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Journal of Inherited Metabolic Disease

Common Data Elements for Clinical Research in Mitochondrial Disease: a National Institute for Neurological Disorders and Stroke project --Manuscript Draft--

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Funding Information:	National Institute of Neurological Disorders and Stroke (HHSN271201200034C)	Ms. Muniza K. Sheikh
Abstract:	<p>ABSTRACT</p> <p>OBJECTIVES: The Common Data Elements (CDE) project was developed by the National Institute of Neurological Disorders and Stroke (NINDS) to provide clinical researchers with tools to improve data quality and allow for harmonization of data collected in different research studies. CDEs have been created for several neurological diseases; the aim of this project was to develop CDEs specifically curated for mitochondrial disease (Mito) to enhance clinical research.</p> <p>METHODS: Nine working groups (WGs), composed of international mitochondrial disease experts, provided recommendations for Mito clinical research. They initially reviewed existing NINDS CDEs and instruments, and developed new data elements or instruments when needed. Recommendations were organized, internally reviewed by the Mito WGs, and posted online for external public comment for a period of eight weeks. The final version was again reviewed by all WGs and the NINDS CDE team prior to posting for public use.</p> <p>RESULTS: The NINDS Mito CDEs and supporting documents are publicly available on the NINDS CDE website (https://commondataelements.ninds.nih.gov/), organized into domain categories such as Participant/Subject Characteristics, Assessments, and Examinations.</p> <p>CONCLUSION: We developed a comprehensive set of CDE recommendations, data definitions, case report forms (CRFs), and guidelines for use in Mito clinical research. The widespread use of CDEs is intended to enhance Mito clinical research endeavors, including natural history studies, clinical trial design, and data sharing. Ongoing international collaboration will facilitate regular review, updates and online publication of Mito CDEs, and support improved consistency of data collection and reporting.</p>	

Dear Dr. Peters, Managing Editor for JIMD:

Thank you and the other reviewers very much for reviewing our submitted manuscript: "Common Data Elements for Clinical Research in Mitochondrial Disease: a National Institute for Neurological Disorders and Stroke project" to the Journal of Inherited Metabolic Disease.

We reviewed all of the comments from your advisors on our manuscript. Based on this advice, we made additions as requested, including presenting the data in a clear, structured format (addition of Table #1) as well as a flowchart (addition of Figure #1). We hope it is now considered for publication and thank you for acknowledging that this is a very important paper for our community. We have also included the names of the participating members of the working groups, listed after the main authors of this paper.

Details about Conflict of Interest, Informed Consent and Animal Rights on page 3 of the manuscript have been added.

COMMENTS FOR THE AUTHOR:

Reviewer #1: I am happy with the revision. Thank you Reviewer #1.

Reviewer #2: no comments. Thank you Reviewer #2.

Reviewer #3: Thank you Reviewer #3 for your comments, which have been extremely helpful. We have added a flow chart, as well as a table with main results. Summary statements regarding CDEs have been published in the literature in similar formats, including Epilepsy CDEs in *Epilepsia* (2011), Traumatic Brain injury to *Journal of Neurotrauma* (2012), spinal cord injury to *Spinal Cord* (2016), and Friedreich ataxia to *Movement Disorder* (2013). We hope that the CDEs for mitochondrial disease will be published in JIMD in this format.

Respectfully submitted,

Amy Goldstein MD

Corresponding Author

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JIMD Original Article

Title: Common Data Elements for Clinical Research in Mitochondrial Disease: a National Institute for Neurological Disorders and Stroke project.

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46 **Synopsis:** Overview of NINDS Common Data Elements development for mitochondrial
47 diseases.
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Compliance with Ethics Guidelines

Conflict of Interest:

John Shoffner has received research funds from the Department of Defense and owns stock in Medical Neurogenetics, LLC.

David Dimmock is a consultant to Audentes Therapeutics, Biomarin, Illumina and Complete Genomics and involved in clinical trials with Genzyme/Sanofi, Biomarin, Shire, Cytonet.

Marni Falk has been a consultant to Mitokyne; received research funds from Cardero Therapeutics, Mitobridge, Raptor Pharmaceuticals, RiboNova, Stealth BioTherapeutics, and Vitaflo International; was a former scientific advisory board member for Perlstein Laboratory, Inc., and is involved in clinical trials with REATA pharmaceuticals.

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4 Amel Karaa, Shamima Rahman, Anne Lombès, Patrick Yu-Wai-Man, Muniza K. Sheikh, Sherita
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6 Alai-Hansen, Bruce H. Cohen, Lisa Emrick, Shana McCormack, David Mirsky, Tony Moore,
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8 Sumit Parikh, Tanja Taivassalo, Mark Tarnopolsky, Ingrid Tein, Joanne C. Odenkirchen, and
9
10 Amy Goldstein have no conflict of interest.

11
12 This article does not contain any studies with human or animal subjects performed by the any of
13
14 the authors.

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16
17 Details of the contributions of individual authors:

18
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20 Sherita Alai-Hansen provided NINDS CDE content and worked on WG summaries.

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22 Bruce Cohen worked on Neurological Assessments summary.

23
24 David Dimmock worked on the Genetics summary.

25
26 Lisa Emrick worked on the Cognitive/Behavioral Outcomes summary.

27
28 Marni Falk worked on the Genetics summary and overall revision of the final manuscript.

29
30 Amy Goldstein worked on the Discussion, Conclusion and edited overall manuscript and
31
32 revisions.

33
34 Amel Karaa worked on the PRO/QoL summary, Results section and edited overall manuscript
35
36 and revisions.

37
38 Anne Lombès edited the Background section; Genetics and Biomarkers summary sections,
39
40 Discussion section and overall manuscript.

41
42 Shana McCormack worked on Endocrinology/Diabetes summary.

43
44 David Mirsky worked on Imaging summary.

45
46 Tony Moore worked on Vision summary and edited overall paper.

