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269th ENMC international workshop: 10 years of clinical trials in Duchenne muscular dystrophy – What have we learned? 9–11 December 2022, Hoofddorp, The Netherlands

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ABSTRACT

There are multiple avenues for therapeutic development in Duchenne muscular dystrophy (DMD), which are highlighted in the first section of this report for the "10 years of Clinical trials in DMD – What have we learned?" workshop. This report then provides an overview of the presentations made at the workshop grouped into the following core themes: trial outcomes, disease heterogeneity, meaningfulness of outcomes and the utility of real-world data in trials. Finally, we present the consensus that was achieved at the workshop on the learning points from 10 years of clinical trials in DMD, and possible action points from these. This includes further work in expanding the scope and range of trial outcomes and assessing the efficacy of new trial structures for DMD. We also highlight several points which should be addressed during future interactions with regulators, such as clinical meaningfulness and the use of real-world data.

1. Introduction and overview

The 269th ENMC workshop was held from the 9th to the 11th of December 2022 and brought together 24 representatives from all stakeholder groups that have sought to advance development of new therapeutics in clinical trials in Duchenne muscular dystrophy (DMD), including patients, advocacy groups, researchers, regulators and trial sponsors, and neuromuscular and clinical experts from 5 European countries (Belgium, France, Italy, Netherlands and the UK) and from the United States. The workshop was organised by N. Goemans, C. McDonald, E. Mercuri and F. Muntoni. The focus of the workshop was to characterise and synthesise learnings from the last 10 years of trials in DMD, and to identify priorities for future works. This was a continuation on the previous ENMC workshop on outcome measures and trials for DMD [1].

DMD is an X-linked recessive neuromuscular disorder, characterised by progressive muscle wasting, loss of motor function and limited survival [2–4]. It is primarily caused by out-of-frame mutations in the dystrophin gene (*DMD*) [5–7], leading to the complete or almost complete absence of dystrophin protein. In some cases, it can be caused by large in-frame mutations removing essential protein domains, although most in-frame mutations are associated with the milder Becker muscular dystrophy (BMD). The importance of maintaining the functional domains of dystrophin are highlighted by rare smaller in-frame mutations which affect critical regions such as the dystroglycan binding domain, which can still result in a DMD phenotype [6]. Boys with DMD broadly pass through four disease stages [8], early ambulatory (predominantly characterised by under 8 years of age, absence of assistive tools), late ambulatory (characterised by presence of assistive devices such as wheelchairs or non-invasive

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ventilation), early non-ambulatory (characterised predominantly by loss of ambulation, motorised wheelchair use for at least 6 months, or the need for cardiac medication) and late non-ambulatory (characterised primarily by loss of pulmonary or gastrointestinal function requiring intervention).

Glucocorticoids (GCs), predominantly prednisolone/prednisone or deflazacort, are the mainstay treatment for the majority of boys with DMD [9], and have been shown to delay key disease milestones such as loss of ambulation, and the age at which ventilatory support is required [3,10–12]. There is increasing real world data into the effects of chronic steroid use including on cardiac function and effect of different regimens on rate of respiratory decline [13–15], but at the same time the burden of the cumulative use of the corticosteroids for bone health, weight and linear growth. Recently novel steroid-derivatives have been developed and one of these, vamorolone, has shown comparative efficacy as current standard of care GC, but with potentially reduced chronic use-related side effects, such as on growth and bone health [16–18].

This ENMC meeting aimed to look retrospectively at the last ten years of clinical trials, to identify novel opportunities to optimize therapeutic development and leverage community-wide involvement. The report captures the presentations at the meeting, along with a prospective plan of action based on these findings. Broadly, we have split the presentations of this meeting into several topics: trial endpoints, their limitations and possible new developments; heterogeneity in the DMD cohort, and how this can be addressed when identifying trial cohorts; the meaningfulness of treatment effects, and what it means for treatments to be meaningful; real world data and how it can be utilised in clinical development.

1.1. Disease modifying treatments in DMD

In DMD there are multiple avenues for therapeutic development. An overview of some of the therapies under development for DMD which are pertinent to this workshop are provided in Table 1. One field that has proven particularly active is the development of mutation specific antisense oligonucleotide (ASO) therapies. These therapies work by modulating splicing in dystrophin pre-mRNA, restoring the reading frame and leading to the expression of partially functional, shortened dystrophin isoforms, similar to the protein found in BMD [19]. These drugs have been developed to specifically target common endpoints of mutations, and there has been particular focus on drugs which skip exons 51, 53 and 45, which 14, 10, and 9 % of all DMD boys are amenable to respectively [5].

Under trial number the currently (August 2023) active trials on clinicaltrials.gov studying this drug for DMD are mentioned or the number of the trial after or during which development was discontinued. Development status refers to the highest phase that has been completed, whether development has been discontinued or whether marked approval has been requested.

The exon 51 ASO skipping eteplirsen (developed by Sarepta Therapeutics) [20,21] was approved conditionally based on clinical benefit in trials by the Food and Drug Administration (FDA), after a significant increase in dystrophin expression was observed in the treated group, but was given a negative opinion by Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) [22]. Prosensa discontinued the development of a similar ASO also designed to skip exon 51 (drisapersen) after the phase III trial (clinicaltrials.gov ID: NCT01254019) failed to show significance in the primary outcome - 6 Min Walking Distance (6MWD) at 48 weeks. Additionally, Prosensa also discontinued their exon 44 skipping ASO PRO044, exon 45 skipping ASO PRO045 and exon 53 skipping ASO PRO053 all of which were in Phase II trials, after the FDA rejection of drisapersen. The development of Wave Life Sciences' exon 51 skipping suvodirsen was discontinued when the interim analysis of the Phase I open-label extension (clinicaltrials.gov ID: NCT03907072) showed no change in dystrophin expression. The exon 53 ASO skipping golodirsen (developed by Sarepta Therapeutics in collaboration with the EU funded SKIP-NMD consortium) also received FDA conditional approval in 2019 after showing a significant increase in dystrophin expression in the treated group but was given a negative opinion by CHMP [23].The exon 53 ASO skipping viltolarsen (developed by NS Pharma, Inc.) has been conditionally approved by the FDA for use in the US and by the Ministry of Health, Labour and Welfare for use in Japan following phase 2 trials showing increase in dystrophin expression in the treated group at 20–24 months (clinicaltrials.gov ID: NCT02740972 & Japic CTI-163,291) [24,25]. Sarepta Therapeutics' exon 45 skipping ASO casimersen has also received approval from the FDA for use in the USA after the phase III trial (clinicaltrials.gov ID: NCT02500381) showed a significantly larger increase in dystrophin expression in the casimersen patients at the 48 week interim analysis [26]. The approval is conditional on clinical effect shown in the ongoing trials. Notably none of the ASO therapies have been approved so far for use in the EU or the UK, as a result of the very different stance between EMA and FDA on surrogate endpoints as a pathway for accelerated conditional approval.

