Outcome measures in Duchenne muscular dystrophy

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Chapter 7

Summary and general discussion

Summary

The overall aim of this thesis was to identify outcome measures in Duchenne muscular dystrophy (DMD), specifically for non-ambulant patients, that are able to detect a clinically relevant difference in a relatively short period of time compatible with the duration of a clinical trial. The use of such outcome measures could lead to smaller sample sizes in such trials with a lower burden for patients.

In **chapter 2**, we reviewed the considerations provided by patients and/or caregivers for not taking part in three observational studies on patients with DMD and one study on patients with Becker muscular dystrophy (BMD). We first assessed if age, travel-time, *DMD* gene mutation and age at loss of ambulation, derived from the national patient registry, the Dutch Dystrophinopathy Database, were comparable between participants and non-participants. This showed that participating patients were overall representative of the eligible sub-population for their study. Exceptions were the lack of patients with distal mutations upstream of exon 63 in all studies, and a younger age of participants in the study that investigated upper extremity outcome measures in non-ambulant DMD patients (chapter 4, 5 and 6). This suggests that studying more advanced disease stages in DMD could be more challenging. The most frequently reported considerations were 'Burden of protocol' (38%), ' MRI' (30%), and 'Travel-time' (19%).
Our results highlighted that nationwide patient recruitment registries can be used to compare participants and non-participants to ensure that observational research is representative of the whole patient cohort. Furthermore, the results suggest that to facilitate and increase patient participation several factors could be addressed: 1) optimizing involvement of patients in the design of new studies, 2) improving the MRI experience, and 3) integrating observational research and clinical care.

In **chapter 3**, we assessed the additive predictive value of vastus lateralis (VL) fat fraction (FF) measured using quantitative MRI (qMRI) to age on loss of ambulation (LoA) in two cohorts: one from the Leiden University Medical Center (LUMC; n=19) and the other from Cincinnati Children's Hospital Medical Center (CCHMC; n=15). We found an excellent interobserver reliability for VL FF determined by qMRI, which supports the feasibility of including muscle qMRI data from multiple centers in studies in DMD. We found VL FF to have added predictive value to age on LoA in the cohort from the LUMC (hazard ratio 1.15, 95% confidence interval 1.05-1.26, p=0.003). This is important because it suggests a direct relation between an important disease milestone and the outcome measure qMRI FF, which is required to use this outcome measure as primary endpoint in clinical trials.
Results could not be replicated in the cohort from the CCHMC (hazard ratio 0.96, 95% confidence interval 0.84-1.10, p=0.569). This may be explained by a limited number of LoA events (three) that occurred in this cohort of less severely affected participants. VL FF results were presented in growth charts, which could be used to stratify patients in clinical trials

with a small number of participants. Although results should be confirmed in a larger cohort with prospective determination of the disease milestone, our results support the use of FF assessed with qMRI as a primary endpoint or stratification tool in clinical trials in DMD.

In **chapter 4** the same approach was used as in chapter 3, but this time in a prospective study and for the relation between qMRI FF of an upper extremity muscle and loss of a milestone in non-ambulant patients with DMD (n=20). We assessed the additive predictive value of elbow flexor FF (48 MRIs) to age on loss of hand-to-mouth movement. Four-point Dixon MRI scans of the right upper arm were performed at baseline and at the 12-, 18-, or 24-month follow-up. Loss of hand-to-mouth movement was determined at study visits and by phone calls every 4 months. Elbow flexor FF predicted loss of hand-to-mouth movement on top of age in non-ambulant DMD patients (hazard ratio 1.12, 95% confidence interval 1.04-1.21, p=0.002). This result further established the relation between qMRI muscle FF and important disease milestones in DMD, thereby backing the clinical relevance of a potential effect of a therapy on qMRI muscle FF. It thus further supports use of qMRI muscle FF as primary endpoint in DMD and potentially facilitates the design of clinical trials via stratification based on disease severity and progression in qMRI FF.

In **chapter 5**, we presented qMRI results of the hand muscles from the longitudinal upper extremity outcome measure study in non-ambulant DMD patients. Fat replacement was minimal (9.7% versus 7.7%, p=0.043) and the T2 relaxation time of the muscle compartment ($T2_{water}$) was increased (31.5 ms versus 28.1 ms, p<0.001) compared to healthy controls. These results indicated that the thenar muscles were in an early stage of muscle pathology in our cohort of non-ambulant patients. Furthermore, the decrease in pinch strength (2.857 kg to 2.243 kg, p<0.001) and Performance of the Upper Limb (PUL) 2.0 total score (29 points to 23 points, p<0.001) over one year showed that there was measurable disease progression within the possible duration of a clinical trial. At follow-up, all participants still had useful function of the hands. Together with the moderate to strong correlation between muscle size and function, these results indicate that the thenar muscles are a valuable and quantifiable target for systemic or local therapy even in later stages of the disease. As a next step in outcome measure research, a direct relation between muscle qMRI or pinch strength and an important disease milestone still needs to be established in DMD.