47
48 Joanne Odenkirchen gave final approval; provided NINDS CDE content.

49
50 Sumit Parikh worked on Discussion and Conclusion sections.

51
52 Shamima Rahman worked on Background section, Genetics summary, Overview and edited
53
54 overall manuscript and revisions.

55
56 Muniza Sheikh worked on overall paper; provided NINDS CDE content.

57
58 John Shoffner worked on Background section and reviewed entire paper.

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60 Tanja Taivassalo worked on Exercise Physiology summary.

61
62 Mark Tarnopolsky worked on Exercise Physiology summary.

63
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66 Patrick Yu Wai Man edited overall draft.

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ABSTRACT

OBJECTIVES: The Common Data Elements (CDE) project was developed by the National Institute of Neurological Disorders and Stroke (NINDS) to provide clinical researchers with tools to improve data quality and allow for harmonization of data collected in different research studies. CDEs have been created for several neurological diseases; the aim of this project was to develop CDEs specifically curated for mitochondrial disease (Mito) to enhance clinical research.

METHODS: Nine working groups (WGs), composed of international mitochondrial disease experts, provided recommendations for Mito clinical research. They initially reviewed existing NINDS CDEs and instruments, and developed new data elements or instruments when needed. Recommendations were organized, internally reviewed by the Mito WGs, and posted online for external public comment for a period of eight weeks. The final version was again reviewed by all WGs and the NINDS CDE team prior to posting for public use.

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4 **RESULTS:** The NINDS Mito CDEs and supporting documents are publicly available on the
5 NINDS CDE website (<https://commondataelements.ninds.nih.gov/>), organized into domain
6 categories such as Participant/Subject Characteristics, Assessments, and Examinations.
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10 **CONCLUSION:** We developed a comprehensive set of CDE recommendations, data
11 definitions, case report forms (CRFs), and guidelines for use in Mito clinical research. The
12 widespread use of CDEs is intended to enhance Mito clinical research endeavors, including
13 natural history studies, clinical trial design, and data sharing. Ongoing international collaboration
14 will facilitate regular review, updates and online publication of Mito CDEs, and support
15 improved consistency of data collection and reporting.
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22 **Keywords:** clinical outcome measures; clinical research; common data elements; computerized
23 report forms; mitochondrial disease
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39 **Introduction**

40 The Common Data Element (CDE) project began in 2005 as part of an initiative by the National
41 Institute of Neurological Disorders and Stroke (NINDS) to assist NINDS-funded investigators in
42 the collection of neuroscientific clinical trial research data in a standardized and consistent
43 fashion (Grinnon et al 2012). The CDEs are content standards that can be applied to various data
44 collection models and are intended to be dynamic and evolve over time, as indicated by research
45 advances. The CDE project is not a database – rather it is a collection of metadata and data
46 standards, used to facilitate sharing and combination of data across studies as a means of data
47 comparison and analysis. Its goal is to develop common definitions for clinical research data as
48 well as the creation of standardized Case Report Forms (CRFs) and instruments. The goals of the
49 NINDS CDE Project are to: 1) *Disseminate standards* for data collection from participants
50 enrolled in neurological disease studies; 2) *Create easily accessible tools* for investigators to
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4 collect study data. These tools should be especially helpful to new investigators and others
5 working with limited budgets; 3) *Encourage focused and simplified data collection* to reduce
6 burden on investigators and practice-based clinicians to facilitate their participation in clinical
7 research; 4) *Improve data quality* while controlling cost by providing uniform data descriptions
8 and tools across NINDS-funded clinical studies (Grinnon et al 2012). As the CDEs were being
9 developed, the number of clinical trials for patients with mitochondrial disease also rose,
10 highlighting the value and urgency of such tools to be developed.
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18 To date, the NINDS CDE database has developed metadata with data standards and instruments
19 for 18 neurological diseases. In the case of mitochondrial disease, CDE validation can be
20 complex due to the broad array of mechanisms causing mitochondrial diseases and dysfunction.
21 This paper reviews the process by which the Mito WGs, an international group of mitochondrial
22 disease experts, developed CDEs to be used in the field of mitochondrial disease research. The
23 draft Mito CDEs were reviewed by the external mitochondrial disease research community prior
24 to finalization and posted to the NINDS CDE website in 2015. The WG participant rosters may
25 be found on the NINDS CDE web page (<https://commondataelements.ninds.nih.gov/>).
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35 **Background**

36 **Brief description of Mitochondrial Diseases**

37 Mitochondrial diseases (also known as disorders of oxidative phosphorylation (OXPHOS),
38 mitochondrial respiratory chain diseases, mitochondrial cytopathies, and mitochondriopathies)
39 are a group of disorders caused by genetic defects that directly or indirectly affect the OXPHOS
40 system, the major energy generating pathway in cells (Chinnery 2014; DiMauro and Schon
41 2003). The prevalence of mitochondrial disease is difficult to establish for many reasons,
42 including their clinical and genetic heterogeneity, challenges in establishing a precise genetic
43 diagnosis, and complexities in patient ascertainment and referral. The prevalence of all
44 pathogenic mutations in both nuclear DNA (nDNA) and mitochondrial DNA (mtDNA) is at least
45 1:4,300 (Gorman et al 2015). Approximately 15% (DiMauro and Schon 2003) of mitochondrial
46 disorders are caused by inherited germline mutations in the mtDNA. Mitochondrial disorders can
47 also be caused by mutations in over 250 nDNA genes (Gorman et al 2016) and dysfunction can
48 be acquired due to adverse environmental effects of drugs and infections (Niyazov 2016). Those
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4 disorders resulting from inherited nDNA or mtDNA gene mutations that have an effect on the
5 structure or function of the OXPHOS system are termed “primary mitochondrial diseases”
6 (Parikh et al 2015). Some mitochondrial disorders affect a single organ, but many involve
7 multiple organ systems and can present with a bewildering array of multisystem phenotypes,
8 including neurologic symptoms and myopathies, visual and hearing loss, as well as cardiac,
9 endocrine, gastrointestinal, hepatic and/or renal dysfunction (Chinnery 2014). Some well-
10 characterized multisystem clinical syndromes have now been recognized as being mitochondrial
11 diseases. Primary inherited mitochondrial diseases encompass hundreds of individual genetic
12 disorders that are heterogeneous and frequently multisystemic, yet share common disease
13 mechanisms and overlapping clinical phenotypes. One challenge, not necessarily unique to
14 mitochondrial disorders, is that there may be great variation between individuals with the same
15 mutation. With respect to mtDNA mutations (e.g., Mitochondrial encephalomyopathy, lactic
16 acidosis and stroke-like episodes (MELAS) mutation), variation may depend on the percentage
17 heteroplasmy (mutation load) in any given tissue and the number of tissues harboring the
18 mutation, adding to the wide phenotypic spectrum and variable disease severity. A
19 comprehensive overview can be found on the North American Mitochondrial Disease
20 Consortium (NAMDC) website ([https://www.rarediseasesnetwork.org/cms/namdc/Learn-
22 More/Disorder-Definitions](https://www.rarediseasesnetwork.org/cms/namdc/Learn-
21 More/Disorder-Definitions)).

