THE NATURAL HISTORY OF PATIENTS WITH MUTATIONS IN *SEPN1 (SELENON) or LAMA2*: A PILOT STUDY

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PROTOCOL SIGNATURE SHEET

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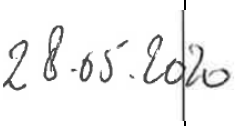
Head of Department: **Prof. dr. Michèl Willemsen**		
Coordinating Investigator/Project leader/Principal Investigator: **Dr. Nicol Voermans**		18-05-2020

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	**ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)**
CV	**Curriculum Vitae**
IC	**Informed Consent**
METC	**Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)**
Sponsor	**The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.**
Wbp	**Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)**
WMO	**Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen**

SUMMARY

Rationale: Patients with mutations in the *SEPN1* gene (nowadays called SELENON gene) suffer from slowly progressive congenital myopathy with early onset rigidity of the spine and potentially life-threatening respiratory insufficiency. The protein encoded by *SEPN1*, selenoprotein-1, functions as an endogeneous antioxidant and executes a role in cellular redox metabolism. The first results of an intervention study using KH176, currently under development for mitochondrial disease, in an animal model (*Sepn1* knock out zebrafish) showed improved muscular function. Patients with mutations in *LAMA2* gene causing merosin-deficient congenital muscular dystrophy (MDC1A) have a similar phenotype as those with mutations in *SEPN1* gene. Key characteristics include congenital hypotonia, delayed motor development and contractures. For them no treatment is available either. Since not much is known about the clinical progression in these two congenital muscular dystrophies, there is an urgent need for natural history-outcome measure studies to reach trial-readiness enabling smooth transition towards clinical trials.
Objective: i) To identify and follow patients withSEPN1- and LAMA2-related congenital muscular dystrophies in The Netherlands (and preferably also in Belgium). Ii) To select outcome measures based on the natural history data.
Study design: Observational 1,5-year study with 6-monthly measurements (four measurements in total).
Study population: Patients with the rare muscle condition caused by mutations in SEPN1 or LAMA2 aged 0-100 years.
Main study parameters/endpoints: A wide variety of tests will be performed to get a full impression of the patient's abilities and disabilities (e.g. muscle strength, walking ability, muscle endurance, activities, participation, quality of life, fatigue). Full body muscle MRI will only be performed in patients who are able to lie still for the full duration of the MRI (~>10 years) and who are not dependent on respiratory equipment.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: We aim to study the natural history of these groups of patients. Since so few SEPN1 and MDC1A patients are available, we will ask both children and adults to participate in this study. This study is a preparation for clinical trials in these conditions and may facilitate the proper conduction of the clinical trials in these conditions. For the patient, the conduction of so many tests is without any doubt burdensome. Therefore, we reduced the number of test to to-our-opinion the absolute minimum. We have discussed our protocol with Spierziekten Nederland and Spieren voor Spieren. We will make a summary of the measurements after the first measurement and at the end of the study, when indicated answering a question from clinical care.

1. INTRODUCTION AND RATIONALE

Patients with mutations in the *SEPN1* gene suffer from slowly progressive congenital myopathy with early onset rigidity of the spine and potentially life-threatening respiratory insufficiency. The prevalence of this condition, above the age of 5 years, based on a Danish study, is estimated around 0.5:1000,000[1]. The estimated number of patients in the Netherlands is therefore around 10-20, which limits the clinical experience that is available for this condition. A relatively recent retrospective cross-sectional study in 41 subjects by our colleagues at the Dubowitz Neuromuscular Centre in London showed that the spectrum of the disease is wider than previously reported[2,3], ranging from patients who lose ambulation to patients with a very stable and mild disease course. This is in line with our limited clinical experience. Since this was a retrospective study, neuromuscular function was not quantified using a standardized set of instruments.
Patients with mutations in *LAMA2*-gene causing merosin-deficient congenital muscular dystrophy (MDC1A) have a similar phenotype as those with mutations in *SEPN1* gene. Key characteristics include congenital hypotonia, delayed motor development and contractures. The clinical manifestations of LAMA2-related muscular dystrophy range from severe, early-onset congenital muscular dystrophy (complete laminin α2 deficiency) to mild, later childhood-onset limb-girdle type muscular dystrophy (partial laminin deficiency)[4].The prevalence of LAMA2-related muscular dystrophy is estimated at 4 in 500.000[5],
For both SEPN1 and LAMA2-related congenital muscular dystrophies no (curative) treatment is available. Experience with quantifying neuromuscular function in these conditions should be obtained before scientifically sound clinical trials can be performed in these conditions.

