.[32,33]

9 | REGULATORY AGENCY INVOLVEMENT

Regulatory agencies, including the FDA, have become actively engaged in clinical trial design and therapeutic development for rare diseases, facilitated by the 1983 US Orphan Drug Act, which has also been adopted by Japan and the European Union. A series of key meetings have brought together clinicians, scientists, patients, caregivers, industry participants, and PAGs. The FDA has prioritized tackling several barriers to clinical trial design, including obtaining consensus on what outcomes might be appropriate to include, without overly burdening families and treating teams, and creating the infrastructure to support international multicentre trials. Several of these key meetings at the FDA were coordinated/sponsored by PAGs and include: Translational Research in Primary Mitochondrial Diseases (2012),[34] "Critical Path Innovation Meeting Regarding Drug Development for Mitochondrial Diseases" (October 2015) (https://ods.od.nih.gov/attachments/CriticalPathInnovationMeetingSummary.pdf), "Mitochondrial Disease Externally-Led Patient-Focused Drug Development Meeting" (March 2019) (https://www.fda.gov/media/131584/download), and "Developing Therapies for Primary Mitochondrial Diseases: Bridging the Gaps" (September 2019) (https://www.fda.gov/news-events/fda-meetings-conferences-and-workshops/developing-therapies-primary-mitochondrial-diseases-bridging-gaps-09062019-09062019). The regulatory environment for novel therapeutic developments in mitochondrial disease has improved greatly as a result of these meetings and open communication. Resources have been developed by regulatory agencies under the FDA, including the Center for Drug Evaluation and Research (CDER), to help with many aspects of selecting outcome measures and clinical trial design, including "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims".

The FDA has generated specific advice for rare orphan disorders as above, given the typical framework for clinical trials, which are notably difficult in rare disease populations. Traditionally, the four Clinical Research Phases for each step of clinical trials are each designed for a different purpose. Phase 1 is typically small-scale, may include healthy volunteers or people with the disorder, and is designed specifically for safety

and to determine safe dosing range of a new drug. Phase 2 enrols more subjects and can last longer, with goals of establishing efficacy and to monitor for side effects. Phase 3 is then even larger, enrolling more patients over a longer period of time to confirm efficacy as well as adverse events. Finally, Phase 4 includes post-marketing studies after FDA-approval, to collect any additional information including risks and benefits. More information is available at: https://www.fda.gov/patients/drug-development-process/step-3-clinical-research#Clinical_Research_Phase_Studies

To date, only one therapy has been approved by the European Medicines Agency (EMA) for a PMD, namely Idebenone for LHON in exceptional circumstances (2015), with continued controversy over its use. Therefore, there is an important unmet need for approved therapies for these debilitating and often fatal disorders. To achieve this goal, it is critical to work closely with regulatory agencies, in partnership with patients, families, caregivers, clinicians, PAGs, and industry to educate all stakeholders about regulatory requirements to obtain approval for novel therapies. Clinicians must actively participate in therapeutic development,conducting natural history studies and developing outcome measures, which are critical foundations for clinical trials. "Orphan drug" and "rare paediatric disease" designations provide additional incentives that can facilitate therapeutic development. Treatment with unapproved therapeutics may be accomplished by an Investigational New Drug (IND) application to the FDA, which provides an opportunity to provide experimental treatment to a patient, but does not mean using lower standards to measure efficacy. Well controlled, rigorous clinical trials of high quality are still required to establish the efficacy of potential therapies and to obtain regulatory agency approvals for their commercial use. The Division of Rare Diseases and Medical Genetics (DRDMG) regulates Investigational New Drug Applications (INDs), New Drug Applications (NDAs), and Biologics Licensing Applications (BLAs) for drugs and biologics intended for the prevention and treatment of Rare Diseases and Medical Genetics. Please see Box 1 for a list of FDA resources.

