# Upper extremity outcome measures in non-ambulant Duchenne muscular dystrophy patients

Published: 01-03-2018
Last updated: 18-07-2024

Primary objective:1. To study the relation between muscle FF and two major clinical endpoints in different phases of the disease in non-ambulant DMD patients. Secondary objectives:2. To explore the use of Microsoft Kinect and Leap Motion in relation...

| | |
|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Neuromuscular disorders |
| **Study type** | Observational non invasive |

## Summary

### ID

NL-OMON50471

**Source**
ToetsingOnline

**Brief title**
Upper limb outcome measures in DMD

### Condition

- Neuromuscular disorders

**Synonym**
DMD patients, Duchenne, Duchenne muscular dystrophy

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Subsidie van Spieren voor Spieren

## Intervention

**Keyword:** Duchenne, Non-ambulant, Outcome measures, Quantitative muscle MRI

## Outcome measures

### Primary outcome

Primary study endpoints:

- Biceps endpoint: Additive predictive value of biceps FF to age on the moment of loss of the ability to bring the hand to the mouth with a 200g weighing cup (supporting elbow on table is allowed), defined by hazard ratio.

- Thenar endpoint: Additive predictive value of thenar FF to age on the moment of loss of the ability to play for 10 minutes on a game console, defined by hazard ratio.

### Secondary outcome

-

# Study description

### Background summary

Rationale:
Duchenne muscular dystrophy (DMD) is a rare X-linked inherited muscle disease caused by mutations in the dystrophin gene. In muscles, the absence of dystrophin leads to inflammation, fibrosis and irreversible replacement of muscle tissue with fat. As a consequence, DMD patients suffer from progressive muscle weakness. Their lower extremities (LE) are affected earlier in the disease course than the upper extremities (UE), which leads to wheelchair dependence around the age of 12, and loss of the ability to move the hand to the mouth in the following, early non-ambulant phase. For patients in the advanced non-ambulant stages of the disease, the preservation of minimal functioning of hand muscles can have a significant impact on participation in daily life, for example due to the ability to use electronic devices, such as a phone or game console.

Currently, no full market-approved drug is available for DMD. However, several drugs are being tested or planned to be tested in clinical trials, and some have obtained conditional approval. Almost all of these trials have focussed on ambulant boys. Although the conduction of placebo controlled trials has appeared feasible, several major problems have been identified.
First, it is difficult to include sufficient patients per trial due to the rarity of the disease. This is even more applicable for drugs targeting specific mutations. Secondly, the regulatory agencies require the use of outcome measures that are unequivocally related to daily life functioning. Development of such outcome measures has taken many years in ambulant patients, but has only started recently in the early non-ambulant phase, and is lacking in the advanced stage of the disease. Thirdly, the natural history of the disease was shown to be very variable, and understanding of the underlying mechanism is lacking. Finally, as the replacement of muscle by fat is considered irreversible, all drugs need sufficient remaining muscle tissue to target. Therefore, extrapolation of results obtained in ambulant boys towards later stages of the disease is not considered appropriate by the regulators.
As a result, there is an urgent need to develop objective biomarkers with a clear relation to clinical endpoints in order to limit the duration of clinical trials, and to reduce the numbers of required participants. Additionally, more advanced techniques to quantify UE motor function may more objectively and better relate to activities in daily life. Finally, it is necessary to document the natural history of the disease in non-ambulant patients and to better understand the underlying causes of its variability.

At present, quantitative MRI (qMRI) is considered the most promising biomarker reflecting essential muscle pathology in DMD. qMRI has been feasible and reliable even in children from the age of five. The most studied parameter is muscle fat fraction (FF). In the LE, the complex relation between FF in the many muscles involved and the main clinical endpoint at that stage, i.e. loss of ambulation, is currently studied by international research collaborations.
In UE, the relation between FF and function is supposed to be less complex, due to the smaller number of muscles involved. The Performance of Upper Limb (PUL) motor scale and DMD upper limb patient-reported outcome measure (DMD Upper Limb PROM) have been validated as outcome measures for UE function in multiple natural history studies. Limitations of the PUL are a ceiling effect in the upper and lower regions of the score and observer-dependence. Microsoft Kinect and Leap Motion are two innovative systems that do not have these limitations, and that could provide better quantification of UE motor function in daily life. The automated score generation may be more easily applied in multicentre trials.

## Study objective

Primary objective:
1. To study the relation between muscle FF and two major clinical endpoints in different phases of the disease in non-ambulant DMD patients.

Secondary objectives:
2. To explore the use of Microsoft Kinect and Leap Motion in relation to the validated PUL scale, DMD Upper Limb PROM, and muscle FF, in non-ambulant DMD patients.
o To compare accuracy between the use of one or two Leap Motion sensors and study the effect of occlusions on submaximal movements.
3. To define biological parameters and qMRI characteristics other than FF, such as diffusion tensor imaging (DTI), contractile cross-sectional area (CSA) and transverse relaxation time (T2) of muscle, in relation to the variability in UE function and UE muscle FF in non-ambulant DMD patients.