Ataluren, developed by PTC Therapeutics, demonstrates an alternative protein restoration approach, whereby ribosomal readthrough of premature stop codons is enabled. This drug targets the 10–15 % of DMD patients with nonsense mutations [27]. It was conditionally approved by EMA for use in the EU [28] after the phase IIb trial (clinicaltrials.gov ID: NCT00592553) showed a non-significant improvement in the primary outcome, the 6MWD, in the treated group, and significant improvement in several secondary outcomes, including the 10-metre walk-run (10MWR) and 4 stair climb (4SC), together with a favourable safety profile. On September 15th 2023, EMA gave a negative opinion on the conversion of conditional approval to full market approval for ataluren.

Another therapeutic approach has been anti-myostatin drugs, including domagrozumab (developed by Pfizer), talditercept alfa (also known as RG6206, developed by Roche/Genentech), and ACE031 (developed by Acceleron Pharma). Despite promising pre-clinical data, in trials (clinicaltrials.gov IDs: NCT02310763, NCT03039686, NCT01099761 respectively) the small increase in muscle mass demonstrated in the treated patients failed to result in improvement in the primary or secondary clinical outcome measures. An overview of these trials and possible explanations for the lack of viability of anti-myostatins in DMD so far is given by Rybalka et al. [29].

There has been significant effort in DMD to repurpose other therapies for use in DMD. One such notable case is that of the selective oestrogen receptor modulator tamoxifen, which despite positive results in a mouse model [30] failed to show improvement on the primary endpoint, the Motor Function Measure D1 in a recently completed clinical trial [30]. Similarly, two erectile dysfunction drugs, tadalafil and sildenafil, showed promise in mouse models [31,32]. However, tadalafil showed no significant effect on the primary outcome (change in 6MWD) at 48 weeks in the phase II trial (clinicaltrials.gov ID: NCT01865084), whilst sildenafil showed no effect on cardiac function at 6 months [33]. Idebenone, which was originally developed as a treatment for Alzheimer's disease, showed promise in mice [34], but research was discontinued after the interim findings of the Phase III trial (clinicaltrials.gov ID: NCT02814019) showed that it would be unlikely to reach the primary endpoint on FVC.

Table 1
Therapeutics discussed at or relevant to the 269th ENMC workshop and their current developmental status and status of market approval. Key - ○: accelerated (US) or conditional (EU) approval, •: negative opinion.

Drug	Sponsor	Biology	Trial number	Development status	Market approval		
					USA -FDA	EU - CHMP	Japan- MHLW
Eteplirsen	Sarepta Therapeutics	ASO for skipping exon 51	NCT03992430, NCT04179409	Phase III completed, confirmatory trial	○	•	
Golodirsen	Sarepta Therapeutics and SKIP-NMD consortium	ASO for skipping exon 53	NCT03532542, NCT04179409, NCT02500381	Phase I/II completed, confirmatory trial	○	•	
Casimersen	Sarepta Therapeutics	ASO for skipping exon 45	NCT03532542, NCT04179409, NCT02500381	Phase III interim analysis promising, phase III ongoing	○		
Drisapersen	Prosensa/ GlaxoSmithKline/ BioMarin Pharmaceutical	ASO for skipping exon 51	NCT01254019	Discontinued (after phase III)			
PRO044	Prosensa/ BioMarin Pharmaceutical	ASO for skipping exon 44	NCT01037309, NCT02329769	Discontinued (during phase II)			
PRO045	Prosensa/ BioMarin Pharmaceutical	ASO for skipping exon 45	NCT01826474	Discontinued (during phase I/II)			
PRO053	Prosensa/ BioMarin Pharmaceutical	ASO for skipping exon 53	NCT01957059	Discontinued (during phase I/II)			
Suvodirsen	Wave Life Sciences	ASO for skipping exon 51	NCT03907072	Discontinued (during phase II/III)			
Viltolarsen	NS Pharma, Inc.	ASO for skipping exon 53	NCT04768062, NCT04060199, NCT04337112	Phase II completed, confirmatory trial	○		○
Ataluren	PTC Therapeutics	Small molecule that restores dystrophin synthesis by allowing ribosomes to read through premature stop codons	NCT01247207, NCT04336826, NCT03179631, NCT02369731	Phase III completed, FDA ongoing, confirmatory trial		•	
Domagrozumab	Pfizer	Anti-myostatin adnectin	NCT02310763	Discontinued (after phase II)			
Taldithercept alfa, RG6206	Roche/ Genentech	Anti-myostatin adnectin	NCT03039686	Discontinued (after phase II/III)			
ACE031	Acceleron Pharma, Inc./ Shire plc	Soluble form of activin receptor type IIB which binds myostatin and related proteins	NCT01099761	Discontinued (after phase II)			
Tamoxifen	University Hospital, Basel, Switzerland	Selective oestrogen receptor modulator	NCT03354039	Discontinued (after phase III)			
Tadalafil	Eli Lilly and Company	Booster of nitric oxide–cGMP signalling	NCT01865084	Discontinued (after phase III)			
Sildenafil	Hugo W. Moser Research Institute at Kennedy Krieger, Inc.	Booster of nitric oxide–cGMP signalling	NCT01168908	Discontinued (after phase II)			
Idebenone	Santhera Pharmaceuticals	Short-chain benzoquinone with strong anti-oxidant activities to improve mitochondrial respiratory chain function and cellular energy production	NCT02814019	Discontinued (during phase II)			
Givinostat	Italfarmaco	Histone deacetylase inhibitor	NCT02851797	Phase III completed, request for market authorisation submitted			
Vamorolone	ReveraGen BioPharma, Inc., Santhera Pharmaceuticals	Steroid-derivative	NCT03439670, NCT05185622	Phase II completed, request for market authorisation submitted			

The Italfarmaco developed givinostat is a histone deacetylase (HDAC) inhibitor. The results from the phase III trial (clinicaltrials.gov ID: NCT02851797) of givinostat showed a significant improvement in the primary outcome (4SC) at 18 months in the treated group compared to the placebo controls. Similar directional results had been obtained in the other secondary endpoint used and Italfarmaco has announced their intention to seek FDA approval on the basis of these top-line results.