The protein encoded by *SEPN1*, selenoprotein-1, functions as an endogeneous antioxidant and executes a role in cellular redox metabolism[6]. Consequently, selenoprotein deficiency causes oxidative stress in muscle cells. Patients with *SEPN1* deficiency therefore not only show striking similarities to patients with classical mitochondrial diseases on certain clinical aspects, but also on the cellular level. We recently confirmed that the cells of patients with *SEPN1*-related congenital myopathy indeed showed increased ROS production and abnormal redox status. Both cellular abnormalities could be counteracted by KH176, a new chemical entity developed for mitochondrial oxidative phosphorylation disturbances. Interestingly, the first results of the experiments in an animal model (*Sepn1* knock out zebrafish) showed improved muscular function. We hypothesize that KH176 is also beneficial for SEPN1-mutated patients.
LAMA2-related muscular dystrophy is caused by mutations in the LAMA2 gene that result in a deficiency or absence of the alpa-2 subunit of laminin 2 and 4. This results in a decrease of the strength and stability of muscle tissue, leading to the signs and symptoms of LAMA2-related muscular dystrophy[5]. Currently, Maastricht UMC+ is taking preparations to start a phase I/II clinical trial involving mesoangioblast cultures for therapy in the near future.

In conclusion, both SEPN1-and LAMA2-related congenital muscular dystrophy patients are rare and no Dutch registry exists. The future clinical trials emphasize the urgent need to identify and follow up these patients and to select optimal outcome measures.

2. OBJECTIVES

Primary Objective:
To identify and follow patients with *SEPN1* and *LAMA2* mutations.

Secondary Objective(s):
To assess the natural history and to select outcome measures based on the natural history data.

3. STUDY DESIGN

This is an observational study.
In both SEPN1- and LAMA2-related muscular dystrophy, we will assess disease severity in 10 patients using different outcome measures every 6 months, during 18 months (one-and-a-half-year study with four measurements). First inclusions will take place in 2020. We expect that within 2 years inclusion will be completed. If more than 10 patients are willing to participate, we will select per muscle disease 10 patients that are representative of the patient population (based on age, gender, disease severity etc.). The remaining patients will be retrospectively analyzed through medical records and will receive questionnaires, which can be completed at home.

4. STUDY POPULATION

4.1 Population (base)

SEPN1 patients (prevalence 0.5:1000,000) and MDC1A patients (4 in 500,000) are rare and no Dutch registry exists.Therefore, we can only estimate the number of patients in the Netherlands and Belgium (n ≈ 20 in each disease group). All patients with *SEPN1 and LAMA2 mutations* within the Netherlands and Belgium will be identified through contact with genetic diagnostic services, rehabilitation centers, and muscle disease experts. A previous pathology study confirmed that 20 patient have been diagnosed with *SEPN1* in the past years in the Netherlands and Belgium. The Stichting Voor Sara welcomed 17 MDC1A patients at their first held patient information day. We expect that more patients will be referred once we start these natural history studies.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- 0-100 years of age
- Willing and able to complete (part of the) measurement protocol
- Willing and able to travel to Nijmegen
- Dutch-speaking
- Genetically-confirmed muscle disease caused by mutations in SEPN1: congenital muscular dystrophy with early spine rigidity or congenital myopathy (multicore/minicore disease, congenital fiber type size disproportion)
- Genetically confirmed muscular dystrophy caused by mutations in *LAMA2*: merosin-deficient muscular dystrophy 1A (early-onset *LAMA2*-related muscular dystrophy) or childhood-onset limb-girdle type muscular dystrophy (late-onset LAMA2-related muscular dystrophy)

4.3 Exclusion criteria

This study doesn't have any exclusion criteria.