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37 Marked variability remains in the diagnostic approaches, treatment, and management of
38 mitochondrial diseases (Parikh et al 2015). Conducting large-scale clinical trials for patients
39 with mitochondrial diseases is difficult, given their extreme clinical variability, biochemical and
40 genetic heterogeneity, and the rarity of each etiology or subtype. Despite all of these constraints,
41 several clinical trials for mitochondrial diseases are underway, none of which are using any
42 mitochondrial disease-specific curated or validated outcome measure for this specific patient
43 group.
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51 **MATERIALS AND METHODS**

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53 Developing CDEs for mitochondrial disorders was challenging due to the heterogeneity of
54 potential disease symptoms that may develop. CDEs reviewed and selected for this project
55 focused on features within and outside the domain of clinical neurology, spanning almost all
56 organ systems. Selected CDEs would benefit the majority of individuals with mitochondrial
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4 disorders and would be linked to appropriate measures to objectively assess disease severity and
5 progression. Therefore, the Mitochondrial Disease CDE WG was divided into nine subgroups to
6 focus on identifying and defining data elements in the following domains: Biomarkers;
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8 Cognitive/ Behavioral/ Psychological; Endocrinology/ Diabetes/ Gastrointestinal/ Nutrition;
9
10 Exercise Physiology; Genetics; Imaging; Neurological Assessments; Patient Reported Outcomes/
11
12 Quality of Life; and Vision. Bi-weekly teleconferences for each WG for a period of six months
13
14 were held until project completion. In order to remain consistent with the overall CDE format,
15
16 the WG recommendations were classified into one of four categories:
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19 Core: A data element for recording essential information applicable to any mitochondrial disease
20
21 study including therapeutic areas and study designs. Consistent with all NINDS disease-specific
22
23 CDE sets, the Core Mito CDEs are a small subset of all available CDEs that are the most specific
24
25 and valuable for all Mito studies.

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27 Supplemental – Highly Recommended: A data element which is recommended for use whenever
28
29 applicable, based on certain conditions or clinical study designs. In most cases, these have been
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31 used and validated with strong psychometrics for use in mitochondrial disease, and are
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33 considered essential for clinical research studies by experts in the field.

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35 Supplemental: A data element which has some evidence of validity and is commonly collected in
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37 clinical studies in mitochondrial disease. Use depends upon the study design, protocol or type of
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39 research involved.

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41 Exploratory: A data element that could be emerging or that requires further validation in target
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43 populations, but may fill current gaps in the CDEs and/or substitute for an existing CDE with
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45 additional evidence.

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47 Pre-existing individual CDEs selected for other clinically similar disease phenotypes were
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49 included and other appropriate instruments were added when available. All were critically
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51 evaluated for appropriateness to mitochondrial disorders even if historical reliability and validity
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53 was accepted for other diseases. Statistical analysis was not performed at this time, as this is not
54
55 applicable for the development and initial description of the Mito CDEs. In the future, statistical
56
57 analyses will help determine if these CDEs can be specifically validated for mitochondrial
58
59 diseases. The draft Mito CDEs were posted on the NINDS CDE website for public review from
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61 November 20, 2014 to January 16, 2015. The final Version 1.0 Mito CDEs were posted on
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63 February 25, 2015, following the incorporation of comments received from public review from
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4 the mitochondrial clinical research community. The process describing the formation of the
5 CDEs is available on the CDE website at
6 <https://www.commondataelements.ninds.nih.gov/CDEStandard.aspx>. Figure 1 illustrates the
7
8 mitochondrial CDE development process.
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11 12 13 **RESULTS**