Research into disease modifying therapies is still very active in DMD, and there are a multitude of trials ongoing – clinicaltrials.gov lists 49 trials of medical interventions which are marked as "not yet recruiting", "recruiting" and "active". These span multiple therapeutic mechanisms, including 12 exon skipping drugs (DYNE-251, eteplirsen, golodirsen, scAAV9.U7.ACCA, AOC 1044, NS-089/NCNP-02, casimersen, DS-5141b, SQY51, vestleteplirsen, viltolarsen and WVE-N531) and ataluren, 3 cardiac therapies (metoprolol succinate, bisoprolol fumarate and ifetroban) and 4 therapies which target inflammatory markers (pizuglanstat, givinostat, pamrevlumab and canakinumab). There are also several trials of novel therapeutic methods, including myoblast infusions, GALGT2 inhibitors, cell based therapy (CAP-1002) and a small molecule muscle stabilizer (EDG-5506).

Additionally, gene therapy development for DMD is ongoing, however it is complicated by the sheer size of the dystrophin gene, which is many times bigger than the capacity of the adeno-associated virus (AAV) vectors in use. Discoveries of patients with large deletions who display BMD phenotypes has opened doors for the development of AAV mediated therapies in DMD using similar mini-dystrophins. At the time of this workshop there were four active trials on clinicaltrials.gov investigating AAV-based micro-dystrophin therapies: delandistrogene moxeparvovec-rokl (developed by Sarepta Therapeutics), fordadistrogene movaparvovec (developed by Pfizer), SGT-001 (developed by Solid Biosciences) and RGX-02 (developed by RegenXBio), along with GNT 0004 (developed by Genethon) which is not indexed on clinicaltrials.gov. Since the 269th ENMC workshop there have been promising developments in gene therapy for DMD in the form of a conditional approval by the FDA for delandistrogene moxeparvovec-rokl (Elevidys) based on phase I/II trial that demonstrated increased expression of Elevidys micro-dystrophin protein [35].

1.2. Room for study protocol improvement in DMD trials

In the opening presentation, F. Muntoni highlighted the diverse list of trial design in trials that failed in DMD in the last decade. F. Muntoni highlighted insufficient treatment exposure time to the medicinal product, heterogeneity in the rate of disease progression [36] (which confounds both in inclusion criteria and ability to discern a clinical response) and insufficient reliability in the primary outcome measures as hurdles to trial construction [37]. Additionally, F. Muntoni identified the high rates of adverse events in some of the clinical trial settings, which had not been anticipated by the preclinical toxicology studies.

Excess confidence in apparently encouraging results in small phase 1–2 studies comparing treated patients with natural history should be avoided, as this lead to overestimation of the expected therapeutic response due to underestimated heterogeneity. This was suggested as a limitation encountered in several products which eventually failed phase 3 randomised placebo-controlled studies. This challenge can be overcome by rigorous propensity-based matching of untreated patients [38].

Frank van Iepren, the founder of Stichting Dromen voor Duchenne presented his perspective on meaningfulness of treatment as an adult with DMD. Frank van Iepren. described the trade-offs involved with understanding treatment meaningfulness, including the timeline of effects (short vs. long-term effects), and how this interacts with the age at start of treatment needed for effective treatment. Frank van Iepren. also discussed patient perception, at that it can be difficult to know what a realistic treatment response for DMD trial enroled patients is.

M. Leffler and E. Vroom also presented multiple thoughts on how the trials in DMD could be better managed (as opposed to designed) to ease burdens and improve outcomes for DMD trial participants. These included the utilisation of outcomes measuring concepts of interest that are relevant and meaningful to patients. They commented that the Duchenne community has questions about the utilization of effective treatments that go beyond what is answered in a clinical trial, such as questions related to optimal dosage, treatment longevity, and the shifting risk/benefit profile of treatments when initiated at different stages of disease progression. They suggested that equitable trial access has not always been achieved in DMD, because those with higher status in the community might be more likely to participate and in the USA wealth is required to for instance for travelling during participation. They presented that due to blinding and insufficient existing data sharing infrastructure between clinical and trials sites, patients sometimes have to undergo the same testing and procedures twice (once to inform care and once as part of the study protocol). Additionally, allowing study subjects to access their data upon study completion would be a way to recognise the dedication and sacrifices of the patients/families whilst helping to inform their post-study care. Finally, it was felt that patients need to be cared for better outside of the trials, and that emergency protocols, access to treatment after the trial and the provision of open label extensions (OLE) were insufficient, whilst pain, fatigue and quality of life (QoL) was not sufficiently captured during or after the trials.

E. Vroom and P. Furlong discussed that there is a level of therapeutic misconception in boys with DMD, where patients and parents can feel disappointed by the size of the observed treatment effect. E. Vroom and P. Furlong highlighted the high burden of trial participation for several of the DMD boys, including being out of school and travelling. They suggested multiple avenues for reducing this burden, including earlier stopping criteria and at home/video assessments once safety/tolerability has been met, or performing bloodwork at local centres. E. Vroom and P. Furlong also initiated a discussion around the communication of various trial aspects from doctors to patients and parents, particularly seeking clarity around how children are selected for trial participation. Discussion on existing standard operating procedures (SOP) to ensure equitable access for participants in trials slots, in use in several of the clinical sites represented in this meeting was discussed and are available on request.

