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Workshop report

Report on the workshop: Meaningful outcome measures for Duchenne muscular dystrophy, London, UK, 30–31 January 2017

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1. Introduction

With the rapid increase in the number of interventional clinical trials in Duchenne muscular dystrophy (DMD) over the past few years, the need for a frank and honest discussion between those designing and using outcome measures has never been greater. In January 2017 clinicians, physiotherapists, imaging experts and patient advocacy group representatives came together for a two day workshop at *The Foundry* in London, UK, for a critical review of the different clinical outcome measures used to date in natural history studies and interventional trials for DMD. Participants were joined on the second day by regulatory and industry stakeholders. Sessions were prepared in advance of the workshop by working groups and were led by experts for specific outcome measures relevant to different stages of boys and men with DMD. The workshop focused on clinical and imaging outcome measures that are used as primary and secondary endpoints in trials and not on exploratory endpoints such as serum biomarkers.

2. Pathomechanism of DMD

DMD is caused by out of frame mutations in the X-chromosomal *DMD* gene leading to a lack of dystrophin expression, which ultimately leads to a loss of muscle fibre membrane integrity, inflammation, fibrosis and replacement of skeletal muscle by fat. Progressive wasting of skeletal muscles, which is correlated with the clinical symptom of progressive weakness, is the predominant pathology in DMD. Skeletal muscle has important physiological functions beyond force generation and helps to regulate circulation, respiration, bone mineralisation and intermediary metabolism, all of which are affected by muscle wasting and contribute to the complex phenotype of DMD.

Besides the structural function of dystrophin, often described as a shock absorber, the sub-sarcolemmal cytoskeletal protein has also been reported to play a role in signal transduction. Despite the fact that dystrophin is expressed in all skeletal muscles, it remains unclear why some muscles seem to be better protected than others, as can be illustrated by muscle imaging. Even 30 years after the discovery and first characterisation of dystrophin, many questions about the precise pathomechanisms of DMD remain unsolved. Furthermore, much of our understanding of the disease is based on animal models and questions remain regarding how much these models can tell us about the pathogenesis of DMD in patients.

3. Drug trials in DMD and the regulatory position

Both the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have published guidelines on clinical investigation of medicinal products for treatment of DMD and Becker muscular dystrophy (BMD) [1,2]. For sponsors, healthcare professionals and patients and families it is important to understand the regulators' view on outcome measures.

There are no specific requirements from the EMA about the tools to be used in DMD trials and the FDA has no list of required or recommended clinical outcome measures. Therefore, it is up to the investigator to demonstrate that those outcomes selected for use in a trial are relevant as the primary endpoints according to the age of the patient and stage of the disease. Novel outcome measures are encouraged where they can be shown to measure clinically meaningful effects with the strong advice from the regulators that patients and patient

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advocacy groups should be engaged in discussions early on the selection and development of efficacy endpoints.

Currently, ataluren is conditionally approved by the EMA, based on placebo-controlled trials [3,4]. In the USA the FDA gave eteplirsen accelerated approval based on a surrogate endpoint (increased dystrophin levels in some of the treated patients) in a trial that had a short placebo group. Nevertheless, the FDA stressed that functional efficacy of this drug has not yet been confirmed and requested the sponsor (Sarepta) to provide evidence of this before 2021 [5].

The group discussed how, based on recent conversations with EMA [6] there is openness to new proposals provided they can be justified. The consensus was that the best way to start this process is through consensus building from experts and a collaborative effort from all stakeholders. A paper/consensus statement should be considered to be drafted in order to inform decision makers and make clear the informed and accepted position from these stakeholders [6,7]. This is important to avoid having the same discussions repeated time and again.

The group also stressed that confirmatory trials should be randomized and double blind placebo controlled. Six months is the minimum for a trial on the improvement of disability but even 12 months is sometimes inadequate for a pivotal study, with longer trials of 18–24 months in some instances recommended, depending on the effect size of the compound under investigation and the sensitivity to change of the primary outcome measure. Recent FDA advice suggests that these longer studies may substantially increase statistical power and should be considered accordingly [2].

Natural history cohorts as control groups *may* be acceptable in the future but only with a clear explanation of their use rather than a placebo group and the regulators should always be engaged early on. Detailed evidence will need to be presented to show that the study is not therefore overly-susceptible to bias [1,2].

4. Current outcome measures: where are the gaps?

4.1. Young DMD boys

Over the past few years it has become more apparent that classifying DMD patients into ambulant and non-ambulant patients is a far too simplistic approach and it is important to develop and validate outcome measures for patients of various age ranges and with a range of motor abilities.

Anne Connolly reported how current trials have so far mainly targeted the more ‘cooperative’ (and ambulant) group of boys > 4–5 years and < 10–13 years. This means that nearly 100% of those less than 5 years are excluded from participating. Both the Bayley III and Griffith scales, have recently been used in studies showing that DMD boys differ in all neurodevelopmental domains compared to healthy controls [8,9]. Regulators welcome discussion with health care professionals and families about the appropriateness of their use in clinical trials [2]. The North Star Ambulatory Assessment (NSAA), a scale specifically designed for DMD, but validated in children from the age of 5 years, has recently been revised to address the functional assessment of younger DMD boys [10]. The items are now divided into expected achievements by specific age categories, and are currently being validated in this younger age range. Eugenio Mercuri suggested using the NSAA as a percentage of the score that should be achieved by a healthy boy of the same age.