4.4 Sample size calculation

We think that we will be able to identify 20 SEPN1 and 20 MDC1A patients in the Netherlands and Dutch- speaking Belgium. Based on our experience in rare diseases, we estimate that ~50% of the patients will participate in the study..

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The following outcome measures will be used in both children and adults:
Degree and extent of muscle weakness: maximal voluntary isometric contraction (measured by MRC scores and handheld dynamometry)
Motor Function Measure
30 seconds sit to stand test
Graded and timed function tests
10 meter walk test
6-minute walking test
Accelerometry for 7 days at home
Hammersmith Functional Motor Scale (HFMS)
Pedriatric balance scale or miniBEST
Vignos and Brooke scale
Range of motion of ankle (contracture Achilles tendon) and elbow
Muscle ultrasound
Whole-body muscle MRI (yearly; above the age of 10 years; no respiratory equipment)
Respiratory function test (above 5 years): forced vital capacity FVC upright and supine, forced expiratory volume in 1 second FEV1, (measured by spirometry), peak cough flow, sniff nasal inspiratory pressure (SNIP), maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP); muscle ultrasound measurement of the diaphragm
ECG (yearly)
Cardio-echography (yearly)
X-ray of the spine (yearly)
DEXA scan (yearly)
Neurological phenotype (e.g. facial appearance, ophthalmoplegia) – only at start of study by experienced (paediatric) neurologist (yearly)

The following questionnaires will be included:
Activlim questionnaire
Borg Rating Scale of Perceived Exertion
Checklist individual strength questionnaire
Egen Klassifikation scale version 2 (EK2)
Functional Ambulation Category (FAC)
Wong-Baker Faces Pain Scale
McGill pain questionnaire
PedsQL generic quality of life, neuromuscular module and Multidimensional Fatigue Scale
SF36 quality of life scale
Individualised Neuromuscular Quality of Life (INQoL)
IPA

5.1.2 Other study parameters

Weight
Height
Demographic parameters (age, sex, age at diagnosis)
Genetic information (mutation)
Medical history, including the 10 most burdensome complaints
Level of education; work

5.2 Study procedures

Ranked alphabetically
See also **Supplementary Table 1**

10 meter walk testThe time in which a patient is able to walk *safely* (!) for 10 meter is noted.

30 seconds sit to stand test -> video+
The patient is asked to stand up from full squatting position as many times as possible within 30 seconds.

6 minute walking test (6MWT)
In the six minute walk test, children are asked to walk (not run, skip, or gallop) as fast as possible, with or without devices and with the opportunity to rest, but not to sit or lay down (timing continues during resting).

Accelerometer
Patients are asked to wear an accelerometer for 7 days, the recommended period.

Activlim questionnaire - above 6 years only
Questionnaire to assess the ability to perform 22 activities of daily life on a 3-point scale from impossible to easy.

Borg Rating Scale of Perceived Exertion
Borg Rating Scale of Perceived Exertion is a way of measuring physical activity intensity level. Perceived exertion is based on the physical sensations a person experiences during physical activity. We will ask patients to score the intensity level at the end of the 6MWT.

Cardiac ultrasound
The usual cardiac ultrasound will be performed using a standardized protocol to obtain images which can be analyzed for cardiac contractility using the 2D strain technology, a detailed software analysis of the images.
The test can be performed in all children.

Checklist individual strength (CIS)
The CIS is a questionnaire rating four subscales: subjective tiredness, concentration, motivation and physical activity. It consists of 20 items on a 7-point scale.

The Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP INTEND) – children < 2 years only

CHOP INTEND has been shown to be valid for the assessment of motor skills of children below 2 years of age.