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15 The nine WGs reviewed a total of 153 CRFs and instruments (56 for Cognitive/ Behavioral/
16 Psychological outcomes, 17 for Neurological Assessments, 28 for Patient Reported
17 Outcomes/QoL, 41 for Exercise Physiology, and 11 for Endocrinology/ Diabetes/ GI/ Nutrition).
18 This resulted in a library of 120 CRF and instruments recommendations divided into 4 domains
19 including: 1) Participant History and Family History, 2) Participant Characteristics, 3)
20 Assessment and Examinations, and 4) Outcomes and Endpoints. Recommendations from the
21 Mito CDE project posted on the NINDS CDE website contain a summary of each instrument, its
22 recommended use, and comparative strengths and weaknesses. Although the CDEs have been
23 developed for the unique purpose of advancing mitochondrial medicine clinical research, several
24 of the CRFs reviewed include ones used on a clinical basis for patient care purposes. The WGs
25 did not develop the CDEs with the intention of utilizing these in clinical care, and further
26 consideration about care guidelines (i.e., diagnostic algorithm, nutrition/exercise guidelines, etc)
27 would exceed the scope of this paper.
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31 Core elements for the mitochondrial disorders included one general core element common to all
32 other disorders reviewed for CDEs, namely the demographic patient/participant characteristics.
33 The WGs did not find any element that was strongly representative of mitochondrial disorders
34 and thus no additional core elements specifically required for all mitochondrial disorders were
35 selected. Of the remaining recommended categories, 17% of the elements assessed were
36 categorized as Supplemental-Highly Recommended, 75% as Supplemental, and 8% as
37 Exploratory. The Highlight Summary Document is available in table format on the CDE
38 webpage
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41 https://www.commondataelements.ninds.nih.gov/Doc/MITO/Mitochondrial_Disease_CDE_Highlight_Summary.pdf. There was no Core elements recommended due to lack of validation in
42
43 mitochondrial disease cohorts. The Supplemental – Highly Recommended instruments (for
44
45 specific disease conditions or types of study) included: Anthropometrics-Vital Signs, Apathy
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4 Evaluation Scale, Automated Self-administered 24-hour Dietary Recall (ASA 24), Barry
5 Albright Dystonia Scale (BADs), Behavior Rating Inventory of Executive Function (BRIEF),
6 Behavior Rating Inventory of Executive Function-Preschool Version (BRIEF-P), Conners 3,
7
8 Diabetes-Related Medical History, Echocardiogram, Genetic Testing Short Form, Genetic
9
10 Testing Clinical Diagnostics, Laboratory Tests and Non-Imaging Diagnostics (Diabetes),
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12 Maximal Exercise Test, Modified Hammersmith Functional Motor Scale (MHFMS-SMA,
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14 MHFMS), Peabody Development Motor Scale II, Pediatric Quality of Life Inventory (PEDSQL),
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16 Pulmonary Function, Scale for the Assessment and Rating of Ataxia (SARA), Sub-Maximal
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18 Exercise Test, Test of Variable Attention (TOVA), The Borg Scale of Perceived Exertion,
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20 Vineland Adaptive Behavior Scales, 2nd Ed., World Health Organization Quality of Life
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22 Assessment (WHOQOL). Table 1 summarizes the CDEs based on Working Group category and
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24 level of recommended use (Core, Supplemental – Highly Recommended, Supplemental,
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26 Exploratory).
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30 **Navigating the NINDS Mito CDE website**

31 The Mito CDEs are available at the NINDS CDE Mito Website. A brief summary of the project,
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33 along with documents to assist in starting a study, are presented on the Data Standards tab of the
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35 Mito disease page. The Mito CDE recommendations are grouped by Domains and Sub-Domains
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37 below this introductory information. CRFs and their accompanying CDEs (listed as “CDE
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39 Details” on the website) can be downloaded as needed. Users are also able to learn more about
40
41 the CDE project by navigating to the Learn menu at the top right of the page, where tutorials, a
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43 project overview and definitions are available
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45 (https://www.commondataelements.ninds.nih.gov/MITO.aspx#tab=Data_Standards).
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48 **WG Results Summary**

49 **Biomarkers**

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51 The Mito Biomarkers WG found that none of the reported biomarkers are consistently altered,
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53 nor have been used to assess mitochondrial disease in every study. For example, elevated lactic
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55 acid, commonly considered to be a biomarker of mitochondrial disease, is not consistently
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57 elevated in blood across all mitochondrial diseases, especially when only a single organ is
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59 involved (e.g., the eye in Leber’s hereditary optic neuropathy). Conversely, lactate levels in bold
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4 are frequently elevated in many pediatric mitochondrial diseases where the oxidative
5 phosphorylation deficiency is often both severe and widespread. The WG also considered some
6 parameters that are absolutely essential, but in only one disease. For example, thymidine and
7 deoxyuridine levels along with thymidine phosphorylase enzymology are only useful in
8 Mitochondrial neurogastrointestinal encephalopathy (MNGIE) syndrome, a very rare genetic
9 disease caused by thymidine phosphorylase deficiency. The WG found the task of defining an
10 extensive list of “specific” parameters difficult because of the high, and steadily increasing,
11 number of different causes of mitochondrial diseases as well as a growing list of new biomarkers
12 (e.g. FGF-21, GDF-15) (Suomalainen 2013; Yatsuga et al 2015). As a result, all biomarkers
13 recommended by the WG are classified as Supplemental and were fully defined in a guidelines
14 document to assist researchers in their studies.
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26 **Cognitive/Behavioral/Psychological Outcomes**

27 A broad range of clinical phenotypes is observed in both children and adults with mitochondrial
28 disorders, with symptoms that may progressively develop and wax and wane in severity over the
29 course of the entire lifespan. As a result, the instruments recommended vary according to age
30 and the specific type of disorder. Furthermore, the scoring and use of the instruments may vary
31 based on the clinical history. Modification of the scoring system for some of the instruments may
32 be recommended to achieve higher sensitivity of symptom assessment (i.e., use of raw scores vs.
33 standard scores). The WG also suggested considering the intended use of the instrument in any
34 given study, such as a natural history to study changes over time in a clinical trial. The WG
35 recommends selecting individual components of the larger tools to study in clinical trials. An
36 example of this would be the use of memory or executive functioning subsets of the NIH
37 Toolbox instead of using the whole instrument. While choosing instrument recommendations,
38 the group did not encounter any tools unique to individuals with mitochondrial disorders and
39 therefore there are no validated tools available for this population of patients.
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53 **Endocrinology/Diabetes/Gastrointestinal/Nutrition**