Further work is needed to better understand the relationship between neurodevelopmental delay and motor function in this population. In some DMD boys, particularly boys with mutations affecting the brain dystrophin isoforms, there is often a delay in achieving motor activities, such as climbing stairs with alternate steps, which are generally achieved at a later age compared to their peers [9]. A better understanding of the expected development of DMD boys with different mutations compared to the age-matched normal population is crucial in order to observe the impact of interventional therapies in this youngest age group. For this reason, a collaborative effort to pool data from different groups/studies is necessary.

Suggested next steps were merging existing datasets from the US and EU (Italy, UK, Belgium, US network) for both developmental scales (Bayley III and Griffith scales) and the NSAA in order to have larger cohorts for boys under 5 years.

Social skills in very young boys should also be evaluated – the element of hyperactivity present in 40% of older children with DMD (via the ADHD test) is likely to also be present in 2 year olds (and younger).

It was also suggested that in the future, muscle ultrasound and/or electrical impedance myography (EIM) may have a possible role in the assessment of young patients.

4.2. Ambulant DMD boys

Most interventional trials in DMD to date have been conducted in ambulant patients using the 6-minute walk distance (6MWD) as the primary endpoint [11]. The 6MWD has been validated in DMD as a global/integrated measure of systems involved in walking. It has been concurrently validated with stride length and cadence (gait pathomechanics), knee extension strength (NM/Kg) (quantitative lower extremity strength), heart rate determined energy expenditure index (biomechanical efficiency), 10 min continuous step activity (endurance) and the NSAA (gross motor skills) [12,13]. In the last decade several studies both in the US and Europe have reported details of its validity and correlation with other measures including quality of life [14,15,16].

Over the past few years the NSAA has gained more attention in ambulant DMD patients. The NSAA measures 17 different aspects of function of increasing difficulty (see Fig. 1).

Each item can be scored from 0 to 2 and the scale provides a global score by adding the scores of the individual items. A lot of work has recently been done to analyse the scale in different ways, such as introducing a linearization that allows conversion of the raw scores into a linear score (0 to 100) [17,18]. The linearized scoring system allows a more psychometrically robust scoring across a wider spectrum of disease stages and is useful for studies of 18–24 months.

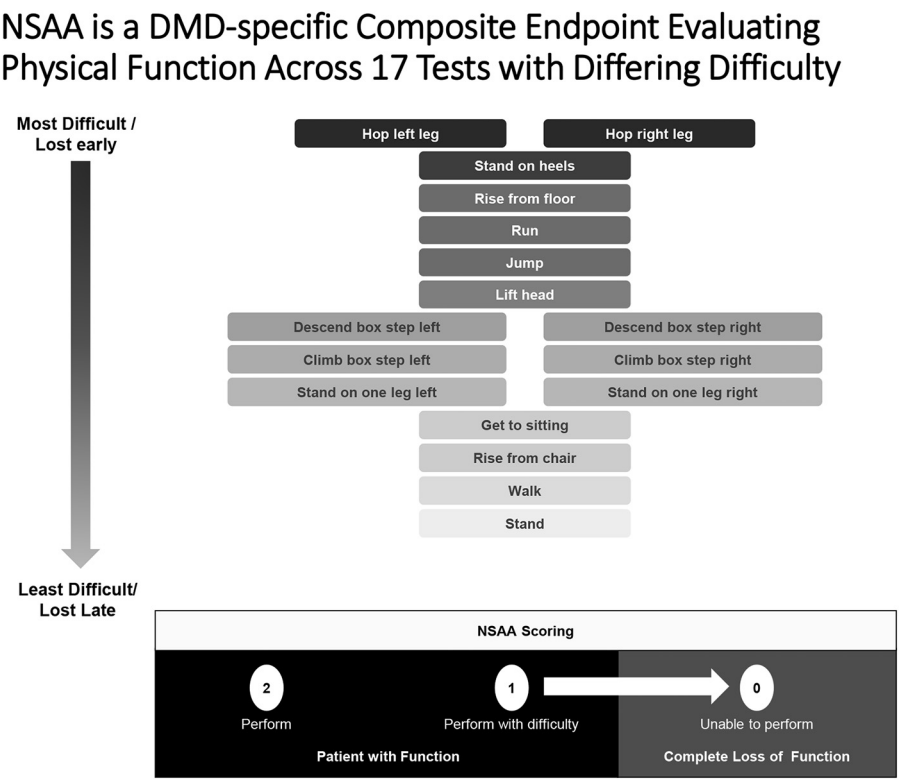

Fig. 1. Schematic depiction of the NSAA tests and scoring method. (Kindly provided by Craig McDonald).

Craig McDonald presented a new way to look at the North Star data – by analysing the loss (or not) of function, i.e. assessing in how many items there has been a loss of function with 'a shift' to a score of 0 that indicates that a meaningful functional activity has been completely lost [19]. This loss of function is often more significant to patients and families than a less granular total score.

During general discussion, industry representatives confirmed that there is increasing interest around the NSAA, particularly now that the scale has been extended for use in much younger boys [10].

The patient community (Alex Johnson) also felt that when called as a patient expert at the EMA, it is often easier to explain how the North Star correlates with a clinically meaningful effect.

