# Optimization of the International Paediatric Mitochondrial Disease Scale

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Primary Objective: To further optimize the IPMDSSecondary Objective(s): To determine in which age-groups the items within the IPMDS are appropriate To determine whether the IPMDS can assessed reliably by research nurses, students and physician...

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Metabolic and nutritional disorders congenital |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON43155

**Source**
ToetsingOnline

**Brief title**
IPMDS

### Condition

- Metabolic and nutritional disorders congenital

**Synonym**
energy metabolism disturbances

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum
**Source(s) of monetary or material Support:** zeldzame ziekten fonds

## Intervention

**Keyword:** children, Mitochondrial disease, Outcome measures

## Outcome measures

### Primary outcome

International Paediatric Mitochondrial Disease Score (IPMDS)

The newly developed International Paediatric Mitochondrial Disease Score (IPMDS) was designed to follow children with a mitochondrial disease in e.g. clinical trials and detailed natural history studies. It consist of the following subdomains: 1. Complaints and symptoms; 2. Physical examination and 3. Functional tests. Its reliability and validity are to be tested in this study.

The scale takes about 35 minutes to perform, of which 25 for Domain 1 and 10 for Domain 2 and 3 each. The patient should be involved in the assessment of Domain 2 and 3 but not necessarily for Domain 1.

### Secondary outcome

na

# Study description

### Background summary

Mitochondrial diseases are the most prevalent inherited metabolic diseases, with an incidence of approximately 1 : 5,000 live births(Schaefer, Taylor et al. 2004). Since mitochondria are present in almost all cells, symptoms can arise theoretically from virtually every organ, but mostly from brain, heart, eye and skeletal muscle(Koopman, Willems et al. 2012). There is not only large variability in the pattern of affected organs, also the degree of disability ranges widely. Whereas some patients remain in mainstream school and are able to achieve e.g. swimming certificates, others die in the neonatal period or

barely interact with their environment.

Currently, there is no cure for mitochondrial diseases but there are some promising results of pharmacological interventions in cells and animals (Koene and Smeitink 2009; Wenz 2009; Viscomi, Bottani et al. 2011; Koopman, Willems et al. 2012) and in some mitochondrial disorders (Hirano, Garone et al. 2012; Koga, Povalko et al. 2012). To assess the effect of these interventions, sensitive, reliable, valid and relevant outcome measures should be used. Because of the heterogeneity and the multisystem nature of mitochondrial disorders, the selection of adequate outcome measures is challenging(Koene, Jansen et al. 2013). A combination of objective, functional, subjective and possibly biochemical endpoints will probably be necessary to be able to compare within the full range of the disease spectrum.

A mitochondrial disease specific follow up tool for children already exists, namely the Newcastle Paediatric Mitochondrial Disease Scale (NPMDS)(Phoenix, Schaefer et al. 2006). This scale was designed to be a concise, pragmatic, quantifiable and multidimensional tool to assess disease progression in children with mitochondrial disorders at the outpatient clinic. The scale is quick (25 min) to administer, reflects the multidimensional nature of the disease and has a more or less holistic approach to disease, containing subjective, objective and functional items. However, in our experience, some items within the questionnaire are rather abstract and difficult to fill out in patients with severe conditions. Therefore, we have adapted the NPMDS to a new, more detailed and more sensitive scoring system to be used in future clinical trials for mitochondrial disease, the International Paediatric Mitochondrial Disease Score (IPMDS). This study has been tested by international colleagues and The feasibility of the IPMDS was good, as indicated by a low number of missing items (4%) and the positive evaluation of patients, parents and users. Principal component analysis of our small sample identified three factors, which explained 57.9% of the variance. Good construct validity was found using hypothesis testing. The overall inter-rater reliability was good (median ICCagreement 0.85; range 0.23 * 0.99). Please see the supplementary files for the IPMDS, the IPMDS manual and the accepted manuscript (supplementary file 1, 2, and 3).

Several questions remain after these validation studies:
i) Which age-groups are the functional items appropriate for?
ii) What is the inter-rater realibility for assessment by research nurses, students and physician assistants (to make implementation of the scale into clinical practice more feasible); and
iii) What is the cause of the low reliability of some of the items within the physical examination part (see supplementary file 4)?