54 Diabetes mellitus, abnormal growth, gastrointestinal (GI) problems and nutrition-related
55 concerns are important features of mitochondrial disease. This WG developed instruments
56 focused on diabetes mellitus, anthropometric measurements, GI symptoms and nutritional
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4 assessment, including diet and use of dietary supplements. The WG acknowledged that the
5 diversity of current approaches to treatment of mitochondrial disease in general and particular
6 subtypes in particular, including nutrition and supplements, leads to difficulties in standardized
7 documentation to enable ready evaluation of their potential impact. Given their importance to the
8 overall health of affected individuals, careful assessment and study of endocrine and GI-related
9 health conditions was recommended. The Office of Dietary Supplements at NIH organized a
10 community meeting and subsequent working group dedicated to further investigation of the
11 impact of nutritional interventions in primary mitochondrial diseases (Camp et al 2016).
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22 **Exercise Physiology**

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24 The Exercise Physiology WG focused on the areas of exercise intolerance, endurance, and
25 exercise recommendations. Exercise intolerance is one of the most prevalent symptoms of
26 mitochondrial disease, especially in adults with mitochondrial myopathy. The WG did not
27 address clinical recommendations on exercise as a treatment, but rather focused on
28 recommended instruments to measure fatigue, exercise intolerance, and ability to exercise. The
29 Borg Scale of Perceived Exertion, The Newcastle Pediatric Mitochondrial Disease Scale
30 (NPMDS), echocardiogram, electrocardiogram, maximum and submaximum exercise testing,
31 and Pulmonary Function Testing were recommended as Supplemental– Highly Recommended
32 tests. The 6 Minute Walk Test is widely used in clinical trials as a reflection of overall exercise
33 capacity, and was considered to be a Supplemental test for mitochondrial disease evaluation as
34 determined by evidence available to the Exercise Physiology WG.
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45 **Genetics**

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47 Inclusion in clinical trials increasingly requires the establishment of a known pathogenic
48 mutation in a mitochondrial disease-associated gene using standard criteria. Thus, establishing
49 an accurate molecular diagnosis is important for clinical trial participation. The Genetics WG
50 made a clear distinction between genetic testing for clinical purposes (i.e., in a CLIA-certified
51 diagnostic laboratory) versus on a research basis. Genetic testing should be performed in an
52 experienced laboratory with clearly defined analytic methodology. Depending on clinical
53 presentation and exact methodology used, such analyses may include next generation sequencing
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4 of relevant nuclear genes in the form of gene panels and/or the exome, genome-wide SNP
5 microarray analysis to detect nuclear chromosomal copy number alterations, and mitochondrial
6 genome next generation sequencing to detect low level heteroplasmy for mitochondrial point
7 mutations or small copy number alterations, real-time quantitative PCR to detect large mtDNA
8 deletions and duplications, and/or quantitative PCR to measure mtDNA genome content in
9 relevant tissues. The specific DNA variant identified should be documented relative to a
10 reference sequence and using established ACMG guidelines (Richards et al 2015). If available,
11 previous publications reporting pathogenicity of the variant should be cited (MacArthur et al
12 2014). Often this is performed through literature or database searches, using online tools such as
13 MITOMAP (Lott et al 2013) and ClinVar (Harrison et al 2016). If the variant is novel, and
14 prediction programs such as PolyPhen and SIFT are used, the specific versions and tools should
15 be cited because, occasionally, multiple programs may issue conflicting predictions. Segregation
16 studies within the family should be performed to confirm expected inheritance patterns.
17 Biochemical studies should be performed in subjects' blood, urine, cells, and/or tissue to confirm
18 mitochondrial dysfunction type and degree, as needed or appropriate. In certain instances, in
19 vitro cellular and/or animal model experiments might be needed to further evaluate the
20 pathogenicity of novel variants of unknown significance.
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37 **Imaging**

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39 The Imaging WG aimed to establish a data form that would be all-inclusive, ideally serving as a
40 reference guide for what imaging data points might be useful to collect when researching
41 mitochondrial disorders. While recommending many existing Imaging CDEs, the WG
42 highlighted several variables in the Mito Imaging CRF that are characteristic of, although not
43 exclusive, to mitochondrial disorders. The most notable elements are the involvement of deep
44 gray nuclei, white matter tracts, and myelination pattern.
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51 **Neurological Assessments**

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53 The spectrum of clinical manifestations of mitochondrial diseases spans every component of the
54 nervous system (i.e., brain, spinal cord, peripheral nerves, autonomic nervous system, and
55 muscle). The scales to capture a specific neurological disability vary in regards to their universal
56 acceptance, sensitivity, complexity, and time-for-completion. As the CDEs are a project of the
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4 NINDS, and several other neurological diseases already had completed CDEs available for
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6 review, the Mito CDE WGs had the benefit of reviewing CDEs for clinically overlapping
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8 disorders including: Friedreich ataxia, epilepsy, amyotrophic lateral sclerosis, multiple sclerosis,
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10 Duchenne muscular dystrophy, stroke, spinal cord injury, and Huntington and Parkinson
11
12 diseases. As many of the progressive neurological disorders have overlapping clinical symptoms,
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14 as well as secondary mitochondrial dysfunction contributing to their pathophysiology, many of
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16 the CRFs from these other neurological diseases were potentially applicable as Mito CDEs.
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19 The WG recommended that the choice of scales for a specific patient or study should include
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21 those that best measure function for the identified disability, and possibly scales that would
22
23 measure function from the pre-symptomatic state for expected disabilities that could be predicted
24
25 to develop by the patient's clinical diagnosis or genotype. The WG aimed to provide a battery of
26
27 neurological tests that would capture small changes in cognitive function, development, motor
28
29 weakness (muscle and nerve), coordination and movement disorders (e.g., ataxia, dystonia).
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31 **Patient Reported Outcomes/Quality of Life (PRO/QoL)**