Suggested next steps were to look at the comparison between the 6MWD and the NSAA shift analysis. Data would be interesting to establish how the 6MWD data correlates to a loss of function on the NSAA.

The workshop participants also felt that is important to establish the reliability of current natural history data in relation to placebo data. Work is in progress to compare the NSAA data with placebo data from interventional studies – it is desirable for this that all available placebo data are shared from studies.

Craig McDonald reported on the reliability and validity of the timed function tests. Prognostic value has been shown for time to stand and loss of stand ability, loss of 4-stair climb and loss of ambulation. Stair climb velocity data is now becoming increasingly available, and this also correlates with a loss of ambulation.

Stride length decreases with DMD disease progression and the ratio of stride length to height is a developmentally-adjusted anthropometric standard indicator of mobility restriction in DMD. This measure (Fig. 2) is useful for interventions targeting muscle mass and strength. Stride to height ratio is a reliable measure in ages 4 years and older and is sensitive to change in mobility over 12 months. Stride length correlates with the 6MWD ($r = 0.94$, $p < 0.0001$) and the timed 10 m and 25 m run/walk velocities ($r = -0.97$ for both, $p < 0.0001$) [20] and has been shown to be responsive to steroids in 4–8 year olds [21].

Activity monitoring of lower and upper limb movements may serve as measures for transitioning patients, as well as in ambulant or non-ambulant patients, thus covering the full spectrum of the patients' conditions [22]. Community based activity monitors may quantify very precisely stride length and stride speed in real life or in a controlled setting. These measures, if properly averaged, are highly reproducible (variability about 3%), show good correlation with the 6MWD and the NSAA and are highly sensitive to change, which theoretically allows the conduction of trials with far fewer patients. However, this requires properly calibrated devices specifically designed to precisely record foot and ankle movements, powerful algorithms able to handle large amounts of data, and specific methods of analysis to isolate clinically meaningful outcomes from a vast number of data points.

Table 1
Correlation between pulmonary function test and muscle strength (CINRG data courtesy of Heather Gordish–Dressman and the CINRG Group).

r^2 values reported	~N	FVC %P	FEV1%P	PEF %P	MIP %P	MEP %P
Time to run/walk 10 m velocity (m/s)	200	0.529	0.517	0.480	0.459	**0.540**
Time to climb 4 stairs velocity (tasks/s)	180	0.450	0.447	0.439	0.408	**0.464**
Time to stand from supine velocity (rises/s)	150	**0.468**	0.466	0.460	0.419	0.435
6MWD (meters walked)	55	0.033	0.044	0.042	0.034	**0.215**
9 hole peg velocity (pegs/s)	115	0.339	0.297	0.321	0.289	**0.372**
Egen Klassifikation	100	0.501	**0.515**	0.478	0.408	0.417
NSAA	60	0.064	0.071	0.047	0.045	**0.118**
Grip strength (lbs)	280	**0.366**	0.338	0.280	0.280	0.318
Elbow extensor strength (lbs)	135	**0.107**	0.097	0.083	0.045	0.105
Knee extensor strength (lbs)	135	0.180	**0.203**	0.195	0.059	0.104

The most significant correlations are in bold.