**Study objective**

Primary Objective:

To further optimize the IPMDS

Secondary Objective(s):
To determine in which age-groups the items within the IPMDS are appropriate

To determine whether the IPMDS can assessed reliably by research nurses, students and physician assistants (to make implementation of the scale into clinical practice more feasible)

To determine the cause of the low reliability of some of the items within the physical examination domain (and adapt the IPMDS or the manual accordingly)*

**Study design**

This protocol includes three separate small observational studies.

Study i) To determine in which age-groups the items within the IPMDS are appropriate
The IPMDS will be performed in healthy children aged 0-18 years. In the first domain, parents and/or the child will be asked questions about e.g. chewing, tiredness, etc (see attachment 1). In the second and third part, children will have to participate in physical examination (neurological examination) and functional tests. The study will take place in the child*s home environment to make them more comfortable.

Study ii) To determine whether the IPMDS can assessed reliably by research nurses, students and physician assistants
In ten patients with, electively admitted to the ward, the IPMDS will be performed by three raters, of which one experienced rater, subsequently. Raters may include: physician assistant, research nurses and medical students.
(These results will be used to facilitate implementation of the IPMDS in daily care.)

Study iii) To determine the cause of the low reliability of some of the items within the physical examination part
In five patients with abnormalities at neurological examination (most of the unreliable items concern neurological examination), electively admitted to the ward, five experienced physicians will rate the previously rated *unreliable* items at the same time (during 1 hour in the morning). Comments on the items and the manual with respect to this patient are noted. After the regular examination programme for the elective admission, 2 raters rate the symptoms again. We hypothesize that rating the patient at exactly the same time will increase reliability, because the severity of the symptoms is likely to fluctuate over the day.
(These results will be used to either adapt the manual or to remove the item from the IPMDS because it is not stable.)

**Study burden and risks**

Since the scoring list is developed for children with a mitochondrial disease, we cannot validate this list in adults or healthy children.

The risk associated with this study is negligible, since the study resembles a regular outpatient clinic visit, only far longer. No intervention or invasive procedures are involved.

The patients included in this study will be elective inpatients. The timeburden for study ii is estimated to be three times 30 minutes, of which 5-10 minute will be functional testing. For the convenience of the patient, we chose to only compare three raters in the same experiment. For study iii, five children with a mitochondrial myopathy and moderate to severe neurological disability will be assessed at the same time by five assessors and later at the day by 2 assessors when they are already admitted to the paediatric ward.
The healthy controls and patients will not benefit from this study; though the risks and burden are also estimated to be very low.

An advantage of the IPMDS to the patient individually might be that it is a more structured analysis of the patient*s health state and it might give a better overview over the patient*s problems than can be obtained in a regular outpatient visit. Therefore, a summary letter with the findings of this study will be sent to all physicians caring for the patient.

However, the advantages are mainly related to the group of mitochondrial disorders. The development and the validation of the IPMDS is required to follow-up patients in great detail. This is warranted for more detailed natural history studies (since the disorder is genetically so heterogeneous, the natural history of the individual biochemical and genetic defects in unknown) and clinical trials (we are e.g. preparing a phase 1/2 trial in this population, but lack a reliable and valid and specific outcome measure for mitochondrial disease progression).

Healthy children: The IPMDS will be performed in a home situation, for the convenience of the child and the parents. No physical examination or blood samples are involved. Timeburden is estimated to be 1 hour for parents, 45 minutes for older children and about 20 minutes for children under 6 years.

# Contacts

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Selecteer

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

## Inclusion criteria

- Study i) Healthy children aged 0-18 years.
- Study ii) Children with a mitochondrial disease admitted for the MItoRoute
- Study iii) Children with a mitochondrial encephalopathy with abnormalities at the neurological examination, admitted for the MItoRoute

## Exclusion criteria

- Study i) Having a known health condition
- Study ii) and iii) The study is estimated to be too burdensome to the patient

# Study design

### Design

**Study type:** Observational non invasive

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Other |

### Recruitment

NL

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|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-09-2016 |
| Enrollment: | 195 |
| Type: | Anticipated |

## Ethics review

Approved WMO

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| Date: | 25-01-2017 |
| Application type: | First submission |
| Review commission: | CMO regio Arnhem-Nijmegen (Nijmegen) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| CCMO | NL58055.091.16 |