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33 The PRO/QoL WG found no QoL CDEs to be essential and thus no instruments were classified
34
35 as Core. The recommended instruments had no differential application to subtypes of
36
37 mitochondrial disease. However, the scales are often dependent on subject age for
38
39 administration, and some are better suited for subjects with higher cognitive skills. Among
40
41 several available QoL scales, the WG determined two that should be Supplemental – Highly
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43 Recommended: the World Health Organization Quality of Life Assessment (WHOQOL) and the
44
45 Pediatric Quality of Life Inventory (PEDSQL). Due to overall limitations, lack of a validated
46
47 instrument, and the heterogeneity of mitochondrial diseases, it was difficult to define universal
48
49 CDEs for QoL within mitochondrial diseases.
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51 **Vision**

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53 The Vision WG recommendations were made to be applicable to all types of mitochondrial
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55 disease. Adequate training of physicians and technicians performing various ophthalmological
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57 tests with ongoing quality control were deemed essential. Several platforms were identified that
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59 are available for visual field perimetry and optical coherence tomography (OCT) imaging. The
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4 chosen tests will largely depend on the preference of the investigators and the specific facilities
5 available in their respective study centers. The WG emphasized the need to ensure that the same
6 platform and acquisition protocol are used across all the centers involved in a given study to
7 allow for direct comparison and/or grouping of data at study conclusion. For visual
8 electrophysiology, it was deemed imperative that testing be performed to incorporate the ISCEV
9 (International Society for Clinical Electrophysiology of Vision) standards.
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16 **DISCUSSION**

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18 The development of CDEs to facilitate mitochondrial disease research is timely, in view of the
19 improvements and implementation of widespread genetic testing that has led to genetically-
20 defined mitochondrial diseases and large patient cohorts. In addition, there has been a recent
21 increase in candidate therapies proposed for these currently incurable disorders, with promising
22 results in several preclinical studies in cell and animal models (Rahman 2015; Nightingale et al
23 2016). The CDE project is an international collaborative effort involving the many key
24 stakeholders in mitochondrial medicine, including clinicians, translational and basic researchers,
25 industry partners, patient advocacy groups, and the NIH. The breadth of our collaborators is a
26 testament to the interest and need for these shared research tools to move the mitochondrial
27 medicine field forward.
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39 The WGs reviewed a total of 153 CRFs and instruments for the possible inclusion in the Mito
40 CDEs. Interestingly, and perhaps not surprisingly, the WGs did not find a single Core data
41 element; demonstrating once again the challenges for clinical research in mitochondrial diseases.
42 The CDEs were categorized based on their prior use in both mitochondrial diseases or similar
43 disorders and whether they were scientifically robust and clinically significant. Together, these
44 CDEs cover almost the entire disease spectrum of these complex multi-systemic disorders, and
45 have been developed with the intention of providing a publicly available resource to facilitate the
46 design of protocols for any clinical study relating to mitochondrial disease. Some caveats should
47 be noted. The Mito CDEs are suggested guidelines rather than definitive requirements for future
48 study protocols and are not intended for use in clinical patient care. Clinical study design should
49 take into account the specific diseases (considering both genotype and phenotype) under study,
50 age group of affected patients and nature of the intervention, and incorporate the most relevant
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4 CDEs, in addition to any other outcome measures that the researchers consider appropriate. The
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6 Mito CDE recommendations are based on current knowledge of a rapidly expanding and
7
8 changing group of heterogeneous disorders, and it is anticipated that, while having a stable set of
9
10 essential elements, these will be dynamic and need to be updated as the field advances and
11
12 specific instruments become validated for use in mitochondrial disease. The NINDS has
13
14 developed oversight committees that will review feedback from the community and adjust the
15
16 CDEs periodically, as needed.
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19 The availability of a global set of CDEs addressing many of the multi-systemic features should
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21 help serve as a starting place to harmonize data collection and ultimately enable the combination
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23 and comparison of outcomes of clinical studies in mitochondrial diseases. Given the diversity
24
25 and spectrum of clinical manifestations seen in these disorders, selection of outcome measures
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27 for clinical research presents a unique challenge. These difficulties are further compounded by
28
29 the rarity of each individual genetic entity of this group of disorders, challenges to robust study
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31 design, and need for substantive funding. It is thus imperative that patient support groups,
32
33 together with mitochondrial disease clinician networks and research consortia, partner with
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35 industry and the FDA to validate these measures, recently discussed at a Critical Path Innovation
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37 Meeting (CPIM)
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39 (<https://ods.od.nih.gov/attachments/CriticalPathInnovationMeetingSummary.pdf>). The
40
41 international collaboration on this CDE project has continued to be fruitful, with projects
42
43 ongoing to harmonize global patient registries, to validate patient-centered outcome measures,
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45 and to create mitochondrial disease specific outcome measures inspired by the CDEs reviewed in
46
47 this project.
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Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Demographics	General Core (e.g., Gender, Birth Date, Race)			
General Health History		Diabetes-Related Medical History	Dietary Supplements, Reproductive and Hormonal History	
Physical Examinations		Automated Self-Administered 24-hour Dietary Recall (ASA 24)	Mitochondrial and Gastrointestinal Diseases Assessment	
Imaging Diagnostics			Brain Magnetic Resonance Imaging (MRI), Brain Perfusion Magnetic Resonance Imaging, Cardiac Magnetic Resonance Imaging (MRI), Imaging – Mitochondrial Disease, Electrocardiogram (ECG), Imaging Guidelines and Definition	Phosphorus Magnetic Resonance Spectroscopy (31PMRS), Two Dimensional Speckle Tracking Echocardiography Imaging
Laboratory Tests/Biomarkers		Laboratory Tests and Non-Imaging Diagnostics (Diabetes)	Biomarkers Guidelines Mitochondrial Disease, Biomarkers in Mitochondrial Disease	