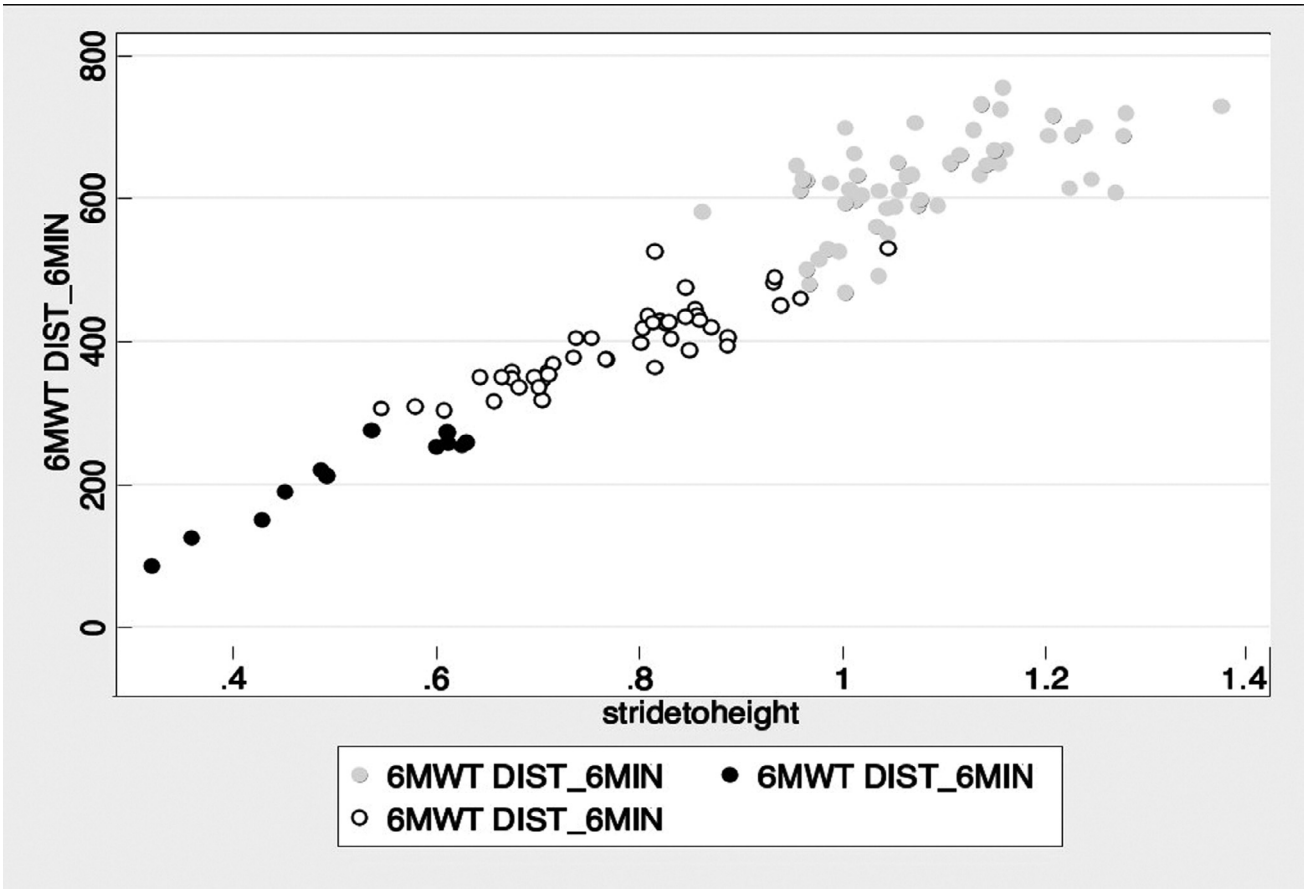

Fig. 2. Stride length/height ratio versus 6MWD in DMD in typically developing youth and boys with DMD aged 4–13 years [20]. (Kindly provided by E. Henricson, C. McDonald).

Several industry sponsored clinical trials in DMD have chosen the 4-stair climb as a primary endpoint. Natural history data on the relation between this and future milestones is scanty however. Pat Furlong commented on the 4-stair climb prompted by a question from industry about its clinical meaningfulness. She was able to give the view of patients and families to say that this measure indicates a level of privacy, self-care and ability to shower for example. It was also discussed that this outcome might be influenced by the reaction time of the tester. It was proposed that a strategy on the 4-stair climb should be built encouraging publication of existing and prospective data to develop a case on consensus supported by evidence.

4.3. Non-ambulant DMD patients

Developing appropriate outcome measures for this group of patients had until recently been neglected, as most interventional trials requested patients to be ambulant. The 6MWD and the NSAA are obviously not appropriate for boys that have lost ambulation and there is now a real need to develop and validate outcome measures for older DMD boys and men.

An important point is that non-ambulatory patients do not form a homogenous group in part because patients who have just lost ambulation have different assessment needs compared to older patients.

Respiratory function has been suggested as a meaningful and standardized outcome measure in non-ambulatory DMD patients and has recently been correlated with other functional and strength measures in both ambulatory and non-ambulatory patients [23] (Table 1).

In discussions about respiratory function it was agreed that Forced Vital Capacity (FVC) and grip strength seem to show good correlation. FVC and Forced Expiratory Volume in 1 s (FEV1) correlate with the Egen Klassifikation (EK) scale [24]. It was generally felt that more longitudinal pulmonary data over at least 2 years are still needed.

Anna Mayhew reported recent progress in developing and validating the Performance of Upper Limb (PUL) measure. The scale has 3 domains (shoulder, upper arm and lower arm/fingers) and allows monitoring of disease progression from proximal to distal in DMD. The scale has been validated, is suitable for multi-centre studies and is being used in several clinical trials [25,26]. Whilst there is a ceiling effect for young ambulatory patients, the PUL can be used across late ambulatory and non-ambulatory patients [27].

A publication of a Version 2 with a shortened protocol is in preparation that is more feasible and reliable in research and clinical setting.

The PUL is influenced by various factors including the Body Mass Index (BMI) and the range of joint movement. It correlates well with the 6MWD [15], the EK scale and the reachable workspace [28].

Other assessment tools have been developed over the past few years. Anna Mayhew and Laurent Servais explained that the MyoGrip, MyoPinch and MoviPlate, (also referred to as the Myo-tools), can be used to measure change in strength against the percentage of predicted strength by age. Reliability and sensitivity to change has been demonstrated [27,29,30]. The Myo-tools have already been used in interventional clinical trials in DMD and more longitudinal data are currently being collected. Grip strength and pinch strength, if normalized for patients' age, demonstrate a continuous decline of about 14% per year, which provides an outcome usable across a very large age range. Activity monitors have also been used to quantify upper limb movements in a controlled setting [22] and longitudinal data are currently collected. Such monitors allow measurements from patients' daily lives to be taken remotely and can be worn by the patient on a continuous basis or as instructed. Sensors are often included in the devices to measure acceleration or posture of the wearer and then transmit this data to a central point for collection and analysis. Additional exploratory outcome measures for the upper limbs are the reachable workspace and the ACTIVE system (video game based).

The impact of Standards of Care (SoC) on these outcome measures for non-ambulatory patients needs to be further evaluated, especially when considered for international, multicentre trials. Contractures and BMI, but also different steroid regimes, may be confounding factors for upper limb outcome measures and it is important to establish strict standard operating procedures (SOPs) for these assessment tools together with high quality training modules.