In **chapter 6** we described results from the longitudinal upper extremity outcome measure study in non-ambulant DMD patients, concerning four innovative new outcome measures of upper extremity motor function using devices from the gaming industry. These outcome measures were developed in the form of a game and they provide a continuous outcome parameter without a maximum score, in order to overcome disadvantages of current outcome measures, such as a floor and ceiling effect, observer dependency, and motivational issues. Active range of motion (aROM) of the wrist and hand was determined using the Leap Motion sensor, and the Microsoft Kinect v2 sensor was used to determine three other

outcome measures. A stepwise approach was used to assess all technological outcome measures on quality control, construct validity, reliability, concurrent validity, longitudinal change and patient perception. The Ability Captured Through Interactive Video Evaluation (ACTIVE) game was used to determine the reached volume of the arms via the Kinect sensor, and showed the most promise in the stepwise approach. ACTIVE differed between patients and healthy controls ($p<0.001$), declined significantly over 12 months (5.6 points, $p=0.030$), and was appraised as being fun by patients. All four outcome measures were also correlated with and compared to results from PUL 2.0. There was a strong correlation of ACTIVE with PUL (rho=0.76). However, the standardized response mean (SRM) of ACTIVE was below 0.8, which is a commonly used threshold to determine responsiveness over time. PUL 2.0 performed similar to ACTIVE on the pervious items of the stepwise approach, but had an SRM above 0.8. Outcome measures based on hardware and software from the gaming industry can overcome problems such as observer dependence and lack of patient motivation. However, lack of insight in constraints of the software and hardware due to intellectual property, and possible software updates and hardware discontinuation, make these outcome measures a black box that could jeopardize their use in clinical trials.

General discussion

For the rare and fatal muscle wasting disease DMD, there is currently no fully approved therapy available beside glucocorticoids .[1] Improved care and glucocorticoids have led to a longer life-expectancy for patients, and therefore they go longer through life in the non-ambulant phase.[2] In this non-ambulant phase patients are progressively limited in their upper extremity functioning and therefore in their independence.[3] This leads to an urgent medical need for non-ambulant DMD patients. Many clinical trials with new drugs currently focus on the ambulant phase of the disease, although there are exceptions (NCT04371666, NCT01027884, NCT04004065). Attaining an effective and approved drug is a long and expensive process. Due to a progressive reduction in muscle tissue to be targeted by drugs, separate clinical trials need to be performed in non-ambulant patients, therefore specific outcome measures are required for this disease stage.[4, 5] These outcome measures should demonstrate sufficient reliability, construct validity, concurrent validity, longitudinal change, accessibility and clinical relevance. For this, natural history data of these outcome measures is required.

The 'best' upper extremity outcome measure

There is no ideal outcome measure. Which upper extremity outcome measure is optimal for a clinical trial differs depending on the targeted population, mechanism of action of the therapy, and the goal of the study.[6] Based on the results in this thesis, the following different types of outcome measures and the types of studies they would be appropriate for will be discussed: 1. clinical outcome measures that require specific patient related tasks, such as Performance of the Upper Limb, 2. patient reported outcome measures, and 3. biomarkers that for example reflect tissue characteristics, such as FF measured using muscle MR.

Clinical outcome measures

Clinical outcome measures often are more aligned with symptoms experienced by the patient compared to biochemical changes at tissue level, such as an increase in dystrophin. Therefore, providing clinical relevance is more straightforward.

Strength measurements are clinical outcome measures that have a relatively direct relation with a treatment effect, but are not inherently clinically meaningful. Pinch strength MyoPinch is an example of such an outcome measure, that is promising in an older and more progressed non-ambulant population in which the PUL 2.0 has reached its ceiling effect. The observed decline in pinch strength over 12 months in our non-ambulant cohort (chapter 5), was in agreement with the slightly older and weaker cohort described by Seferian et al.[7] The patients' view on strength tests was similar to PUL 2.0. After establishing clinical relevance of pinch strength via its ability to predict loss of a milestone, it could be used as outcome measure in the (late) non-ambulant phase.