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Genetics		Genetic Testing Short Form, Genetics Testing Clinical Diagnostics	Genetic Testing Short Form, Genetics Testing Clinical Diagnostics	
Non-Imaging Diagnostics		Echocardiogram	Holter Examination	
Vision			Vision Mitochondria Disease OCT Guidelines, Vision Mitochondrial Disease Test Guidelines, Vision Mitochondrial Disease Visual Fields Guidelines	
Vital Signs and Other Body Measures			Vital Signs	
Academic Achievement			American National Adult Reading Test (AmNART)	
Adaptive		Vineland Adaptive Behavior Scales	Adaptive Behavior Assessment Scale (ABAS-II), Delis Kaplan Executive Functioning System (DKEFS), 2nd Ed. (Vineland-II)	

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Attention		Conners III	Delis Kaplan Executive Function System (DKEFS), National Institutes of Health (NIH) Toolbox, Test of Variable Attention (TOVA)	
Ataxia and Performance Measures		Scale for the Assessment and Rating of Ataxia	International Cooperative Ataxia Rating Scale (ICARS)	
Cognitive			Automated Neuropsychological Assessment Metrics (ANAM), Axon Sports Computerized Cognitive Assessment, Brief Test of Adult Cognition by Telephone (BTACTION), Cambridge Cognitive Assessment Revised (CAMCOG-R)	
Dementia			Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE), Montreal Cognitive Assessment (MoCA)	

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Emotional/Behavioral		Apathy Evaluation Scale	ALS Depression Inventory (ADI-12), Apathy Scale (AS), Autism Diagnostic Interview (ADI), Autism Diagnostic Observation Schedule (ADOS), Beck Anxiety Inventory (BAI), Brief Infant Toddler Social Emotional Assessment (BITSEA), Brief Psychiatric Rating Scale (BPRS), Cambridge Behavioral Inventory – Revised, Center for Epidemiological Studies – Depression Scale (CES-D), Child Behavior Checklist (CBCL), Child Depression Inventory (CDI), Children Depression Inventory – 2 (CDI-2), Columbia Suicide Severity Rating Scale (CSSRS), Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Generalized Anxiety Disorder (GAD-7), Hamilton Anxiety Rating Scale (HAM-A), Hamilton Depression Rating Scale (HDRS), Irritability Scale, Modified Overt Aggression Scale (MOAS), Montgomery-Åsberg Depression Scale (MADRS), Mood Disorder Questionnaire (MDQ), Problem Behaviours Assessment HD – Short Version (PBA-S), Social Responsiveness Scale (SRS)	
Executive Functioning		Adaptive Behavior Assessment System-II		

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
		(ABAS-II) *, Behavior Rating Inventory of Executive Function (BRIEF) *, Behavior Rating Inventory of Executive Function – Preschool Version (BRIEF-P) *		
Motor/Physical Function		Borg Rating of Perceived Exertion (RPE) Scale, Modified Hammersmith Functional Motor Scale for Children with Spinal Muscular Atrophy (MHFMS-SMA/MHFMS-Extend), Peabody Developmental Motor Scale II (PDMS-2), Barry Albright Dystonia Scale (BADs)	6 Minute Walk Test, Physical Activity Questionnaire for Adolescents (PAQ-A), Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI), Burke-Fahn-Marsden Movement Scale (BFMMS), Newcastle Mitochondrial Disease Adult Scale, Newcastle Pediatric Mitochondrial Disease Scale (NPMDS), Unified Dystonia Rating Scale (UDRS)	2 Minute Walk Test, Alberta Infant Motor Scale, Gross Motor Function Measure (GMFM-88, GMFM-66), Motor Function Measure (MFM), Physical and Neurological Examination for Subtle Signs (PANESS), International Pediatric Mitochondrial Disease Score (IPMDS)

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Intellectual Functioning			Kaufman Assessment Battery for Children, Leiter International Performance Scale-3 (Leiter-3), Reynolds Intellectual Assessment Scale (RIAS), Wechsler Abbreviated Scale of Intelligence Scale – Fourth Edition (WAIS-IV), Wechsler Intelligence Scale for Children-IV (WISC-IV), Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)	
Language			Boston Diagnostic Aphasia Exam (BDAE-III), Boston Naming Test (BNT) – 30-item version, Clinical Evaluation of Language Fundamentals (CLEF-4), Comprehensive Assessment of Spoken Language (CASL), Expressive One-Word Picture Vocabulary Test, New Reynell Developmental Language Scale (NRDLS), Peabody Picture Vocabulary Test 4 th Edition (PPVT-4), Preschool Language Scales-Fifth Edition (PLS-5)	
Memory		Amyotrophic Lateral Sclerosis Depression Inventory-12 (ADI-12) *	Memory Assessment Scale, Summary of Recommendations for Global Outcome, Wechsler Memory Scale IV (WMS-IV)	
Muscle Strength Testing			Manual Muscle Testing-Using the Medical Research Council Muscle Grading Scale, Maximum Voluntary Isometric Contraction Testing (MVICT)	

Domain	Instrument or CDEs			
	Core	Supplemental - Highly Recommended	Supplemental	Exploratory
Neuropsychological Testing			Bayley Scales of Infant Development (Bayley III, BSID)	
Pulmonary Function Testing/Respiratory Status		Pulmonary Function		
Quality of Life		Pediatric Quality of Life Inventory (PEDIQL), World Health Organization Quality of Life Assessment (WHOQOL-BREF)	Child and Adolescent Scale of Environment (CASE), Child and Adolescent Scale of Participation, Craig Handicap and Assessment Reporting Technique (CHART-SF) – Interview version, Craig Handicap and Assessment Reporting Technique (CHART-SF) Paper version, Quality of Life in Neurological Disorders (Neuro-QOL), Short Form 36-Item Health Survey (SF-36)	EurQol-5 Dimension Questionnaire, Family Strain Questionnaire Assessment of Preschooled Children’s Participation), Pediatric Quality of Life Inventory Multidimensional Fatigue Scale
Visual-Spatial Processing			Judgment of Line Orientation (Benton JLO)	

Table 1. Common Data Elements based on Working Group and Level of recommendation (Core, Supplemental - Highly Recommended, Supplemental, Exploratory).