DEXA scan

The bone density of the spine and hip will be measured by a DEXA scan

Egen klassifikation version 2 (EK2)

The EK2 is a questionnaire that was designed to measure functional ability of activities in daily living in non-ambulant Duchenne muscular dystrophy patients. This questionnaire is only available in English. Therefore, only patients older than 16 years who have a sufficient understanding of the English language will be asked to complete this questionnaire.

Functional Ambulation Category (FAC)

The FAC assesses functional ambulation in patients.

Graded and timed function tests-> video+

The time it takes to complete functions of the lower extremity will be assessed with the time it takes to climb 5 stairs, to rise from the floor and the 'Timed up and Go'.

Individualized Neuromuscular Quality of Life (INQoL)

The INQoL is a validated muscle disease specific measure of quality of life, which can be used for individuals or large samples.

Hammersmith Infant Neurological Examination (HINE)

HINE is designed to be a simple and scorable method for evaluating infants from 2 months to 2 years of age. It includes 3 sections that assess different aspects of neurologic function, including neurological examination, developmental milestones and behavioral assessment.

Hammersmith Functional Motor Scale (HFMS)

The HFMS was originally developed to assess the physical abilities of children with non-ambulant Spinal Muscular Atrophy (SMA). It consists of 20 items that were considered as important to measure the physical functioning of those patients.

Impact of Participatie en Autonomie (IPA) – adults only

Questionnaire about participation and autonomy in daily life.

Full body muscle MRI

A full body muscle MRI (quantitative and qualitative) will be performed in patients who are able to lie supine and still for 60 minutes (~> 10 years old) and who are not dependent on respiratory equipment.

Maximal voluntary isometric contraction -> video+

Both hands will be tested for maximal voluntary isometric contraction using a hand held dynamometer. Also strength of the m. quadriceps and m. biceps brachii are measured using dynamometry. Three attempts will be noted bilaterally.

McGill pain questionnaire

Questionnaire in which the location, level and characteristics of pain are assessed.

Mini Balance Evaluation System Test (miniBEST)

The miniBEST evaluates balance control by scoring of exercises that belong to one of the following categories: anticipatory postural changes, reactive postural control, sensory orientation and walking.

Motor Function Measure (MFM)
Motor function in patients (aged 2-62 years) with neuromuscular diseases (ambulant or non-ambulant) can be measured with the Motor Function Measure. The MFM is a scale which consists of 32 items in three dimensions: standing position and transfers, axial and proximal motor function, distal motor function.

Muscle ultrasound
Ultrasound quantification of the leg, arm, back and abdominal muscles, as well as the diaphragm, will be performed.

Neurological examination
The promovendus (MD) and/or an experienced (paediatric) neurologist will do a full neurological examination at the start of the study, including muscle power measurements and hand-held dynamometry. A shortened version of the neurological examination will be performed every subsequent visit.

PedsQL generic quality of life – children only
The PedsQL generic quality of life questionnaire consists of 23 questions in four domains: Physical, Emotional, Social, and School Functioning. It has been translated and subsequently validated into many languages, including Dutch.

PedsQL neuromuscular module (PedsQL NMM) – children only
The PedsQL NMM questionnaire consists of 25 questions in three domains: Neuromuscular disease, communication and family resources.

PedsQL Multidimensional Fatigue Scale (PedsQL MFS) – children only
A questionnaire assessing subjective fatigue in three domains, namely General Fatigue Scale, Sleep/Rest Fatigue Scale, and Cognitive Fatigue Scale.

Pediatric balance scale – children only
The Pediatric Balance Scale is a modified version of the Berg Balance Scale that is used to assess functional balance skills in school-aged children with mild to moderate motor impairments.

Pulmonary function
In those patients able to follow commands, pulmonary function (forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) , maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP)) will be assessed. The FVC will be assessed in lying and in sitting position to assess the contribution of the diaphragm.

Range of motion ankle and elbow
The range of motion of the ankles and elbows is noted bilaterally.

SF36 quality of life scale – adults only
Measure for quality of life with 36 items.