10 | VALIDATION OF OUTCOME MEASURES

The heterogeneous and rare nature of PMDs, together with the lack of validated outcome measures, impedes the ability to conduct robust clinical trials.[32] As new clinical trials are designed and implemented for mitochondrial disease, we can continue to make critical improvements in terms of utilization of outcome measures. Biomarkers need to be robust enough to measure progression, improvement or stability in natural history studies, and clinical improvement in therapeutic interventions. Clinical measurements need to be validated, and although a curated list of CDEs has been compiled by the NINDS, none of the CDEs for mitochondrial disease have been validated specifically for this patient cohort, with the exception of NMDAS, NPMDS and IPMDS. Consensus workshops have been convened, engaging all stakeholders in the process and using Delphi criteria to derive expert agreement. Developing the most optimal outcome measures for mitochondrial disease will require global harmonization, prospective longitudinal data on patient cohorts including robust natural history studies, patient registries, and partnerships between patients, their families and caregivers, clinicians, scientists, industry, regulatory agencies, and PAGs.

Validation of biomarkers, with early engagement of regulatory agencies, is essential to ensure that the outcome measure is acceptable for use. Validation of a biomarker includes that of the actual assay measurement in addition to showing that the biomarker is a valid surrogate endpoint for a clinical effect. Rating scales have been developed, and may be utilized to show clinical relevance when correlating with biomarkers to demonstrate a change from baseline. Biomarkers need to be objective, with low likelihood of responding to placebo or bias. Measurements should be free of bias, not relying on patient effort, with low placebo effect. Additional factors include accounting for the location and seasonality of the clinical trial, especially when an outcome measure such as distance of daily walking is used, which is likely to be reduced in extreme weather conditions.

11 | CONCLUSIONS AND PRACTICALITIES

Selecting outcome measures for PMD has been challenging due to lack of validated, clinically relevant biomarkers, the heterogeneous nature of genotypes and phenotypes of mitochondrial disease, the need to individualize endpoints based on patient-prioritized symptoms, the lack of natural history studies, and the lack of consensus among all the potential stakeholders. Understanding the longitudinal natural history of PMD through prospective studies is required to understand the full clinical phenotype, morbidity and mortality, and essential in selecting outcome measures to inform the design of interventional clinical trials.

Owing to the multisystemic and heterogeneous nature of these disorders, patients must be able to prioritize and select which outcomes they wish to see improve

in a clinical trial. A collection of selective outcome measures has been proposed, which would allow specific, individual endpoints for prospective natural history studies and randomized controlled interventional trials. Objective measures that are clinically meaningful are critical for proving efficacy, in order to obtain regulatory agency drug approval.

In order for interventional clinical trials to determine whether a novel therapy for PMD is efficacious, the following steps are necessary: (a) identify biomarkers and other assays for screening panels of molecules in preclinical models of PMDS, (b) establish patient registries and central repositories of human samples, (c) initiate natural history studies using outcome measures that can also be utilized in therapeutic intervention trials, (d) develop alternative clinical trial designs for ultrarare, small populations while striving for randomized controlled trials if possible, (e) create and maintain industry partnerships to support and sustain clinical trials for rare conditions, and (f) regulatory agencies to provide opportunities and platforms for international research collaborations and information sharing.

In the end, we as a community have to agree on the best candidates and work together to validate them in our disease population. We also need to agree *how* we will validate the proposed outcome measures, for example through Delphi criteria to agree upon outcome measures by expert consensus. We need longitudinal data in individual patients to determine utility of specific outcome measures. The situational context must be taken into account, considering the need for the correct outcome measure for the clinical setting (age, specific disorder) and specific question (acute needs, stop progression vs reversing symptoms). Trials need to be run efficiently, in a reasonable time frame, yet for sufficient time to show a change in outcomes, whether improvement, lack of progression or lack of deterioration; therefore it is imperative that we understand the natural history of these disorders and find outcomes that will be predictable. Finally, there is a need for global harmonization and international collaboration.

The entire mitochondrial medicine community, including patients, families, caregivers, clinicians, scientists, industry, PAGs, and regulatory agencies, have been openly communicating in a collaborative fashion to find proven, effective therapies for primary mitochondrial disease. Meetings such as the Wellcome Trust Mitochondrial Medicine conference in December 2019 provide a forum to have active discussion and debate about selection of the outcome measures, to be used in natural history studies and clinical trials, which will provide objective measurements which are clinically meaningful and capture patient-prioritized, predominant symptoms.