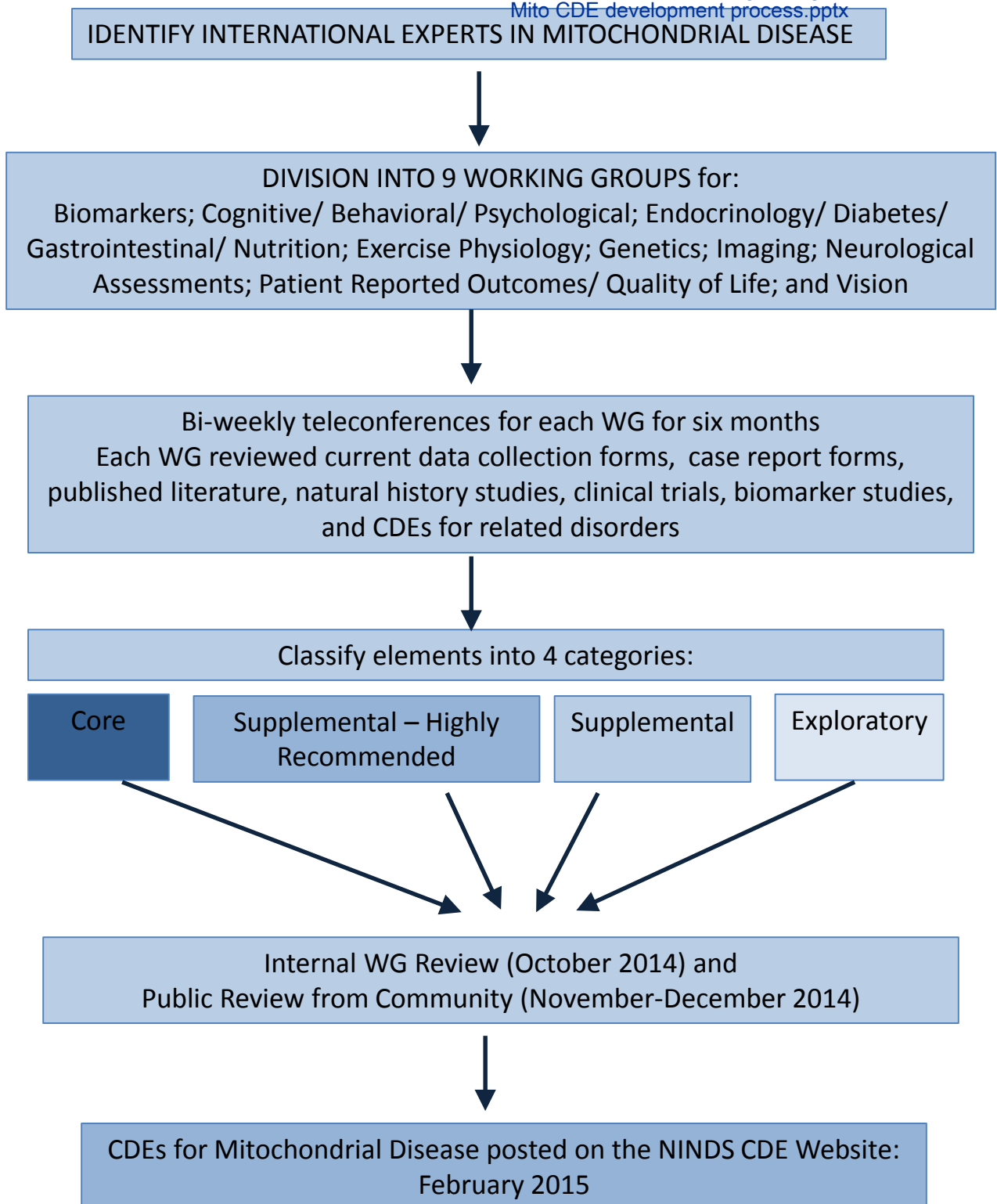


Figure 1. Flowchart illustrating the Mito CDE development process.



Form for Disclosure of Potential Conflict of Interest

Mandatory Submission Form for Manuscript No. B011-D-16-00391

The purpose of this form is to provide readers of your manuscript with information about your other interests that could influence how they receive and understand your work. All authors are responsible for the accuracy and completeness of the submitted information. The corresponding author is requested to sign and submit the scanned form together with the revised manuscript through Editorial Manager.

1. The Work Under Consideration for Publication

Did you or your institution at any time receive payment or services from a third party for any aspect of the submitted work (including but not limited to grants, data monitoring board, study design, manuscript preparation, statistical analysis, etc...)?

This includes:

- Grants
- Consulting fee or honorarium
- Support for travel to meetings the study or other purposes
- Fees for participation in review activities such as data monitoring boards, statistical analysis, end point committees, and the like
- Payment for writing or reviewing the manuscript
- Provision of writing assistance, medicines, equipment, or administrative support.

 No, financial relationships that present a potential conflict of interest
 Yes, the following financial relationships are present (explain on separate sheet).
2. Relevant financial activities outside the submitted work

Does any of the submitting author have financial relationships (regardless of amount of compensation) with entities in the bio-medical arena that could be perceived to influence, or that give the appearance of potentially influencing, what you wrote in the submitted work. This includes:

- Board Membership
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- Grants/grants pending
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- Royalties
- Payment for development of educational presentations
- Stock/stock options
- Travel/accomodatiois/meeting expenses unrelated to activities listed

 No, financial relationships that present a potential conflict of interest
 Yes, the following financial relationships are present (explain below)

- I serve on the Scientific & Medical Advisory Board of the United Mitochondrial Disease Foundation
- I am current President of the Mitochondrial Medicine Society

3. Other relationships

Are there other relationships or activities that readers could perceive to have influenced, or that give the appearance of potentially influencing, what you wrote in the submitted work?


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Author

Signature, Date

AMY GOLDSTON

 January 3, 2017

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