2. Trial outcome measures in DMD

In E. Mercuri's opening remarks, it was highlighted that the field of outcomes for DMD has changed significantly since the first ENMC workshop in 2007 [1], where conversation led to the development of the Performance of Upper Limb (PUL). The PUL was developed collaboratively with patients, parents and advocacy groups; it is however clear that further patient reported outcomes (PROs) are needed. E. Mercuri commented that the gold standard clinical care outcomes in DMD are the key time-to disease progression/disease staging/disease progression outcomes: loss of ambulation, initiation of ventilatory support or loss of hand-to-mouth, but that these key milestones cannot be appreciated in short trials. Additionally, E. Mercuri stated that disease staging

remains crucial as patients have a pre-defined progression [8]. Consequently, a whole disease outcome would be a tool library with relevance across the disease stages and this is currently lacking. E. Mercuri discussed that the main focus of drug-development currently is on the late-ambulatory phase, where patients are declining moderately. In this population we rely on outcome measures that are robust, validated, reliable and have identified meaningfulness to patients. The FDA and EMA are focused on minimal clinically important difference (MCID), with emphasis on interpretable clinical meaningfulness, especially in instances of low magnitude statistical change, the need to combine validation of the individual measures, their relevance for the disease and the use of statistical properties such as Rasch analysis to ensure the correctness of their construct. E. Mercuri described the difference between strength and function in DMD, and that improved strength does not necessarily lead to improved function.

F. Muntoni summarised how the distinctive mechanisms of action of the therapeutic compounds have profound implications on the expectation of detecting a clinically significant difference. F. Muntoni described for example how GC have both an anti-inflammatory effect and anabolic effect in the dystrophic muscle [39–41]. This results in improved muscle strength and function which can be measured within weeks of initiation but does not prevent the long-term progressive muscle damage characteristic of DMD, leading to limited long-term impact on disease progression. A dystrophin restoration strategy that aims at replacing – hypothetically – normal levels of normal dystrophin protein expression, would struggle to match the results of corticosteroids in the short term, because it would at best compensate for loss of ~ 30 % force generation [42]. However, the real value in restoring "only" 15 to 30 % of normal dystrophin is that this would prevent further muscle deterioration by offering protection against muscle damage induced by eccentric exercise. After years of treatment, this protection against exercise induced damage is expected to lead to very different disease trajectories from untreated patients with major anticipated change in disease outcome. On short term clinical trials, say 6 months or less, corticosteroids would be more effective than a very effective dystrophin-restoration strategy. Therefore, long-term trials are necessary to demonstrate the effect of dystrophin-restoration strategies. Further complicating is that it is currently impossible to restore a full level of full-length dystrophin. Drugs either restore "quasi-dystrophin" Becker-like dystrophins using exon skipping therapies, or a shortened and smaller micro-dystrophin used in AAV gene therapy trials. Currently, ASOs achieve levels of dystrophin that are much lower from those expected to provide complete protection of muscle from exercise induced damage, although there is hope that next generation compounds used in ongoing clinical trials could substantially change the observed levels. As for the AAV, the levels reported in several of the ongoing clinical trials are encouraging as substantial protection of exercise induced damage can be expected, provided protein levels exceeding the 20–30 % bar are consistently found. These examples demonstrate that the clinical trial design needs to be adjusted to the mechanism of action of the studied compound. The further away one goes from the "proximal" lack of dystrophin, for example developing a drug that selectively and exclusively addresses muscle fibrosis, the more complex it is to anticipate the clinical response and its timeline.

2.1. New trial outcome measures

L. Servais presented the Stride velocity 95th centile (SV95C), a new outcome provided by wearable magneto-inertial sensors. Such sensors can be used in non-ambulant (39) or in ambulant (40) patients and allows to continuously capture movements in DMD boys [43,44]. Briefly- the SV95C represents the velocity of the 5 % most rapid strides spontaneously performed by a patient during a minimum period of 50 h. By studying the stride velocity and averaging on long term period, the SV95C avoids the inherent variability in patients that has been inherent in other wearable technologies such as step counts. Additionally, by studying the maximal stride, the sensitivity to positive or negative change is increased. The outcome was qualified by EMA in 2019 as a valid secondary endpoint, based on its metric properties, (including reliability, external consistency, robustness, and sensitivity to negative change [45,46]), and as a primary endpoint in early 2023, based further on its clinical validity and sensitivity to positive changes [47].

M. Leffler presented on the Duchenne Video Assessment (DVA) [48–50], a new, video assessment outcome measure recorded by caregivers for boys with DMD. The DVA captures the ease of movement and the acquisition of compensatory actions across 17 "score cards" such as "climb 5 stairs", "stand up from couch" and "eat 10 bites". The dedicated app alerts caregivers and patients of the data collection window, and every video is sent for quality review by data monitors and is scored by DVA-certified physical therapists who can be blinded to both timepoint and treatment. The DVA has been found to have high inter- and intra-rater reliability, and cross-sectional construct validity has been established. The longitudinal, observational ARISE study is currently being conducted to evaluate the longitudinal measurement properties of the DVA.

K. Naarding presented results from a study of how gaming devices could be used to develop new upper extremity motor function outcomes in DMD. 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. K. Naarding described how the ACTIVE game performance differed between DMD 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. There was a strong correlation between the ACTIVE and the PUL (rho=0.76) [51]. K. Naarding highlighted that intellectual property constraints lead to a lack of transparency around these gaming devices, which could undermine their utility in outcome measure development.

2.2. Avenues for trial outcome measurement development

T. Duong presented an overview of the potential for using composite outcomes, which combine multiple, cross-domain measures, in trials in DMD. T. Duong highlighted that theoretically these composite scales are more likely to measure disease progression compared to individual measurements and avoid the computational complexity of multiple testing in trials. Some benefits include a lifespan approach to addressing a multi-organ disease that reduces floor-ceiling effects of some of the current scales. One limitation is that these outcomes must first be understood psychometrically in order for them to be considered for trials. Composite outcomes could be used to reduce the floor and ceiling effects in the current outcomes and give context for a multi-system disease progression. T. Duong highlighted previous approaches to composite outcomes in DMD, which included combining biomarkers, multi-organ outcomes and creating prognostics scores for loss of ambulation [52–54]. T. Duong pointed to the benefit of using machine learning, particularly to the utility of supervised and unsupervised machine learning in composite outcome development and biomarker discovery.

3. Heterogeneity disease progression rates in DMD and their impact on study protocols

There was a significant focus at the conference on discussing how certain trial protocols have sought to address heterogeneous disease progression rates in DMD. For future study protocols, it is crucial to understand which factors need to be considered in trial design in order to recruit cohorts who are most likely to display therapeutic effect in the trial follow-up period.