Pat Furlong highlighted the need for more information on outcome measures for older and adult patients. Young adults are often left out of clinical trials. She emphasised the importance of considering interventional studies in which they can be included where the primary outcome is safety, even where efficacy studies are not open to them.

A general discussion, involving industry representatives, regulators and health care professionals involved in care and clinical trials helped to identify further gaps or additional issues for outcome measures development. These can be broadly summarised into a few topics

1. Need for reliable longitudinal natural history data of patients with different mutations in larger cohorts and at different stages of the disease.
2. Need for measures that can be used across ambulatory and non-ambulatory patients.
3. Need for endpoints that reimbursement authorities (payers) accept.

In discussion of the above points, it was noted that FVC can be measured independently of ambulatory status, but accurate height measurement is also needed for % predicted value, which can be difficult in non-ambulant older boys/young men [23]. Currently, the standardized measure of ulnar length provides the most accurate way to estimate height in a DMD population.

Patient groups raised the importance of monitoring and measuring cardiac outcomes, as these are outcomes that do not require a patient to be ambulatory.

4.4. Patient reported outcome measures (PROMs)

Patients are at the centre of every trial and it is therefore very important to listen to what patients think are relevant and meaningful trial outcomes. The role of patient reported outcome measures (PROMs) is becoming increasingly important in clinical studies. The patient perspective is also given high value by regulators and Health Technology Assessment (HTA) authorities with a specific recommendation from the FDA that drug developers should gain further input from patients and caregivers into the most appropriate outcome measures to be selected in trials [2]. Studies have been conducted on the collection and value of PROMs in Europe and it is clear that these measures are highly country specific, depending significantly on social support available.

Meanwhile in the US, a Cooperative International Neuromuscular Research Group (CINRG) study has undertaken an investigation of happiness and found that the area of the world in which people with DMD live seems to have the biggest impact on their happiness [31,32].

Traditionally questionnaires are used to collect patients' perception about the efficacy of an intervention, but it can be

stressful for families if repeatedly asked questions about how a child is and how much they are struggling.

Nathalie Goemans (University of Leuven, Belgium) reported the existing PROMs that have been used in DMD, focusing on a recent effort to develop, as part of collaborative work of clinicians, physical therapists and patients, a module specifically designed to assess a number of activities that are clinically meaningful to patients and their carers, but cannot be observed/assessed in a clinical setting. This module, called upper limb PROM (UL PROM) is being validated in clinical routine and in clinical trials in conjunction with the PUL [33].

Data from Erik Henricson on the construction and validation of the Duchenne muscular dystrophy Lifespan Mobility Scale or DMD-LMS [34] was presented by Nathalie Goemans. This new promising instrument is applicable across the age and disease severity spectrum of DMD. Items from a number of standardized instruments and health-related quality of life scales were utilized to create three domain subscales according to the WHO-ICF (1) mobility, (2) maintaining posture and positioning of the body in space, and (3) lifting, carrying and manipulating objects. Final items were chosen based on properties such as correlation with other commonly used instruments, ability to show change over 1-year, minimal clinically important difference changes and responsiveness to steroids. The DMD-LMS correlates with transitions across clinically meaningful functional milestone groups. It is a promising PRO for DMD clinical trials.

Elizabeth Vroom discussed tools that record health related quality of life (HRQoL) in children with DMD. Regulators and payers are also keen to see reliable data on HRQoL measures for DMD, which is currently being discussed with HTA groups (discussed further at a meeting organised by Duchenne UK, January 2017). Elizabeth Vroom reported a literature review of 13 HRQoL instruments [35] and concluded that there is not yet an optimal QoL scale for DMD. Only two validated and reliable HRQoL instruments are available for DMD, the PedsQL and PARS-III. These are also included in the revised DMD SoC guidelines [36,37,38]. Commercial sponsors should be encouraged to build in a QoL measure into a clinical trial. Patient advocacy groups point out that HRQoL instruments can be used to measure progressive loss of function in DMD. Interestingly, even against a background of loss of function, happiness remains fairly steady over the course of disease, apart from periods when milestones are lost, which illustrates how important it is to maintain motor function. It will be important to collect more data and to test HRQoL instruments in different populations to make sure language is used appropriately.

In general discussions, there was consensus that while PROMs are extremely useful and should be used, caution should be exercised not to expect a strict correlation with functional changes. Since QoL measures were introduced, it has been recognized that they do not always correlate with changes in disease progression [35].

There is a tendency to extrapolate a poorer QoL from loss of function. However, this is not necessarily always the case [39]. Functional health might decline but life satisfaction often dips at the loss of function and then increases again with adaptation (this is also known from other conditions). In recent studies this extrapolation is indeed shown not to be the case and that the QoL reported by older patients living with DMD is rather more determined by their ability to take part in personally meaningful activities [40].

Patient representatives felt that it was important to be able to capture key measurements at home and use these when assessing the effect of a drug in addition to clinical measures which only occur periodically, not every day. Happiness is also easier to measure at home.

Alex Johnson asked whether data such as video diaries showing activities like children getting in and out of a car more easily is admissible by regulators. It was suggested that the EMA will consider all types of data (with appropriate protection of privacy). Even anecdotal data may be taken into account, as well as individual cases. On patient reported outcomes, the EMA should be provided with information about what is meaningful including patients' and caregivers' perspectives.