Vignos and Brooke scale

The Brooke and Vignos scales provide ordinal ordinal-level data to assess the upper and lower extremity functions.

Wong-Baker Faces Pain Scale

The Wong-Baker Faces Pain Scale was originally created for children to help them communicate about their pain.

X-ray of the spine

A full spine X-ray will be made in a lateral and anteroposterior direction in a sitting position. While lying on the side, a flexion-extension X-ray will be made.

6. SAFETY REPORTING

We don't expect any adverse events.

7. STATISTICAL ANALYSIS

The data will be presented per patient per test. Missing data will not be replaced.

	0 months	6 months	12 months	18 months
SEPN001				
SEPN002				
MDCA001				
MDCA002				

7.1 Primary study parameter(s)

Primary Objective:
To identify and follow patients with SEPN1 or LAMA2 mutations.

Secondary Objective(s):
To select outcome measures based on the natural history data.

Since the numbers in this study will probably be very low, data will be analyzed based on a) the correspondence of test results to our clinical observation of the patient (face validity, will be assessed at each occasion), b) the fluctuation of the results in combination with the patient-reported disease progression, c) floor and ceiling effects, d) variation and variability of the data and e) the opinion of the patient about which test reflects his/her disease severity.

We will use descriptive statistics (mean, median, SD, 95%-CI) in order to summarize the features of SEPN1 and MDC1A patients.
We will perform (Spearman's) correlation analysis and non-parameterical testing to test e.g. correlation between age and difference between ambulatory and non-ambulatory patients. In order to assess disease progression between subsequent measuring moments, we will perform the Wilcoxon signed-rank test (nonparametric continuous paired data) andtheMcNemar'stest (categorial paired data).
To visualize the correlation between several parameters, we will show our results in Scatter Plots. Spaghetti Plots will be used to show disease progression.
The low number of included patients will be kept in mind while we will interpret our results.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version, date, see for the most recent version: www.wma.net) and in accordance with the Medical Research Involving Human Subjects Act (WMO).

8.2 Recruitment and consent

We will contact the patients known at our centre via their treating physicians with a letter in which we ask them to participate in this study. They will be asked to return the

answering form by mail.
We will contact colleagues at other neuromuscular and rehabilitation centres to identify patients. Patients will be contacted by their treating physician.
We will also recruit through patient organizations. An advertisement is placed on the website and/or social media of these organizations, or a patient information letter is sent to the patients known to have this condition.
We will also recruit via our own social media.

8.3 Objection by minors or incapacitated subjects

If children object to participate in this study (defined as: the promovendus (MD) is not able to motivate the child to perform the measurements, also not after a 30-minute break in which the child was able to play and have a snack), the study will be ended for that participant.

8.4 Benefits and risks assessment, group relatedness

We aim to study the natural history of these groups of patients to prepare the groups of these disorders for clinical trials which are in preparation. Since so little patients are available, we will ask both children and adults to participate in this study. This study is a preparation for clinical trials in these conditions and may facilitate the proper conduction of the clinical trials in these conditions. For the patient, the conduction of so many tests is without any doubt burdensome. Therefore, we reduced the number of test to to-our-opinion the absolute minimum. In addition, we will call every patient two weeks after each visit to the hospital to discuss and evaluate the burdensomeness of the research day(s). We have discussed our protocol with Spierziekten Nederland and Spieren voor Spieren. We will make a summary of the measurements after the first measurement and at the end of the study, when indicated answering a question from clinical care.

8.5 Compensation for injury

The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO). This insurance provides cover for damage to research subjects through injury or death caused by the study.
The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

8.6 Incentives

No incentives, we will try to arrange a nice present for when the study is complete (e.g. a trip to the zoo). Travel costs and lunch are reimbursed. If patients are expected to be at the hospital for two subsequent days in order to complete all measurements, they will be offered a free overnight stay at the Radboud hotel or another (nearby) accommodation that fits their requirements.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

All records identifying the patients will be kept confidential and, to the extent permitted by the applicable laws and/or regulations (Dutch Personal Data Protection Act), will not be made publicly available.
Patient data is coded using codes not reducible to the patient, on patient initials or birth-date, e.g. SEPN001, SEPN002, or MDCA001, MDCA002 etc.
The Coordinating and Principal Investigators and their designee will have access to the source data and to the key of the code during the study. After publication of the study, the

key will be in an encrypted document only on the Coordinating Investigators hospital hard drive (which is regularly backed up).