The PUL 2.0 is an established outcome measure in non-ambulant patients. In chapters 4, 5 and 6, we showed an annual decline of 3 points in our cohort of patients who lost their

ambulation up to six years before study entry. This was similar to the decline in a recent study including 90 non-ambulant DMD patients, in which patients had an intermediate to fast decline (4-8 points) in the patients with entry level 2 to 6, and a small decline in patients with entry level 0-1 (1 point).[8] In our cohort, patients had an entry level of 2-5 points. The predicted sample size of 39 participants per study arm for PUL is smaller than for other previously studied outcome measures in non-ambulant DMD, which demonstrates the PUL's sensitivity to change.[9] The patient's view on the PUL was also demonstrated to be favorable (chapter 6). Despite disadvantages of observer-dependency and a floor and ceiling effect, we propose the PUL 2.0 as the preferred choice of outcome measure in studies that include per study arm 40-50 non-ambulant DMD patients with an PUL 2.0 entry level of 2-6 points.

In our data, the ACTIVE had a much larger predicted sample size per study arm (169 patients, chapter 6), compared to a study in spinal muscular atrophy (SMA, 28 patients).[10] This seems to demonstrate a higher sensitiveness to change of ACTIVE in these patients treated with nusinersen, although it can probably be attributed to the effectiveness of nusinersen.[10] The patient's view of ACTIVE was similar to PUL, except that ACTIVE was more tiring. An important limitation for using outcome measures, such as ACTIVE, are software updates which are out of control of the researchers. At the time of writing this thesis, a software update for ACTIVE had already taken place and the Microsoft Kinect v2 sensor had been taken out of production.[11] To overcome the constraints imposed by software updates, it is essential to share analysis algorithms with the community or even make them openly available, and/or to have a standardized validation process to ensure that software updates do not affect the outcome measure results. Although PUL was more sensitive to change in the non-ambulatory stage compared to ACTIVE, ACTIVE might be more sensitive to change in the (late) ambulatory stage, where patients have more retained shoulder function.

The PUL and ACTIVE are examples of outcome measures that are determined by observers and cameras/computers respectively. Observer dependent outcome measures, such as PUL and North Star Ambulatory Assessment, require training, are prone to inter- and intra-observer variability, and often have a ceiling effect.[8, 12] Their outcome also often has an ordinal scale, which hampers the use of linear statistics.[8, 12] Outcome measures determined by cameras/computers, such as ACTIVE and MyoPinch, require limited training and have continuous scales, but do require a sometimes expensive setup. They are also prone to software updates and sometimes have difficulty to register patient movements properly. Currently, patients also need to visit study sites to collect data for these outcome measures, while patient representatives stimulate the use of measurements that can also be performed from home, thereby removing the burden of traveling (chapter 2).[6] Future studies should aim to apply clinical outcome measures within the home environment.

Patient reported outcome measures

Outcome measures can also be patient reported questionnaires that can be performed from home. The DMD Upper Limb Patient Reported Outcome measure (PROM) did not show

significant change over 12 months in our small cohort of non-ambulant patients (*n*=13; chapter 5). A major advantage of the PROM is that data can be acquired off-site and that it can be filled in by parents for patients with neuropsychiatric comorbidity, such as autism spectrum disorder. Off-site completed forms are sensitive to missing data, but this can be overcome by prompt checking of received forms. The use of PROMs is advocated by patient representatives and the European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA), although currently it should still be supported by objective or functional outcomes.[4-6, 13] If PROM would demonstrate change over time in a larger cohort of non-ambulant patients, it could be the preferred outcome measure in large studies that strive for limited site visits and wish to be able to include non-ambulant DMD patients with neuropsychiatric comorbidity.

Biomarkers

The biomarker qMRI muscle FF reflects the increasing amount of fatty tissue within skeletal muscle with disease progression in DMD, and therefore is seen as a marker of loss of muscle tissue. It has been studied extensively in ambulant DMD.[14-30] qMRI FF data of the upper extremities in DMD patients is still sparse, because of the smaller muscle mass and position away from the center of the MRI, which decreases the image quality and frequently causes artefacts.[29] In non-ambulant DMD patients there is the extra challenge of contractures, burden of transport and travelling, difficulty to find a comfortable position in the scanner, and with increasing disease severity contra-indications of spinal fusion and daytime assistive ventilation become more prevalent (chapter 5).[6] Chapter 4 and 5 added to the available literature and suggested positioning on the side to overcome the issue of positioning the upper extremity muscles away from the center of the MRI.