3.1. Approaches and learnings from previous trials

M. Klein presented findings from several trials conducted in the DMD space by PTC Therapeutics in the last decades [55,56]. M. Klein discussed how DMD is a challenging disease for therapy development, and that there will likely be no "miracle therapies" as recently observed in other rare neuromuscular diseases. One challenge of DMD is the heterogeneity of genetic causes, which leads to differences in disease severity, progression and treatment response. M. Klein discussed how collection of natural history and patient registry data can help to contextualise the variability of this change. M. Klein highlighted several features of good trial design which included sufficient length, a comprehensive approach to GC management, sensitive and practical outcomes, baseline stratification and remote visits to lighten patient and carer burden. An additional focus was placed on alignment with regulatory authorities to ensure product registration.

P. Bettica presented findings from the successful phase 3 givinostat trial (clinicaltrials.gov ID: NCT02851797). P. Bettica discussed how crucial the choices of primary endpoint, study duration and patient population are, but that each of these is interconnected. The primary endpoint of the change in 4SC was chosen as givinostat aims to preserve muscle mass. The longer follow-up of 18 months was chosen despite previous studies having 48-week follow-up, and this proved effective as interim analysis at 48 weeks showed a smaller effect. P. Bettica noted that no one endpoint is perfect, and that despite all secondary endpoints being in favour of givinostat, it could perhaps be easier to utilise a composite endpoint especially if this was acceptable by regulators. However, P. Bettica reiterated that the topline results showing consistency across outcomes of function, strength and morphology provided the strongest evidence.

M. Binks presented lessons learned from the Pfizer DMD clinical trials. M. Binks highlighted that heterogeneous disease progression rates are still a significant barrier to identifying homogeneous trial cohorts, and that a target trial cohort would be on those boys for whom loss of ambulation is predicted within 12–24 months of trial initiation. One factor that could help with cohort identification is muscle MRIs. As one of the investigators for domagrozumab [57], M. Binks summarised the trial findings: there was no effect on the 4SC, the primary functional endpoint, whilst a significant effect could be detected on lean thigh muscle volume and T2 mapping which is a surrogate for fat fraction [58]. M. Binks detailed that the domagrozumab control group will now be used as the controls to a new phase 1 DMD study. M. Binks cautioned that whilst the FDA has approved 45 drugs on external control evidence, regulators will likely never accept external controls as primary evidence in trials, and that Pocock's criteria [59] for accepting historical control data are still relevant. M. Binks highlighted particularly that a precisely defined and consistent standard of care is essential for utilising external controls in DMD.

3.2. Prediction of outcomes in trials

J. Signorovitch emphasised that in DMD drug development it is crucial to identify the most important baseline prognostic factors, and to ensure that clinical trial arms are well-matched or balanced on these factors at baseline. Otherwise the heterogeneity in disease progression rates across DMD patients, especially in the late-ambulatory stage, adds noise to clinical trial outcomes and increases trial sample sizes, durations, and risk of failure. The identification and use of factors which are strongly predictive of disease progression is therefore imperative to achieving smaller, faster, higher powered trials, and avoiding baseline imbalances that cloud interpretation of drug effects [60]. In other fields, clinical predictive tools and risk scores are widely used in care management, clinical trial design, drug labels and guidelines. In DMD, factors with modest predictive value of 1-year changes in ambulatory motor function include age, steroid type, exon skipping amenability and motor function outcomes at baseline. However, J. Signorovitch highlighted that the best prediction comes from combining multiple measures, especially measures of baseline motor function, into a composite score that synergistically increases prognostic accuracy for 1-year motor function outcomes [61–64]. It was emphasized that age alone is not a strong prognostic factor for 1-year motor function, and that reliance on age for baseline stratification has already clouded the interpretation of randomized trials in DMD. J. Signorovitch recommended that trialists pre-specify baseline adjustment, and stratification of randomization, for the strongest evidence-based prognostic factors or composite scores, since this approach increases power, does not raise trial validity concerns, and is an approach to which regulators have long been amenable.

K. Naarding presented results on the use of quantitative MRI (qMRI)-derived vastus lateralis (VL) fat fraction (FF) on loss of ambulation age prediction in a cohort from Leiden University Medical centre. The VL FF was found to have significant added predictive value (hazard ratio 1.15, $p = 0.003$) [65]. Similarly, qMRI-derived elbow flexed FF was found to have significant additive predictive value on age at loss of hand-to-mouth function (hazard ratio 1.12, $p = 0.002$) [66]. This may suggest that the addition of qMRI results in inclusion criteria could help to define and stratify participants in a clinical trial for their risk of experiencing disease milestones.

G. Stimpson presented results on the effect of steroid-independent growth on loss of ambulation risk in boys with DMD. G. Stimpson highlighted that height gain and weight gain are correlated with an increased risk of loss of ambulation. Notably, a child with a yearly weight gain 0.25 standard deviations greater than an average child has a 90 % (95 % CI: 33 %, 171 %) greater risk of loss of ambulation.

C. McDonald presented results of a study which sought to identify and use readily available clinical parameters as predictors of risk of loss of ambulation. C. McDonald highlighted, for example, that when 10MWR time is greater than 10 s, this is predictive of universal loss of ambulation within 1 year. The study used machine learning to identify 6 risk groups based on time to rise from floor (RFF), 10MWR and 4SC, and showed that the relative age at loss of ambulation in these groups was distinct using Kaplan Meier analysis. Removing 4SC resulted in 5 risk groups, which were also distinct using the Kaplan Meier analysis. C. McDonald highlighted that this adds to what is already observed, that a 2–3-point decline in North Star Ambulatory Assessment (NSAA) is associated with the rapid loss of two items followed by loss of ambulation [67].

4. Meaningfulness in treatment effects

The meeting also focused on the meaningfulness of outcomes used in clinical trials to both the patients and the parents/carers. Parts of this discussion focussed on making sure that the current scales used in DMD were meaningful, whilst it highlighted the

need for future scales to centre patient meaningfulness in their development.

4.1. Understanding what is meaningful to patients and parents

G. Stimpson presented centile curves for the NSAA in boys with DMD between the age of 5 and 16 who had initiated GC, and described that centiles for the 10MWR velocity and RFF velocity were also in development. G. Stimpson highlighted that centiles have a specific utility in contextualising both the NSAA total score and short-term change for patients and parents/carers, particularly in the late-ambulatory stage, where decline in motor function is rapid. Additionally, further work is needed to understand an individual's stability on the centiles, and in particular, what divergence from the centile is consistent with an abnormal change in motor function.

