Overview

Mitochondrial Disease Working Group: Neurological Assessments

The National Institute of Neurological Disorders and Stroke (NINDS) Mitochondrial Disorders (Mito) Neurological Assessments Common Data Elements (CDEs) Working Group (WG) consisted of individuals from North America and Europe with expertise in both pediatric and adult neurology in mitochondrial disorders. The WG carefully reviewed the relevant literature and neurological tools that have been successfully utilized in mitochondrial disorders and other progressive neurological disorders. In addition many of the members in this team of experts were able to provide insight into the ease of utility of certain numbers of these tools, based upon their prior experience with them tools in mitochondrial clinical trials. Because mitochondrial disorders affect all parts of the nervous system, the WG needed to find verified scales that could quantitate disorders of cognitive development and decline, motor function, disorders of coordination and movement, nerve function and muscle function. Most of these scales are widely available within most medical centers and the WG gathered those scales that are in use, as well as scales that have been developed that may not be in common use. Once the initial scales were identified, a PubMed search for additional scales was performed. Each of the tools was carefully evaluated for its method of administration, qualifications required of the examiner, time to administer, target group (i.e., age reference range), utility and feasibility burden to the patient, reliability evidence (i.e., specificity and sensitivity to detect changes), relevance to the patient, and strengths and weaknesses. The chosen tests were then classified as Core, Supplemental (including whether they were Highly Recommended) or Exploratory.

The spectrum of clinical manifestations of mitochondrial diseases is great, and spans across organ systems. Every component of the nervous system (brain, spinal cord, peripheral nerves and muscle) may be affected as well. The nomenclature used to describe mitochondrial disorders is constantly developing but there is no specific correlation between mitochondrial phenotypes and genotypes. For example, Leigh syndrome (the phenotype) can be caused by dozens of mutations involving mtDNA and many nuclear genes. Mutations in *POLG* cause 6 general phenotypes as well as disorders that appear like Charcot-Marie-Tooth disease and Leigh syndrome. Even within a family sharing the same genotype, the phenotypic presentation may differ from subject to subject due to epigenetic and environmental factors. In the case of mtDNA-inherited disorders, the phenotype may differ depending upon the ratio of mutant to wild-type mtDNA (heteroplasmy) in a given cell or tissue, the tissue-specific threshold for disease expression as well as disease modifying mutations in the nuclear DNA. Many of the scales are age-specific, so as patients cross age-lines, the choice of scale will change. Therefore the available instruments must span the entire spectrum of neurological and developmental

disabilities. The scales within a specific neurological disability vary in universal acceptance, sensitivity, complexity and time-for-completion.

The WG recommends that the choice of scales for a specific patient or study should include those that best measure function for the identified disability, and possibly scales that would measure function for expected disabilities that could be predicted by the patient's phenotype or genotype. Consideration of patient age, the predicted ability of a patient or group of patients to participate in the scale, time to complete the scale and cost also are critical factors to be considered. For example, the pediatric and adult Newcastle Mitochondrial Disease Scales evaluates a broad range of effects on different organ systems for a composite evaluation. For these CDE recommendations, we focused on identifying scales with specific detail and high sensitivity for evaluating different aspects of the neurological system.

The WG focused on providing a battery of neurological tests that would capture small changes in multiple neurological systems including scales of cognitive function, development in children, motor weakness (muscle and nerve), and scales for coordination and movement disorders (e.g., ataxia, dystonia). One challenge that is not necessarily unique to mitochondrial disorders, is that within a given genotype (e.g., MELAS due to mtDNA mutation), there may be great variation between individuals with the same mutation, depending upon the percentage heteroplasmy of mutant to wild-type mitochondrial DNA in a given tissue, the number of tissues involved and the age of presentation of dysfunction in a given tissue (threshold effect) as well as within the course of a given individual which may make predictions of a 'typical' trajectory highly challenging. Furthermore, in the evaluation of the effect of a given therapy on the cognitive function in children, all evaluations must take into consideration, the age-specific normal developmental profile of the child. In such cases, comparisons of the clinical phenotype in cross-over studies (on-off-on) would allow comparisons between different time periods of development to ascertain whether there is a statistically significant difference in rate of acquisition of milestones 'on' and 'off' a given therapy. Providing tools with great sensitivity for a given neurological system and tools for each system should allow small changes to be documented.

The WG contends that the great majority of the measurement scales chosen, though highly likely to provide sensitive measures of neurological function in mitochondrial disorders, have not yet been formally validated in this clinical population. Moving forward, the validation of these scales in mitochondrial treatment trials will therefore need to be prioritized in the future.

Summary Recommendations

READ ME: This is a recommendations summary document of the instruments - sorted alphabetically. Details of the recommendations follow this spreadsheet in the form of information documents (e.g., Notices of Copyright).

Instrument / Scale Name *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *(e.g., Core, Supplemental, Exploratory)*	Domain	Subdomain
Barry Albright Dystonia Scale (BADS)	Supplemental–Highly Recommended for measuring dystonia	Outcomes and End Points	Physical/Neurological Examinations
Bayley Scale of Infant and Toddler Development III (BSID-III)	Supplemental	Outcomes and End Points	Neuropsychological Testing
Burke-Fahn-Marsden Movement Scale	Supplemental	Outcomes and End Points	Physical/Neurological Examinations
Gross Motor Function Measures (GMFM-88, GMFM-66)	Exploratory	Outcomes and End Points	Performance Measures

Instrument / Scale Name *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *(e.g., Core, Supplemental, Exploratory)*	Domain	Subdomain
International Cooperative Ataxia Rating Scale (ICARS)	Supplemental	Outcomes and End Points	Ataxia and Performance Measures
International Pediatric Mitochondrial Disease Score (IPMDS)	Exploratory	Outcomes and End Points	Physical/Neurological Examinations
Modified Hammersmith Functional Motor Scale (MHFMS-SMA, MHFMS)	Supplemental–Highly Recommended as a primary outcome measure in mitochondrial disease treatment trials of young non-ambulatory children with SMA.	Outcomes and End Points	Performance Measures
Motor Function Measures	Exploratory	Outcomes and End Points	Performance Measures

Instrument / Scale Name *Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs*	Classification *(e.g., Core, Supplemental, Exploratory)*	Domain	Subdomain
Peabody Development Motor Scale II	Supplemental–Highly Recommended for measuring deterioration and short-term improvement in pediatric mitochondrial disease patients.	Outcomes and End Points	Performance Measures
Scale for the Assessment and Rating of Ataxia (SARA)	Supplemental–Highly Recommended for measuring ataxia	Outcomes and End Points	Ataxia and Performance Measures
The Newcastle Mitochondrial Disease Adult Scale	Supplemental	Outcomes and End Points	Physical/Neurological Examinations
The Newcastle Pediatric Mitochondrial Disease Scale	Supplemental	Outcomes and End Points	Physical/Neurological Examinations
Unified Dystonia Rating Scale	Supplemental	Outcomes and End Points	Physical/Neurological Examinations