Currently, qMRI FF is not yet approved by regulatory agencies as primary endpoint for clinical trials. Regulators state that they will consider all outcome measures, but that clinical relevance has to be demonstrated. An extensive and time-consuming reviewing process is required for formal approval, such as for the stride velocity 95th centile, which is now approved as secondary endpoint.[6, 31] To establish clinical relevance of qMRI muscle FF we studied and demonstrated its additive predictive value to age on loss of the disease milestones ambulation and hand-to-mouth movement (chapter 3 and 4). This predictive value to age was required in addition to previous correlations between FF and clinical outcome measures, because DMD is a progressive disease and any parameter that changes consistently over time, such as shoe-size, would correlate to a declining functional measure. By assessing the additive predictive value of qMRI muscle FF on top of the predictive value of age, we demonstrated the independent predictive value of qMRI muscle FF. The additive predictive value of qMRI FF of the lower extremities to LoA was also demonstrated by a recent study which showed a similar relation.[32]

The vastus lateralis is the preferred muscle to study in the ambulant phase, because of its sensitiveness to change in that phase and relation with ambulation.[18, 33] For the upper extremities, there is no consensus on which muscle (group) to use, but based on the

demonstrated clinical relevance of qMRI FF of the elbow flexor muscle group, we propose to use this muscle in the early non-ambulant phase. After approval by the regulatory agencies to use qMRI muscle FF as primary endpoint, its sensitiveness to disease progression could lead to shorter trials with potentially a lower burden for patients, although MRI remains less preferred by some patients. It would be most suitable for studies that seek to include a small number of patients from the age of 5 years old up to the early non-ambulant phase.

Determining clinical relevance of outcome measures used in clinical trials

As discussed previously, clinical relevance is essential for each outcome measure, before it can be used in clinical trials. An ideal way to demonstrate clinical relevance in a progressive disease is via the relation of an outcome measure to predict the moment of loss of an important disease milestone. Such a milestone needs to exist for every disease stage. Loss of the milestone has to be unequivocal and easy to determine, and preferably it can both be reported by patients and determined by an observer, which is the case for the ability to ambulate and bring a filled glass to the mouth. This requires extensive natural history studies with long-term follow-up, which leads to a high burden for participants and thus problems in participation (chapter 2). These large studies are especially necessary to determine the exact clinical relevance of an outcome measure, such as which percentage of slower increase in FF due to a therapy would lead to 2 years later LoA. A solution for these long-term studies with a high burden for patients is to integrate natural history studies in visits that take place as part of the outpatient clinical care (chapter 2). When important outcome measures are integrated in such visits, these can also be used for clinical trial phase IV, the post-marketing surveillance phase. In the Netherlands, for this reason the Duchenne Center Netherlands has set-up a training program for physiotherapists and occupational therapists from Academic Medical Centers and rehabilitation centers, to be able to gather high quality data as part of the regular outpatient clinical care. Data can be collected prospectively in the national patient registry, the Dutch Dystrophinopathy Database, and in the national biobank for DMD and BMD.

Even for the seemingly straightforward milestone LoA, different definitions have been used in literature, such as the inability to perform the 10 meter walk/run test at hospital visits or a score ≤25% on the D1 subscale about standing position and transfers of the Motor Function Measure.[20, 28, 34, 35] Similar to another study[34], we defined LoA as the patient being unable to walk 5 meter without assistance or orthoses, and determined this by conducting a detailed interview at each hospital visit (chapter 3). Because it has a large impact on daily life when patients become wheelchair bound, in our view it was feasible to determine LoA to a month's precision. Nowadays, captured photo's/video's on smartphones can also aid in defining this disease milestone. To increase precision without increasing the burden for patients and continue milestone determination when restrictions were in place due to the COVID-19 pandemic, a phone call each quarter could be performed. We propose for all

stakeholders to use similar methodology to determine LoA, because it allows for off-site determination of this milestone.

For the upper extremity, different definitions of an hand-to-mouth function have been included in the Brooke upper extremity scale, PUL and PROM, and have also been used as milestone.[3, 36-38] Our definition was moving a filled glass (total weight 200gram) independently to the mouth using the right hand and allowing support of the elbow on a table (chapter 4). We chose the right hand for a direct relation with the elbow flexor muscles of the right upper arm on qMRI, but for other purposes it can be advisable to use this milestone for either the dominant or both hands. [3, 36, 37] More than 40% of hand-to-mouth movement can be attributed to the biceps brachii and brachialis muscles.[39] Moving a small weight to the mouth is part of vital daily life activities, such as drinking, eating and performing personal hygiene such as brushing teeth unaided. Patients and families assisted in the development of the PUL and PROM, and incorporation of the hand-to-mouth movement in these outcome measures confirmed its clinical relevance for patients and parents.[37, 38] The proposed method of determination of the milestone is again via a detailed interview at each hospital visit and a phone call each quarter.