M. Leffler, E. Vroom and Frank van Iepren. discussed what it means for a treatment to have a meaningful effect for the patients and parents. Short term effects of note that they highlighted included better/longer walking and only improved muscle strength, whilst the long-term side effects of chronic treatment (such as steroids) that trouble people with DMD include increased bone fractures. They highlighted that whilst 1 % more muscle strength may not be clinically significant in terms of how outcome measures are calculated to satisfy the statistical constructs, it can be very meaningful for patients in the preservation of independent function. They discussed also that treatment meaningfulness is directly affected by treatment expectations, and consequently the importance of disease appropriate staging. They noted in particular that in later disease stages the likelihood of a "large" treatment effect is less plausible, however, the preservation of small amounts of function is extremely meaningful. Additionally, patients are also more likely at older ages to have heard of other failed trials and be dissuaded from joining the trial.

S. Hendrix presented on the utility of using percentage slowing of disease progression (calculated as the difference in change between the treated and placebo groups as a proportion of the change observed in the placebo group) as outcome in trials in cohorts with degenerative diseases. When disease progression is linear for an outcome, this percentage slowing is equivalent to the disease progression time that is delayed by treatment, a measure called time savings. When disease progression is more rapid over time, as in DMD, the same percentage slowing will represent longer time savings if the treatment is administered at an earlier disease stage. S. Hendrix described how time savings can be easily calculated for any outcome, can be compared over multiple outcomes and these calculations are easily interpretable also by the lay members of the public when presented relative to time treated. Another approach presented by S. Hendrix is to determine deviation from a disease trajectory. This led to the discussion of responders versus non-responders, and particularly the benefit of this method over traditional MCIDs, which are always specific to specific patient populations

4.2. Calculating meaningfulness in outcomes

T. Duong presented on approaches for defining thresholds of clinical meaningfulness in outcome measures, including the anchor-based MCID and the distribution-based minimal detectable change (MDC). Distribution-based methods depend solely on statistical approaches founded on psychometric soundness, whilst anchor-based methods relate to the ability of a change in score to predict the occurrence of a clinically meaningful milestone as described by the patient [68]. This anchor can be related to QoL, clinical management or function and dynamic throughout disease stages. T. Duong suggested that meaningfulness relate back to 5 DMD stages based on mobility status [69–71]. A 2006 report from the FDA supports the use of multiple approaches in determining minimal important differences specific to the disease stage and population [72]. In DMD, meaningfulness has been addressed using both MCID and MDC methods [68,73–77]. There are advantages to each of these techniques but based on review of literature in other progressive diseases, meaningfulness should be calculated based on longitudinal assessment of data combined with other clinical measures of relevance. T. Duong highlighted a four-level approach to determining quality of evidence for estimates of meaningfulness [68], and remarked that in DMD meaningfulness estimates are predominantly only level 3 or 4 evidence (generated from natural history studies or clinical databases). Outcome meaningfulness is crucial in trial design to determine sample sizes and endpoint selection that may impact clinical practice. T. Duong concluded that the process of identifying clinical significance must move beyond statistical significance and that its reporting may have impact on treatment access and interpretation of expected results across the entire disease spectrum.

E. Henricson presented results from a study on anchor-based MCID in DMD, focusing on relating health-related QoL to multi-systemic disease progression. E. Henricson discussed that measures from similar proximal domains (functional health) are most likely to move together with traditional clinician-reported outcomes (ClinRO) [78]. However, with QoL outcomes, there is a clear distinction between functional activity (such as ability to hop) and habitual activity (such as ability to transfer). E. Henricson highlighted that distribution-based MDC methods are useful in describing concurrent change but are dependant on the disease severity of the cohort. For example, estimates of the MDC of the PODCI Global score can range from 2 to 5.5 points dependant on disease severity subgroups. E. Henricson discussed also anchoring change scores for functional and QoL measures [79]. Finally, E. Henricson highlighted that clinically reported outcomes can be anchored to PROs via a calibrated internal scale.

5. Real-Word data (RWD) and external controls

The collection, quality and utility of RWD was discussed extensively at the ENMC meeting. There was also considerable discussion of new trial designs and tools which could help ease therapeutic development in DMD.

5.1. Quality of real-world data

P. Furlong discussed an approach for establishing data collection beyond specialist centres in the USA. So far, Parent Project Muscular Dystrophy (PPMD) have certified 36 Duchenne care centres and this certification included data quality requirements. P. Furlong highlighted that this data will be extracted from electronic health records in a dedicated system. P. Furlong discussed the focus on PROs whilst the ClinROs are not standardised and of lower quality. One particular focus here is the recording of loss of ambulation date by the patients.

P. Furlong and J. Signorovitch jointly presented the case for collecting RWD to improve care for patients with DMD. They emphasized the need for a collaborative effort to establish the infrastructure necessary for collecting and utilizing RWD in DMD. Ongoing PPMD efforts include the establishment of the Duchenne Registry, integrating electronic health records data, and establishing data governance and sharing protocols for research purposes. A key focus of their presentation was the potential utility of RWD for healthcare researchers in addressing pressing questions in DMD, especially with the advent of multiple effective therapeutics, which cannot be addressed in a timely way via clinical trials, such as treatment prioritisation and the comparative

effectiveness and safety of potential combination therapies. RWD in DMD can also be utilised by sponsors and regulators, such as in providing external controls for long-term extension studies and real-world assessments of treatment effectiveness. Additionally, payers such as insurance companies and government health authorities, can use RWD to inform drug coverage, evaluate the cost-effectiveness of treatments, and to inform outcomes based contracting with sponsors.

P. Furlong and J. Signorovitch highlighted room for improvement of the RWD landscape in DMD, showing that in 55 care centres in the USA there was no functional measure that was consistently recorded for the majority of patients. This motivated a study, in collaboration with the NorthStar Clinical Network, on a concisely recorded ambulatory assessment derived from the NSAA items [80]. This 6-task proxy score explained 95 % of variability in NSAA scores and predicted NSAA scores within ±1.8 units. The next steps in the study include surveying care centres to understand the barriers to broad and consistent assessment, and opportunities for near-term improvements in the breadth and consistency of documenting motor function.