9.2 Monitoring and Quality Assurance

Monitoring will take place

9.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

9.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

9.5 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

9.6 Public disclosure and publication policy

We will publish our data, independent on the outcome.

10. STRUCTURED RISK ANALYSIS

This study does not concern any product: medicinal product, food product, or medical device. There is a small risk for minor injury, e.g. when a patient falls. However, since we use all functional test using movements to which most patients are familiar (i.e. walking, transfers, etc), the patient will be able to estimate his/her own risk. We don't include tests in which we push patient to their physical limits. We conclude that this study has a negligible risk.

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Supplementary table 1

		Ambulant patients	Non-ambulant patients	Time (min)	Every assessment	Yearly
Functional outcome measures	CHOP INTEND (< 2 years old)	x	x	'short period of time'	x	
	Hammersmith Infant Neurological Examination (HINE) (< 2 years old)	x	x	'quick'	x	
	Muscle power measurements (≥ 2 years old) Hand-held dynamometry (≥ 5 years old)	x	x	5	x	
	Motor Function Measure-20 (2-7 years old) Motor Function Measure-32 (> 7 years old)	x x	x x	30 40	x	
	30 seconds sit to stand test (≥ 2 y/o)	x	x	1	x	
	Graded and timed function tests (≥ 2 years old)	x		15	x	
	10 meter walk test (≥5 years old)	x		1	x	
	6-minute walking test (≥5 years old)	x		7	x	
	Functional Ambulation Category (≥5 y/o)	x	x	1	x	
	Hammersmith Functional Motor Scale (HFMS) (≥2 years old)		x	12	x	
	Vignos and Brooke scale (≥ 2 years old)	X	X	2	x	
	Pediatric balance scale (2 – 17 years old)	x		15	x	
	Mini Balance Evaluation System Test (≥18 years old)	x		15	x	
	Range of motion of ankle (contracture Achilles tendon) and elbow	x	x	4	x	
	Accelerometry for 7 days at home (non-dominant hand, ≥2 years old)	x	x	-	x	

Clinical endpoint/questionnaires	Checklist individual strength questionnaire (≥18 y/o)	x	x	10	x	
	Individualized Neuromuscular Quality of Life Questionnaire (INQoL) (≥18 y/o)	x	x	20	x	
	Activlim questionnaire (≥6 years old)	x	x	3	x	
	PedsQL generic quality of life, neuromuscular module and Multidimensional Fatigue Scale (2-17 years old)	x	x	15	x	
	Egen Klassifikation scale version 2 (EK2) (≥ 16 years old and good understanding of the English language)		x	10	x	
	Wong-Baker Faces Pain Scale (≥2 y/o)	x	x	1	x	
	McGill pain questionnaire (≥12 years old)	x	x	15	x	
	Impact on Participation and Autonomy (IPA) (≥18 years old)	x	x	20	x	
	SF36 quality of life scale (adults only)	x	x	5-10		
	Borg Rating Scale of Perceived Exertion	x	x	1	x	
	Neurological examination and medical history	x	x	30	x	
Surrogate endpoints	Respiratory function test (≥ 5 years old)	x	x	30	x	
	ECG (≥ 2 years old)	x	x	5		x
	Cardio-echography (≥ 2 years old)	x	x	30		x
	X-ray of the spine (≥ 2 years old)	x	x	15		x
	Muscle ultrasound (including ultrasound of diaphragm)	x	x	90	x	
	Muscle MRI (≥ 10 years old)	x	x	60		x
	DEXA scan (≥ 2 years old)	x	x	20		x