ACKNOWLEDGMENTS

We thank Dr Akira Ohtake for helpful discussions in the preparation of this manuscript. Amy Goldstein is funded by the CHOP Mitochondrial Medicine Frontier Program. Shamima Rahman receives grant funding from the National Institute of Health Research Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Hospital Children's Charity, and the Lily Foundation.

ORCID

Amy Goldstein https://orcid.org/0000-0001-6593-5905
Shamima Rahman https://orcid.org/0000-0003-2088-730X

REFERENCES

1. Pfeffer G, Majamaa K, Turnbull DM, Thorburn D, Chinnery PF. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev*. 2012;4:CD004426.
2. Rahman J, Rahman S. Mitochondrial medicine in the omics era. *Lancet*. 2018;391(10139):2560-2574.
3. Karaa A, Rahman S, Lombès A, et al. Common data elements for clinical research in mitochondrial disease: a National Institute for Neurological Disorders and Stroke project. *J Inherit Metab Dis*. 2017;40(3):403-414.
4. Mancuso M, McFarland R, Klopstock T, Hirano M, consortium on Trial Readiness in Mitochondrial Myopathies. International workshop: outcome measures and clinical trial readiness in primary mitochondrial myopathies in children and adults. Consensus recommendations. 16-18 November 2016, Rome, Italy. *Neuromuscul Disord*. 2017;27(12):1126-1137.
5. Koene S, Hendriks JCM, Dirks I, et al. International Paediatric Mitochondrial Disease Scale. *J Inherit Metab Dis*. 2016;39(5):705-712.
6. Schaefer AM, Phoenix C, Elson JL, McFarland R, Chinnery PF, Turnbull DM. Mitochondrial disease in adults: a scale to monitor progression and treatment. *Neurology*. 2006;66:1932-1934.
7. Phoenix C, Schaefer AM, Elson JL, et al. A scale to monitor progression and treatment of mitochondrial disease in children. *Neuromuscul Disord*. 2006;16(12):814-820.
8. Barshop BA, Naviaux RK, McGowan KA, et al. Chronic treatment of mitochondrial disease patients with dichloroacetate. *Mol Genet Metab*. 2004;83(1–2):138-149.
9. Chinnery P, Majamaa K, Turnbull D, Thorburn D. Treatment for mitochondrial disorders. *Cochrane Database Syst Rev*. 2006;(1):CD004426.
10. Pfeffer G, Horvath R, Klopstock T, et al. New treatments for mitochondrial disease-no time to drop our standards. *Nat Rev Neurol*. 2013;9(8):474-481.
11. Keshavan N, Rahman S. Natural history of mitochondrial disorders: a systematic review. *Essays Biochem*. 2018;62(3):423-442.
12. Wedatilake Y, Brown RM, McFarland R, et al. SURF1 deficiency: a multi-centre natural history study. *Orphanet J Rare Dis*. 2013;8:96.