N. Goemans presented the results of a survey designed to assess the quality of the RWD and natural history (NHD) data collected as part of the collaborative Trajectory analysis Project. This included data from the Leuven DMD database, North Star UK, CINRG DNHS, iMDEX, imaging DMD, CCHMC, and DMD Italian collaborative group. The survey's focus was on SOPs used, data management, quality checking procedures and availability of specific data elements and documentation in order to better understand possible use cases for these data including regulatory or health appraisal uses. N. Goemans reported that the level of documentation and data management was higher in the dedicated natural history studies as opposed to the real world/natural history data, but that overall, the data across all sources was of a high quality. A key improvement would be recording the reason for missingness (i.e. inability to perform the function vs. non-compliance vs. not conducted). N. Goemans reported that the data sources generally allowed research by persons involved in data collection, however other uses including for regulatory submissions or analysis by sponsors or payers was reliant on investigator approval. Despite this, some of the data sources have already been used in a regulatory or health appraisal setting.

5.2. Utility of real-world data in DMD trials

S. Ward presented insights into how sharing of real-world data (RWD) can help to support and advance trial design and regulatory approval. S. Ward presented the case study of the identification of at-risk genotypes after several similar anti-transgene Severe Adverse Effects were observed by the sponsors (Sarepta, Solid-Bioscience, Pfizer and Genethon) of four adeno-associated Gene Therapy trials (clinicaltrials.gov IDs: NCT05096221, NCT03368742, NCT04281485 and EudraCT ID 2020–002,093–27 respectively)[81]. Some research questions, for example determining the impact of the genetic heterogeneity in DMD on change NSAA total score over the duration of a one-year clinical trial requires very large patient cohorts, beyond those of a single centre/network, S. Ward framed this as a use case for federating analyses of data across multiple centres and networks and highlighted the work already done using the trial placebo arms and natural history studies as external controls, and demonstrating how these different populations follow indeed a very similar trajectory when relevant baseline characteristics are taken into account [82]. S. Ward discussed that one current blocker to this work is the burden of unique queries, and that a standardised framework would increase ease and flexibility here. Additionally, developing data sharing frameworks will allow trialists to draw from a broader evidence base for when it comes to discussions with regulators.

M. Guglieri presented an update on the TREAT NMD DMD registry, a federated network including 41 registries collecting data on DMD patients. Of these, 17 collect a standardised core dataset, which includes more than 100 unique data items and provides a detailed glossary to ensure consistency in data collection. Member registries are mainly operated by hospitals, university and/or patient organisations and TREAT-NMD includes clinician-entered, patient-entered, and patient-entered-clinician-verified data. M. Guglieri detailed how, in 2022, TREAT-NMD completed the first step of securing EMA qualification for the use of the spinal muscular atrophy (SMA) registries for post marketing efficacy studies and provision of natural history data. Ongoing work is focusing on addressing key areas identified by the EMA, including the consent process and data collection in a federated registry model. TREAT NMD aims to expand the work and experience gained in SMA to other diseases and plans to start this process for DMD in 2023.

E. Vroom presented an update on the activities of the EU Duchenne Patient Organisation. E. Vroom highlighted Duchenne Data Foundation's newly established Duchenne Data Repository, which collects and stores dystrophinopathy data globally. E. Vroom also presented that the Duchenne Data Platform, TREAT-NMD and EURO–NMD have all achieved FAIR (Findability, Accessibility, Interoperability, and Reuse of digital asset) status, and E. Vroom highlighted this was at a low cost for high benefit. Additionally, E. Vroom discussed the level of interaction the Duchene Patient Organisation have with EMA, who are supportive of the FAIR-ification of data in rare diseases. There is ongoing discussion with regulators on how PRO's and patient preference can be incorporated into drug development and approval pipelines.

C. McDonald presented lessons learned Sarepta 9001–102 gene therapy trial. This trial was a placebo-controlled RCT, where the cohorts were stratified only by age (4–5 and 6–7 years). The primary endpoint was change in NSAA (not% change in NSAA). The younger cohort was well balanced between the placebo and treated groups, and there was a statistically significant improvement in both groups, with more points gained on average in the gene therapy group after 48 weeks. However, in the older cohort, due to an unforeseen imbalance, the baseline NSAA score was worse in the treatment group compared to placebo, and no improvement was observed in the treated group of children after 48 weeks. In this older group, the placebo patients with baseline raise from the floor of 3 s were expected to be stable, while the treated group with > 5 s were expected to decline. A reasonable hypothesis is that the lack of divergence of the trajectories of treated vs untreated patients relates to this stratification unbalance. In a post-hoc analysis, when the whole Sarepta cohorts were compared to matched natural history patients (tadalafil [83], CINRG DNHS and for-DMD [84]) using propensity weighting, a 2.3 NSAA point improvement was observed in the treated group vs. an 0.1 NSAA point decline in the propensity matched external control group.

K. Naarding presented results of a review of the reasonings given by patients and/or caregivers for non-participation in observational studies on patients with DMD (3 studies) and BMD (1 study). Participating patients were overall representative of the eligible population, except for that participants in one DMD study were younger compared to non-participants, and no inclusion of any patients with more distal mutations (downstream of exon 63) in all studies. K. Naarding reported that the most frequently reported considerations for patients and/or caregivers were "burden of protocol" (38 %), "the inclusion of an MRI scan in the protocol" (30 %), and "travel-time" (19 %) [85]. These

results show that it is important to keep checking in any study if participants are representative of the population.

5.3. New approaches to trial design using real-world data

P. Furlong presented on "Basket trials" as an acceleration platform. This framework would utilise a master protocol, which would enforce standardisation of multiple trial aspects, including recruitment criteria, standards of care and follow-up times. Multiple therapies could then be trialled with a shared placebo cohort. Prior to the coronavirus pandemic this protocol was on track for a category C meeting with the FDA. P. Furlong highlighted that this work needs industry and infrastructure buy-in, but that several sponsors had expressed an interest at the Duchenne drug development round table. S. Hendrix highlighted the potential utility of Bayesian Adaptive Trial designs, where there are multiple treatment arms, one set of inclusion criteria and one shared placebo arm. Over time, the treatment arm with the most observed treatment effect have increased likelihood of receiving patients.