Previous studies used 'no useful function of the hands' as upper extremity disease milestone of hand function in the late non-ambulatory stage.[3, 40] In our longitudinal upper extremity outcome measure study in DMD, no patients have reached this level of inability and a previous study showed that the time interval between loss of hand-to-mouth function (median 15 years) and loss of useful function of the hands (median 23 years) is large.[3] Compared to ambulant patients, non-ambulant patients spend significantly more time on playing (online) video games, which in recent years has become an important tool for social interaction.[41] We proposed a disease milestone of hand function that should fall within the described time interval and is more applied to daily life, i.e. the ability to play a video game for 10 minutes using a game controller (chapter 5). Developers of game controllers focus increasingly on accessibility to all, which has led to new devices such as the Xbox Adaptive Controller.[42, 43] Amongst our study participants, many patients switched over the course of the study from a traditional game controller to smaller game controllers, such as the Nintendo Switch.[42] A longer follow-up duration in our study should clarify whether playing video games for 10 minutes using a game controller is a useful addition to the disease milestone toolbox in DMD.

Future perspectives

The ideal outcome measure does not exist, but there is an optimal outcome measure for every clinical trial in non-ambulant DMD patients based on the mechanism of action of the therapy, disease phase and the study design.[6] Currently, the PUL 2.0 seems to be the preferred primary outcome measure for skeletal muscle function in a clinical trial in larger non-ambulant population with a PUL entry level of 2-6.

Several gaps in research are still present and need to be addressed. Demonstrating clinical relevance is important for all outcome measures and is supported by regulators. The PUL 2.0 has already been used as primary endpoint in clinical trials, but it has not yet been established what a decline of one or two points on this scale means functionally for the patient or which difference would be clinically relevant. This could be studied by assessing the ability of PUL 2.0 to predict loss of an important disease milestone. This is also the case for the MyoPinch, PROM, and ACTIVE. We proposed hand to mouth function and gaming as disease milestones for the upper extremity. Although the PROM and PUL and the items they contain have been developed with feedback from patient representatives, no extensive studies on patient preferences in disease milestones have been performed.[37, 38] This knowledge on disease milestones would aid in developing studies to assess clinical relevance of a detected change and of outcome measures as a whole, such as the PUL 2.0, MyoPinch, PROM, and ACTIVE. For PROM, also sensitivity to change over time in a larger cohort of non-ambulant DMD patients is required before it can be considered as primary endpoint in clinical trials. Furthermore, the sensitivity to change of ACTIVE is currently too low for it to be considered as primary endpoint in clinical trials. A study in a less severely affected DMD patient population with more retained shoulder function would provide insight whether ACTIVE is more sensitive to change in that population. For qMRI FF, clinical relevance in relation to important disease milestones in general has been established. It is, however, important to have a quantitative estimation on the percentage change in FF that is needed for a single year delay in reaching a disease milestone. qMRI muscle FF could also be used as primary endpoint to study the effect of a local therapy and compare differences between a treated and untreated arm in small trials. As a first step, the natural history of qMRI muscle FF in the left and right arm has to be compared.

Some of the described gaps in research can be addressed by integrating important outcome measures, which are assessed partly for research, into visits as part of the outpatient clinical care. In the Netherlands, a biobank has been set-up by the university medical centers to capture clinical care data without requiring extra effort from patients, so that additional studies that are integrated in care do not have to gather these data separately.

In this thesis, we found that the PUL 2.0 seems to be the preferred outcome measure for skeletal muscle function in clinical trials for non-ambulant DMD patients at this time. The assistance of patients and parents in the development of PUL 2.0 supports its clinical relevance, but its ability to predict loss of a milestone would further aid in establishing the clinical relevance of PUL 2.0. qMRI muscle FF was shown to detect clinically relevant change, but poses practical disadvantages in non-ambulant patients and is less preferred by patients and therefore not ideal for large patient groups. MyoPinch, PROM and ACTIVE were also identified as promising outcome measures, but gaps in knowledge need to be addressed first. Use of these outcome measures could lead to smaller sample sizes and/or a shorter duration of trials with a lower burden for patients. Finally, even in advanced stages of the

disease, clinically relevant muscles are relatively preserved and therefore warrant our effort to search for effective treatments for these patients as well.

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