

## Overview

### **Mitochondrial Disease Working Group: Endocrinology/Diabetes/Gastrointestinal/Nutrition**

The development of the Mitochondrial Disease (Mito) Endocrinology / Diabetes / Gastrointestinal / Nutrition (Endo/DM/GI/Nutrition) Common Data Elements (CDEs) was a multi-tiered process which required compilation, review, and re-review of validated instruments and case report forms (CRFs) by means of monthly meetings. New forms were not created until the Working Group (WG) reviewed currently available CRFs and CDEs. The main goal of the project was to allow the reproduction of mitochondrial disease studies universally.

The WG began by reviewing the relevant literature and discussing endocrine problems that are most common in primary mitochondrial disease, and thus would be most likely to be the focus of clinical investigation. From a review of the relevant literature, it was concluded that both diabetes and abnormal growth were prevalent. Thus, the group focused on ensuring that a thorough diagnostic evaluation could be captured with tools or instruments. The WG also evaluated currently used tools for broadly characterizing the impact of mitochondrial disease on health to ensure that it captured all problems within the scope of endocrine-, GI-, and nutrition-related investigations. For diabetes, the WG wished to situate the diagnostic evaluation within what is recommended more broadly by the American Diabetes Association and other diabetes-specific professional organizations. For abnormal growth, it determined that clear guidance with respect to obtaining anthropometric measurements would be most helpful, as well as documentation of nutrient status and dietary supplement intake. For this reason, the group's scope expanded to include Nutrition and GI, as a clear understanding of these important dimensions of health is critical to a growth evaluation. For the balance of endocrine problems, it sought to obtain a general survey of the presence or absence of these; additional questions would need to be formulated and be based on the investigators' purposes.

There were no distinctions made between different types of mitochondrial disease, and the WG instead focused on endocrine phenotypes that may be common across diseases. The diabetes-specific instruments, for example, are applicable to any patient with mitochondrial disease who carries a diagnosis of diabetes.

As noted above, endocrine problems, including diabetes, abnormal growth, as well as GI problems and nutrition-related concerns are important features of mitochondrial disease. With respect to diabetes, the recommended instruments focus on careful documentation of the criteria used to make a diagnosis of diabetes in a patient with mitochondrial disease. With respect to growth evaluation, the importance of making consistent anthropometric measurements as well as consistent application of available age- and sex-specific growth

standards was emphasized. GI assessment largely focuses on obtaining an accurate description of symptoms. Nutritional assessment involves obtaining complete and comprehensive records of nutrient intake, and included a discussion of best practices for capturing supplement use.

Typically, existing scales (e.g., pediatric or adult Newcastle Mitochondrial Disease Scales) aim to broadly evaluate the effect of endocrine/GI/nutrition impairment on overall health. For these CDE recommendations, the WG also focused on characterizing the nature of the specific disease process(es) themselves. Because for some of these endocrine/GI conditions, no mitochondrial disease-specific instruments existed, elements were gathered from instruments developed for related conditions and adapted for this purpose. As a result, future work will need to focus on their optimization and validation in the mitochondrial disease population.

One challenge that was faced, not unique to endocrine/GI problems, is the wide range of manifestations of mitochondrial disease, both between individuals and even over the life course in a specific individual. There is not necessarily a “typical” trajectory, nor is the pathophysiology of organ- or system-specific conditions always well-understood, therefore the scope of potential investigations is also broad. Thus, the time frames over which data are gathered and reported are important to identify.

Additionally, there were many opportunities identified to prospectively evaluate the impact of mitochondrial disease on endocrine and GI health. These included the need for consistent and standardized longitudinal follow-up to build on previous estimates of the age- and mutation-specific incidence and prevalence of these problems. In addition, the impact of these conditions on patient health and well-being, and thus prioritization of clinical investigations, remains an important area of investigation. The WG appreciated the range of current approaches to treatment, in particular, nutrition and supplements, where even documenting these in a standard way to evaluate their potential impact can be a challenge. Given their importance to the overall health of affected individuals, careful assessment and study of endocrine- and GI-related health conditions is warranted.

**READ ME:** This is a recommendations summary document of the instruments/measures/case report forms - sorted alphabetically. Details of the recommendations follow this spreadsheet in the form of information documents (e.g., Notices of Copyright) or case report forms (CRF).

Table 1 Endocrinology Diabetes Gastrointestinal Nutrition Working Group Recommendations

Instrument / Scale / CRF Name <i>Name and acronym of the instrument/measure that is recommended for inclusion in the CDEs</i>	Domain	Subdomain	Classification (e.g., Core, Supplemental–Highly Recommended, Supplemental, Exploratory)
Anthropometrics – Vital Signs CRF	Assessments and Examinations	Vital Signs and Other Body Measures	Supplemental/Supplemental–Highly Recommended. Select CDEs are highly recommended for studies focused on growth, nutrition, and endocrine or gastrointestinal disease in specified aged groups.
Automated Self-Administered 24-hour Dietary Recall (ASA 24)	Assessments and Examinations	Endocrinology/Diabetes/Gastrointestinal/Nutrition	Supplemental–Highly Recommended for studies that require dietary assessments.
Diabetes-Related Medical History CRF	Assessments and Examinations	Endocrinology/Diabetes/Gastrointestinal/Nutrition	Supplemental/Supplemental–Highly Recommended. Select CDEs are highly recommended for any study focused on diabetes mellitus in mitochondrial disease.

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Dietary Supplements used in Mitochondrial Disorders CRF	Assessments and Examinations	Endocrinology/Diabetes/ Gastrointestinal/Nutrition	Supplemental
Laboratory Tests and Non-Imaging Diagnostics (Diabetes) CRF	Assessments and Examinations	Endocrinology/Diabetes/ Gastrointestinal/Nutrition	Supplemental/Supplemental–Highly Recommended. Select CDEs are highly recommended for diagnosis/monitoring of diabetes.
Mitochondrial and Gastrointestinal Disease CRF	Assessments and Examinations	Endocrinology/Diabetes/ Gastrointestinal/Nutrition	Supplemental
Reproductive and Hormonal History CRF	Assessments and Examinations	Endocrinology/Diabetes/ Gastrointestinal/Nutrition	Supplemental