5. Better drugs or better outcome measures?

Eugenio Mercuri reported a critical review of the results of recently completed clinical trials in DMD highlighting how the studies suffered from the lack of natural history data available at the time the trials were designed.

Natural history studies performed concurrently with clinical trials have defined a number of points that helped to better understand the results and can be used in future studies to better define inclusion and stratification criteria:

1. There is a large variability of disease progression in ambulant DMD boys, ranging from possible improvements to fast deterioration.
2. It is possible to identify factors that can predict disease progression on the 6MWD and can be used as inclusion or stratification criteria. These include baseline values, age, steroid treatment and type of mutation. Most of the work has been performed on the 6MWD.
3. Combining the 6MWD with other clinical (timed function tests, age) and imaging (magnetic resonance imaging, MRI - fat fraction) assessments further enhance the predictive value and the possibility to identify patients with differing disease progression.
4. There is no ideal outcome measure that could be used for all the studies. The choice of outcome measure for a study should reflect the mechanism of action of the tested compound, the duration of the study and the cohort included.
5. It is important that, as learned with the 6MWD, whatever measure is used, longitudinal natural history data should be available to be able to predict what is expected in the placebo arm of the study, possible trajectories, or to identify and pre-specify subgroups of patients that may be more suitable to demonstrate the efficacy of a treatment in a certain interval of time [41].

Based on these results, rather than over-criticising individual measures used in the past, the community needs to be careful not to praise new outcome measures too quickly, as their validation will require a lot of natural history work to put us in the same position as we are with current outcome measures.

There has been a recent international effort to have a more statistically sound approach to the identification of disease trajectories as shown in studies from the Collaborative Trajectory Analysis Project (cTAP), reporting the categorization of natural history trajectories in DMD progression [42] and how a number of variables (age, timed function tests, height, weight, BMI, 6MWD) can provide a global score that defines a trajectory of progression [14].

The results emerging from the cTAP were seen as powerful, but the early findings need to be further validated in other data sets and ideally compared to placebo data from recent interventional studies.

During general discussion there was consensus among the participants that when it comes to selecting outcome measures, even if families and industry would ideally want the broadest inclusion criteria, a more selected population is more appropriate when the time frame of the study is limited, also taking into account the mechanism of action of the drug. If the mechanism of action of a drug is restoring dystrophin expression, aiming to slow down disease deterioration, and the duration of the study is just 12 months, possible differences between treated and untreated patients will only be seen in a sub-set of patients who, on the basis of the natural history data, are likely to show deterioration in that time frame. It is not suggested to exclude broader populations from a study, but it is important to focus early analysis on the identified target sub-set. The further and wider response of a drug will be seen in a longer follow up.

This prompted further discussion raised by families and industry related to the need for placebo groups and length of the blind phase. The discussions suggested that where prolonging the blind phase would appear to be necessary to increase the level of evidence, 12–18 months of placebo studies are generally accepted. However, it would be difficult for many families to undertake a two year placebo trial.

The family perspective at the meeting also suggested that attitudes to a long placebo arm may be stage specific. For a 5-year-old the chance of being in a placebo arm for 2 years might be acceptable, but not so for a 9-year-old, as these might be the "last two years" when the boy is still ambulant.

There was the suggestion that more effort is required to understand if and how natural history data can be used alongside or versus placebo studies. At the current time, regulators are not necessarily ready to accept natural history data to replace placebo arms in DMD studies. The FDA's recent guidance to industry "strongly recommends randomized placebo-controlled trials" [2]. Whilst regulators will consider natural history data, more work is needed to rely on this being acceptable and in the meantime it is likely that large treatment effects would be needed to make data from externally controlled trials convincing [1,2]. Family representatives reported frustration at the lack of data-sharing and highlighted the need to make the best use of precious placebo and natural history data, asking industry to commit to making placebo data available. There was even a suggestion that advocacy groups could take a stand by discouraging parents from taking part in trials if they do not agree to share data.

The general discussion also focused on the need to have similar SOPs for the assessment of outcome measures and the creation of a common 'data dictionary'. Different centres may have different ways of applying the same measure, e.g. choosing different times / points to stop a test (sometimes based on safety) and this should be standardised.

Other points included the need to better establish the outcome measure to evaluate the transition from ambulant to non-ambulant patients and the importance of involving younger DMD patients in clinical trials, to prevent the deterioration of the disease from its very early phase. Work is ongoing to improve outcome measures for this population, but it was also discussed that regulators may accept the extrapolation of efficacy results from an older population to a younger population with better preserved muscles, as long as safety data for the age group were available.

6. Understanding non-invasive measurement of muscle pathology

Several interventional clinical trials in DMD have started using muscle MRI measures as secondary and in some cases even as primary endpoints. The main reason to focus on imaging outcome measures is the objectivity of the quantitative assessment, assuming of course that the patient is compliant and strict SOPs for imaging protocols are followed. Pierre Carlier explained the principle advantages of the three-point Dixon technique that allows the quantification of fat by MRI within a region of interest, normally single or multiple slices in a distinct muscle. Quantification of fat within a muscle at a specific time point makes it possible to measure an increase of fat or a loss of muscle tissue over time. The challenge, as with many of the other outcome measures discussed, is collecting sufficient natural history data over a longer time period in a broad range of patients at different ages. Pierre Carlier pointed out those MR endpoints (MRI and MR spectroscopy, MRS), including cardiac imaging, have only been used in just over 20 DMD studies. Another challenge is the clinical meaningfulness of the pathological changes over time. Patient trajectories as illustrated by the cTAP may be difficult to predict by MRI alone, but a combination of MRI and other outcome measures could be useful.