**Study design**

Study design and methods:
This observational study will be conducted at the Leiden University Medical Center (LUMC). Patients will be included in the following groups:
- DMD_AA: Able to move the hand to the mouth with a 200 gram (200g) weighing cup (supporting elbow on table is allowed) and Able to play for 10 minutes on a game console.
- DMD_UA: Unable to move the hand to the mouth with a 200g weighing cup (supporting elbow on table is allowed), but Able to play for 10 minutes on a game console.
- DMD_UU: Unable to move the hand to the mouth with a 200g weighing cup (supporting elbow on table is allowed) and Unable to play for 10 minutes on a game console.

Patients in group DMD_AA and DMD_UA will undergo qMRI of the right upper arm and hand, Kinect, Leap Motion, and functional tests at baseline, 12 months, and 18 months follow-up. Patients in group DMD_UU will undergo the tests at baseline and 12 months follow-up. Clinical follow-up to determine loss of either biceps or thenar clinical endpoint will be done by telephone calls for a maximum of 4 years. Fifteen healthy age matched controls are needed for calibration of DTI and CSA values. Ten will undergo the qMRI and clinical assessment only once at baseline. Five healthy controls, aged 18 years and older, will have an MRI scan also at 12 and 18 months for MRI quality control.
For the primary objective, qMRI will yield FF data of the biceps and thenar muscles. These will be fitted to a logarithmic model, after which the resulting data is analysed in a survival analysis with time varying covariates, together with the dates on which the clinical endpoint was reached. This Clinical Endpoints Model (CEM) yields a hazard ratio.
For the second objective all functional test results will be correlated to DMD Upper Limb PROM results and biceps and thenar FF at baseline. Moreover, the association between change in functional tests scores and DMD Upper Limb PROM scores, biceps and thenar FF over the 1-year and 6-months follow-up periods will be evaluated.
The third objective will be analysed using linear regression analyses, in which the different biological parameters and qMRI characteristics will be used to

explain variability in UE function (i.e. Kinect, Leap Motion and DMD Upper Limb PROM results), and in biceps and thenar FF.

### Study burden and risks

Nature and extent of the burden and risks:
This study has no invasive procedures. Subjects with contraindications for MRI will be excluded. There are no known risks known associated with the use of MRI, Kinect and Leap Motion or the applied functional tests. Participants have no direct personal benefit from participating in this study. The data will support the design of future clinical trials in non-ambulant DMD patients.

## Contacts

**Public**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL
**Scientific**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2333ZA
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Elderly (65 years and older)

### Inclusion criteria

Inclusion criteria for non-ambulant boys and men with Duchenne muscular dystrophy:
1. Age 8 years or above.
2. Non-ambulant defined as not able to walk five meters indoors unaided.
3. The diagnosis of DMD must be confirmed by genetic testing. , Inclusion criteria for male healthy controls:
1. Healthy age-matched boys and men of 8 years or older. , Inclusion criteria for Leap Motion sub study healthy controls:
1. Healthy men or women aged 18 years or older.

### Exclusion criteria

Exclusion criteria for non-ambulant boys and men with Duchenne muscular dystrophy:
1. Exposure to an investigational drug within 6 months prior to the start of the study.
2. Intellectual impairment that would interfere with the possibility to follow instructions.
3. Inability to lie still for 45 minutes.
4. Recent (< 6 months) UE surgery or trauma.
5. Continuous daytime artificial ventilation either via non-invasive ventilation or tracheostomy. Nocturnal non-invasive ventilation is not a contraindication to the study.
6. Metal implant.
7. Other contraindications to MRI exposure (*Vragenlijst MRI onderzoek*)., Exclusion criteria for healthy controls:
1. Any muscle disease.
2. Recent (< 6 months) UE surgery or trauma.
3. Contraindication to MRI exposure (*Vragenlijst MRI onderzoek*)., Exclusion criteria for Leap Motion sub study healthy controls:
1. Any condition affecting functioning of the hand and lower arm.

## Study design

### Design

| | |
|---|---|
| Study type: | Observational non invasive |

| | |
|---|---|
| Intervention model: | Other |
| Allocation: | Non-randomized controlled trial |
| Masking: | Open (masking not used) |
| Control: | Active |
| Primary purpose: | Other |

### Recruitment

NL

| | |
|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 23-03-2018 |
| Enrollment: | 65 |
| Type: | Actual |

## Ethics review

Approved WMO

| | |
|---|---|
| Date: | 01-03-2018 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 06-12-2018 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 11-07-2019 |
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br>metc-ldd@lumc.nl |

Approved WMO

| | |
|---|---|
| Date: | 24-08-2020 |

| | |
|---|---|
| Application type: | Amendment |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# 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 | NL63133.058.17 |