13. Garone C, Taylor RW, Nascimento A, et al. Retrospective natural history of thymidine kinase 2 deficiency. *J Med Genet*. 2018; 55(8):515-521.
14. Broomfield A, Sweeney MG, Woodward CE, et al. Paediatric single mitochondrial DNA deletion disorders: an overlapping spectrum of disease. *J Inherit Metab Dis*. 2015;38(3): 445-457.
15. Hikmat O, Tzoulis C, Chong WK, et al. The clinical spectrum and natural history of early-onset diseases due to DNA polymerase gamma mutations. *Genet Med*. 2017;19(11):1217-1225.
16. Schulz A, Ajayi T, Specchio N, et al. Study of intraventricular cerliponase alfa for CLN2 disease. *N Engl J Med*. 2018;378(20): 1898-1907.
17. de Laat P, Rodenburg RR, Roeleveld N, Koene S, Smeitink JA, Janssen MC. Six-year prospective follow-up study in 151 carriers of the mitochondrial DNA 3243 a>G variant. *J Med Genet*. 2020. https://doi.org/10.1136/jmedgenet-2019-106800.
18. de Laat P, Rodenburg RR, Roeleveld N, Koene S, Smeitink JA, Janssen MC. Six-year prospective follow-up study in 151 carriers of the mitochondrial DNA 3243 A>G variant. *J Med Genet*. 2020 May 21:jmedgenet-2019-106800. https://doi.org/10.1136/jmedgenet-2019-106800. Epub ahead of print. PMID: 32439810.
19. Steele HE, Horvath R, Lyon JJ, Chinnery PF. Monitoring clinical progression with mitochondrial disease biomarkers. *Brain*. 2017;140(10):2530-2540.
20. Zolkipli-Cunningham Z, Xiao R, Stoddart A, et al. Mitochondrial disease patient motivations and barriers to participate in clinical trials. *PLoS One*. 2018;13(5):e0197513.
21. Yatsuga S, Povalko N, Nishioka J, et al. MELAS: a nationwide prospective cohort study of 96 patients in Japan. *Biochim Biophys Acta*. 2012;1820:619-624.
22. Köhler S, Carmody L, Vasilevsky N, et al. Expansion of the human phenotype ontology (HPO) knowledge base and resources. *Nucleic Acids Res*. 2019;47(D1):D1018-D1027.
23. Stacpoole PW, Shuster J, Thompson JLPS, et al. Development of a novel observer reported outcome tool as the primary efficacy outcome measure for a rare disease randomized controlled trial. *Mitochondrion*. 2018;42:59-63.
24. Karaa A, Haas R, Goldstein A, Vockley J, Cohen BH. A randomized crossover trial of elamipretide in adults with primary mitochondrial myopathy. *J Cachexia Sarcopenia Muscle*. 2020; 11:909-918. https://doi.org/10.1002/jcsm.12559.
25. Koene S, van Bon L, Bertini E, et al. Outcome measures for children with mitochondrial disease: consensus recommendations for future studies from a Delphi-based international workshop. *J Inherit Metab Dis*. 2018;41(6):1267-1273.
26. Yatsuga S, Fujita Y, Ishii A, et al. Growth differentiation factor 15 as a useful biomarker for mitochondrial disorders. *Ann Neurol*. 2015;78(5):814-823.
27. Raman S, Chentouf L, DeVile C, Peters MJ, Rahman S. Near infrared spectroscopy with a vascular occlusion test as a biomarker in children with mitochondrial and other neuro-genetic disorders. *PLoS One*. 2018;13(7):e0199756.
28. de Beaurepaire I, Grévent D, Rio M, et al. High predictive value of brain MRI imaging in primary mitochondrial respiratory chain deficiency. *J Med Genet*. 2018;55(6):378-383.
29. Sormani MP, Bruzzi P. MRI lesions as a surrogate for relapses in multiple sclerosis: a meta-analysis of randomised trials. *Lancet Neurol*. 2013;12(7):669-676.
30. Hovsepian DA, Galati A, Chong RA, et al. MELAS: monitoring treatment with magnetic resonance spectroscopy. *Acta Neurol Scand*. 2019;139(1):82-85.
31. Alves CAPF, Teixeira SR, Martin-Saavedra JS, Guimarães Gonçalves F, Lo Russo F, Muraresku C, McCormick EM, Falk MJ, Zolkipli-Cunningham Z, Ganetzky R, Vossough A, Goldstein A, Zuccoli G. Pediatric Leigh Syndrome: Neuroimaging Features and Genetic Correlations. *Ann Neurol*. 2020 May 22. https://doi.org/10.1002/ana.25789. Epub ahead of print. PMID: 32445240.
32. Pitceathly RDS, Keshavan N, Rahman J, Rahman S. Moving towards clinical trials for mitochondrial diseases. *J Inherit Metab Dis*. 2020 Jul 3. https://doi.org/10.1002/jimd.12281. Epub ahead of print. PMID: 32618366.
33. Russell OM, Gorman GS, Lightowlers RN, Turnbull DM. Mitochondrial diseases: hope for the future. *Cell*. 2020;181(1):168-188.
34. Moraes CT, Anderson V, Mohan C. Workshop participants. Translational research in primary mitochondrial diseases: challenges and opportunities. *Mitochondrion*. 2013;13(6):945-952.

How to cite this article: Goldstein A, Rahman S. Seeking impact: Global perspectives on outcome measure selection for translational and clinical research for primary mitochondrial disorders. *J Inherit Metab Dis*. 2020;1–15. https://doi.org/10.1002/jimd.12320