Hermien Kan explained what kind of different measures MRI and MRS offer and how they are assessed. Analysing imaging data, one can calculate the cross sectional area of a muscle, the fat fraction, the contractile cross sectional area, global T2 values (MRI), water T2 values (MRS) or ^{31}phosphorus metabolites (MRS) (Table 2).

It is important to come to an agreement in which muscles to measure pathology and how to measure it. Imaging data

Table 2
Comparison of the measures provided by different MR imaging and spectroscopy techniques (kindly provided by Hermien Kan).

	T1w	Dixon	^{1}H MRS	T2 fat sat	T2 no fat sat	^{31}P MRS
CSA	√	√	✗	+/−	+/−	✗
FF	✗	√	√	✗	√	✗
cCSA	✗	√	✗	+/−	+/−	✗
Global/MRI T2	✗	✗	+/−	✗	√	✗
Water/MRS T2	✗	✗	√	+/−	√	✗
T2 heterogeneity	✗	✗	✗	+/−	√	✗
^{31}P metabolites	✗	✗	✗	✗	✗	√

Key: √: suitable; + /−: usable but with problems; ✗: not suitable.

for upper limbs in DMD are still sparse, as quantitative MRI is more complex to perform in upper limbs (arms), but several groups are currently collecting more data. Imaging the heart by MRI is also well established, but requires different protocols to those used for imaging skeletal muscles. Patient representatives would understandably like to collect imaging data from the heart, upper and lower limbs together, but this would require longer acquisition times, which makes the investigation more expensive and is not always compatible with the compliance of the patient, especially younger patients. There is consensus that the Dixon method is currently a very good way to look at the fat fraction in a muscle. However, using the fat fraction as an outcome measure in young boys is challenging, as they have a low fat fraction in early stages of the disease. There is also some fat in the muscles of healthy controls (approx. 1–6% depending on the muscle and age). In young children MRS might be a good complement to MRI in quantifying muscle fat fraction. One needs to keep in mind that MRI and MRS in patients younger than 5 years of age might be difficult to carry out due to poor compliance and may require sedation or general anaesthesia.

Glenn Walter is one of the investigators in the ImagingDMD consortium (http://www.imagingdmd.org/), a multicentre project that collects natural history data in DMD patients by applying MRI and MRS. He illustrated how different muscles show statistically significant changes over time in different age groups. He confirmed that the Dixon technique is excellent when a muscle shows moderate to high levels of fat infiltration, but that ^{1}H MR - spectroscopy may be the better method in younger patients, with low levels of muscle fat. Ongoing developments with Dixon imaging to minimize noise bias [43] and unwanted gradient effects are expected to improve reliability at low fat fractions [44]. He stressed the importance of psychosocial support to obtain high quality imaging/spectroscopy data due to participant compliance and retention. The ImagingDMD investigators have learned that it is extremely important to make patients and families feel welcome and valued. Imaging non-ambulatory patients is more of a logistical issue, as patients may have developed contractures, may find transport and travel more difficult and be difficult to position in a scanner. Dirk Fischer (University of Basel, Switzerland) has used MRI as a secondary endpoint in interventional clinical trials and supported the use of the Dixon technique as a reliable and reproducible outcome measure in DMD studies [45].

7. Muscle biopsy analysis as an outcome measure

Traditionally muscle biopsies have been used to diagnose boys with DMD and almost all early phase interventional trials used muscle biopsies to either show target engagement by increased dystrophin expression or an improvement in histology. Since the diagnosis of DMD is now primarily based on clinical grounds and genetic testing and since non-invasive imaging techniques like MRI can provide helpful insights into skeletal muscle pathology, muscle biopsies in clinical trials are reviewed more critically.

Alex Johnson contacted DMD families before the workshop to ask them for their opinions on biopsies. There were several concerns from those who have had muscle biopsies as part of a clinical trial, but it should be remembered that the quotes that were presented were only from a small group of families and it was not clear how representative they were. It was reported that scars were a constant reminder that the boys are different.

Interestingly, clinicians reported that families were generally more concerned before a biopsy than afterwards, as the procedure is often not as invasive or painful as anticipated. They explained that most boys are not affected by the actual intervention. Some clinicians expressed the view that boys were more concerned about repetitive blood sampling than about biopsies. It may be that families feel unable to report their concerns and anxieties to clinicians and are more comfortable discussing this with another parent.

The patient representatives felt that it would be helpful if boys and families receive results from biopsies and that it is unacceptable when biopsies are lost or unusable for the trial analysis. Sharing data that are relevant for the integrity of the trial is clearly a concern for pharmaceutical companies and this should be considered and discussed to reach agreement between all stakeholders.

Listening to the concerns of patients and families is very important and generally parents do understand that in many trials biopsies are not optional but mandatory and necessary for assessing drug efficacy. It is important that patients and parents can be assured that robust procedures for collecting and analysing biopsies are in place, which regulators agree with the proposed analysis procedures and that unusable samples must not occur. Remaining tissue should be stored in a biobank and made available to the wider DMD research community.

