Core Outcome Set for Liver Transplant in Mitochondrial Neurogastrointestinal Encephalomyopathy (MNGIE): the COLT-MNGIE Project- Protocol

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Introduction

Mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is a rare autosomal recessive disease characterized by marked mitochondrial DNA (mtDNA) maintenance abnormalities. Clinical manifestations predominantly involve intestinal (weight loss, cachexia, diarrhea, intestinal pseudo-obstruction) and neurological (polyneuropathy, ptosis, ophthalmoparesis, leukoencephalopathy) symptoms and signs. To correct the nucleoside imbalance responsible for mtDNA maintenance abnormalities, several therapeutic options are proposed, including permanent enzyme-replacement treatments, namely hematopoietic stem cell transplantation (HSCT) and orthotopic liver transplantation (OLT). HSCT and OLT are complex treatment procedures whose efficacy should be clearly defined by outcomes that are relevant for patients and clinicians. MNGIE is often misdiagnosed, given its rarity and non-specific symptoms, thereby making it unlikely that consistent evidence from clinical controlled trials will be available. Therefore, consistency in research methods on MNGIE is of pivotal importance, particularly in defining efficacy and safety outcomes. A Core Outcome Set (COS), defined as the minimum that should be measured in a clinical trial for a particular condition [1] is warranted to adopt consistent, clinically meaningful, and useful outcome measures for MNGIE.

Objective

The aim of the COLT-MNGIE project is to develop a COS to be used in research on the efficacy, safety and value of permanent enzyme-replacement treatments for MNGIE.

Methods

The COLT-MNGIE project is promoted by the MITOCON advocacy group for people affected by mitochondrial diseases. COS will be developed according to the Core Outcome Measures in Effectiveness Tri-

als (COMET) Initiative standards and recommendations [2] by means of a mixed method approach including scoping literature review, focus groups and surveys with key informants (people with MNGIE and carers/family members). In addition, consensus among an international multidisciplinary group of experts will be reached by means of Delphi method on clinical and instrumental outcomes. The COS list will be shared by all stakeholders in a final meeting.

Results

- *Stakeholders involved:* A multi-stakeholder scientific advisory group (SAG) provided methodological and organizational guidance. Clinicians who participated in the previous Consensus Conference on MNGIE (Hirano 2021) and all healthcare professionals involved in the management of MNGIE were invited to participate in this project. Persons with MNGIE were involved globally through patient advocacy groups on mitochondrial disorders.
- *Information sources:* A scoping literature review identified a preliminary list of outcomes: nucleoside levels, thymidine phosphorylase, hepatic function, type of nutrition, body weight, gastrointestinal symptoms, neurological, pain and quality of life. These outcomes were organized into the categories of diagnostic/instrumental and clinical treatment outcomes.
- *Consensus process:* The development of the COS is ongoing and will be achieved according to two procedures:

1. PROMs: The interviewed participants will be asked to score each of the PROMs proposed by means of a scale of 1 to 9 (1 to 3 'not important', 4 to 6 'important but not critical' and 7 to 9 'critical'). The mean of the scores will be calculated and the PROMs scoring in the range of "important" or "critical" levels will be included in the final COS).
2. Delphi survey method: a consensus definition among healthcare professionals will be performed by means of a Delphi survey method. Participants will be provided the list of outcomes developed through the scoping review and asked to score each of the outcomes a 1 to 9 scale (1 to 3 'not important', 4 to 6 'important but not critical' and 7 to 9 'critical') (Guyatt 2011).. Timing of assessment and measurement tool and technique will be specified for each outcome. For the purpose of this project, consensus is defined as agreement of a substantial majority (≥ 80%) of experts according to one of the above reported categories (not important, important but not critical, critical). The items assigned to the 'important' or 'critical' categories will be included in the final list. The items assigned to the 'not important' category will be excluded. The items with disagreement will be brought forward to a second Delphi round.

- *Analysis*: The final meeting will involve the SAG, all the content experts who participated in the Delphi survey and MITOCON representatives. The results of the qualitative structured interviews with persons with MNGIE (list of PROMs) and the Delphi survey (list of clinical and instrumental outcomes) will be presented and discussed.

Conclusions

The development of a COS for permanent enzyme-replacement treatments in MNGIE is essential for ensuring consistent evaluation of treatment efficacy, safety, and value. This COS will standardize outcome measures, making them relevant and meaningful to both patients and clinicians. Ultimately, the COLT MNGIE project will enhance the comparability and effectiveness of research in this rare disease, improving clinical practice and patient care.

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