Table 3
Outcome measures that may be appropriate depending on the stage of disease. (from contributions from workshop participants).

Stage	Infant/Young Children	Ambulant (age ≥5 yrs)		Non-Ambulant
Clinical outcome measure	Bayley III: ≤3.5 yrs NSAA: ≥3 yrs TFTs: ≥4 yrs may expect increased rate of skill acquisition close to norms	6MWD NSAA TFTs LE / UE HHD / Grip	Stride length/height Stride velocity PRO: PODCI	PFTs PUL Reachable workspace UE HHD / Grip PRO: PROM UL
Imaging	US: <5 yrs	MRI ≥5 yrs (LE / UE)		MRI ≥5 yrs (UE)
Blood biomarkers	Proteomics; miRNA			
Biopsy (dystrophin)	1–2 (POC): WB, IF, Mass spectrometry (if higher levels of dystrophin expected); Fold changes of dystrophin			

Key – yrs: years of age; NSAA: North Star ambulatory assessment; TFT: timed function test; 6MWD: 6 minute walk distance; LE: lower extremity; UE: upper extremity; HHD: hand held dynamometry; HT: WB: Western blot; IF: immunofluorescence; PODCI: pediatric outcomes data collection instrument; PFTs: pulmonary function tests; PUL: performance of upper limb; PRO: patient reported outcome; PROM: patient recorded outcome measure; US: ultrasound; MRI: magnetic resonance imaging; miRNA: micro-ribonucleic acid; POC: proof of concept.

For trials that aim to increase dystrophin expression or the expression of another muscle protein, it is extremely important to precisely quantify that protein in muscle biopsy samples, especially as this might be a potential future surrogate marker. Experience has shown that quantifying small increases in protein expression in biopsies obtained in clinical trials can be very challenging. Francesco Muntoni explained what work needs to be done to get reliable results from biopsies. It was suggested that ideally one would relate the presence and abundance of dystrophin to the residual muscle mass. It still needs to be defined what normal dystrophin levels are and what the variability of dystrophin levels between normal muscles and between healthy individuals is. There is also no consensus about which muscle should be biopsied at which stage of the disease and how a biopsy may affect other outcome measures. Furthermore, there needs to be a better understanding of dystrophin expression in severe BMD and in intermediate DMD/BMD phenotypes. Informing patients and parents about the relevance and the challenges of muscle biopsy analyses is also important.

8. Mechanisms of action: different drugs require different outcome measures. What do we expect from drugs, how should we measure this?

A session on the relationship between the mechanisms of action of certain drugs was chaired by Thomas Voit, Volker Straub, and Craig McDonald. Despite consensus about a range of outcome measure for trials in DMD, the efficacy of different drugs depending on their mode of action would need to be assessed by the use of specific outcome measures – a summary of this is given in Table 3. A phase 3 trial that assesses different steroid regimes, like the FOR-DMD trial (http://for-dmd.org/en/) would, for example not require muscle biopsies, whereas an early phase trial with a new antisense oligonucleotide that is supposed to induce exon skipping and dystrophin restoration would require muscle biopsies at baseline and at least once after treatment. It is therefore important to ask what one would expect from the drug to be tested and how to best measure this.

The goal is to tailor trial design and outcome measures to the particular target mechanism. Therefore it is also important to understand the disease mechanism in DMD, keeping in mind that it is not easy to extrapolate from animal models to humans.

8.1. Gene therapy

Thomas Voit pointed out that there are currently at least four separate initiatives that are pursuing gene replacement therapy in DMD. Which outcome measures should these initiatives use for the early phase trials? One could envisage that a company would like to look at dystrophin expression in muscle biopsies, at T2 changes by MRI or at serum markers for an immune response. The choice of outcome measure will very much depend on the phase of the trial, pre-existing knowledge of the drug mechanism and effect size, and on the age group of patients the drug is tested in. The best population for gene therapy to show safety at lower doses would preferably be an adult, non-ambulatory population. For subsequent higher dose studies, still looking at safety, ambulant patients might be preferable, as a clinical benefit might also be observed. For a gene therapy efficacy trial one would target patients as early as possible, to make sure that muscle mass (target tissue) is still preserved and can be maintained.

8.2. RNA modification

Past and current trials targeting RNA modification, e.g. exon skipping or stop-codon read through, in DMD have shown that treatment duration is extremely important. On the other hand the effect size of new compounds may be much improved, which illustrates that standard recipes for the selection of outcome measures cannot be developed. Until there are compounds with a bigger effect size the field needs longer trials or to select a subset of patients with stricter enrolment criteria. The selection of outcome measures will again depend on the phase of the trial, the anticipated effect size and the age group of patients.

9. Final remarks

A better understanding of the relationship between clinical progression in DMD and any endpoint in the clinical trial timeframe would be very helpful to industry and is required by regulators in order to ensure that endpoints used are acceptable to them and later to HTA bodies and payers.

The discussions throughout this two-day workshop highlighted both the need and the commitment to reach a consensus within the community, to involve all stakeholders and to enter urgent discussions with regulators in order to ensure that appropriate outcome measures are validated and accepted for use in an ever-increasing number of clinical trials in DMD. Undertaking this in a coordinated and cooperative manner, will improve the chance of showing efficacy (or lack of efficacy) for emerging therapies.

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