T. Martinez gave an overview of a Clinical Trial Simulation (CTS) tool on behalf of the Duchenne Regulatory Science Consortium (D-RSC) at the Critical Path Institute. D-RSC was co-founded by PPMD and convenes stakeholders from the drug development industry, academic and clinical researchers, non-profit research foundations and patient advocacy groups, and regulatory experts. The CTS tool uses the D-RSC's integrated DMD database, which spans 13 clinical trials, 5 natural history studies, 3 clinical studies and 1 patient registry. The goal of the CTS is to allow trialists to repeatedly simulate possible trials in order to optimise the parameters, such as the inclusion criteria, sample size and duration. D-RSC has developed two separate workflows, one submitted to EMA's Qualification of Novel Methodologies pathway and the other submitted to the FDA's "Fit-for-Purpose" initiative for drug development tools. The final briefing document is under review by the FDA. In November 2022, the EMA issued a letter of support of the model-based Clinical Trial Simulation Platform for Duchenne Muscular Dystrophy.

The utility of a "rescue protocol", whereby if a trial participant in the placebo arm is observed to have a clinically meaningful decline in a ClinROs is switched to an open label arm was also discussed by F. Muntoni, C. McDonald and J. Signorovitch One potential risk associated with this trial design is the subjectiveness of the outcome measures, and F. Muntoni mentioned the more objective MRI assessments for switch over decisions.

6. Conclusions and workshop deliverables

The workshop participants agreed on important lessons that were learned from 10 years of clinical trials in DMD and decided together on next steps.

6.1. Consensus on what we have learned from clinical trials in DMD in the last decade

6.1.1. Trial outcome measures

Outcome measures encompass various levels of investigation from the molecular level to QoL. Clinical outcome measures used in the past decade have proven more reliable than once feared. Although subject to influence from non-measurable effects (e.g. motivation, fatigue), the majority of outcomes in DMD demonstrate high test-retest reliability. There is also concordance between outcomes in natural history datasets and placebo-controlled arms, which illustrates that there does not appear to be a measurable placebo effect.

Consensus was reached that composite endpoints involving different levels of investigation are worth exploring as a means to reduce heterogeneity and increase sensitiveness to change over time. This effort could either be conducted for different disease stages or a composite endpoint could potentially span multiple disease stages. Additionally, the new concept of slowing of the decline of trajectories should be explored, also to understand its potential value as outcome measure.

Biopsies are still required for many clinical trials. The participants voice a strong wish to minimize the number of biopsies in clinical trials and per clinical trial. The participants would like to demonstrate the redundancy of baseline biopsies.

6.1.2. Heterogeneity in DMD and the effect on study protocols

In the last decade there has been considerable improvement in the understanding of the variability in disease progression rates in DMD. The observed mix of trajectories results in high variance in clinical trials. Sponsors have sought to reduce variance by using strict inclusion and exclusion criteria to enrol patients who are in a more predictable disease phase: slowly declining but still able to walk. Early efforts to define this demographic using age, baseline function in the primary endpoint, and presence or absence of steroids, had mixed results. In the last few years, prognostic models have proved to be important in explaining variance in 48-week trials; by considering a combination of functional measures, use of steroids, height, weight, and BMI at baseline, it is possible to explain up to 40 % of the variability in disease progression rates at one year. Understanding these prognostic factors can guide clinical trial design and can increase power when applied to analysis of trial results. The participants discussed also the combination of different MRI observational studies and placebo arms in order to study and improve prediction of disease trajectories and loss of function. Some participants of the workshop are involved in these efforts.

The participants learned that a typical 12-month clinical trial may be insufficient to discern the effectiveness of exon-skipping drugs. Although increases in dystrophin level may be evident within 12 months, the impact of increased dystrophin on clinical function is clearer over time and with the levels of dystrophin induced by first generation antisense compounds, a minimum of 18–24 months is necessary to appreciate divergence from untreated patients.

The participants voiced the concern that regulatory agencies advise clinical trials to meet the full statistical power when studying the effect of the drug on multiple endpoints, instead of on a specific primary endpoint. Currently, there is no guidance on the required effect to be measured in these multiple endpoints, which might lead to primary and secondary endpoints being treated equally, asking for statistical significance and thereby increasing the chance of failed trials in potentially effective drugs. S. Hendrix added that non-significant secondary endpoints that are in the same direction of an effect of the drug still support the primary endpoint. Testing on these multiple endpoints also increases the burden for participating patients and families. The participants agreed to discuss alternatives to multiple endpoint clinical trials in future engagement with regulatory agencies.

The participants notice an increased difficulty to recruit patients from a limited number of eligible patients in competing clinical trials, especially in the older/adolescent population. A major increase in the burden is due to safety assessments like extra hospital visits for blood draws or prolonged in-hospital stays for IV drug administration. There is also little influence on the type and number of drugs that are developed. The participants would like to improve the selection based on preclinical data and feasibility of the protocols and to discuss with EMA and FDA how they weigh practical issues regarding safety assessments in their protocol evaluation. Patient representatives voiced the wish for a clear standardized operating procedure in case one patient could

potentially participate in multiple trials or if a limited number of participants is required while many patients are eligible and willing to participate. These SOPs are followed in some trial sites, but the community could benefit from communicating which procedures are followed. At the same time, the clinicians observe that due to the large number of trials, it is seldom the case that more patients want to participate in a particular trial than are allowed at a certain site.

Patient representatives also voiced the concern of a lack of communication between clinical trial personnel and care providers, which could lead to a lack of care. The risk might be increased when the trial and care site are in different countries or states. The participants propose a standardized operating procedure to ensure care is continued during clinical trial participation.

Participants notice that sponsors and Contract Research Organizations use different methods to make case report forms, which leads to unnecessary queries. Harmonization of case report forms could decrease the time cost for trial sites.

6.1.3. Meaningfulness in treatment effects

Clinical meaningfulness of outcome measures is of vital importance, but the definition can differ depending on the stakeholder: patients, parents, clinical evaluators, physicians, regulators, payers. The answer requires weighing the burden and side effects of treatment with a defined extent of benefit, so that regulators can make a balanced decision and clinicians can properly counsel families. Furthermore, families are in need of extensive counselling prior to clinical trial participation in order to manage expectations, both on the possible clinical benefit and risk and on the potential discontinuation of a trial that has failed to meet the endpoint despite perceived clinically relevant benefit for the patient. A clear definition of clinical meaningfulness is needed in order to anchor outcome measures to the same concept. MCID is often used as a parameter to define clinical meaningfulness, but different ways to calculate MCID exist with different implications and the MCID concept may not be applicable in across the entirety of a progressive disease where the clinical meaning of the same result may differ in different stages of the disease. The participants agreed to discuss the topic of clinical meaningfulness and MCID with regulatory authorities.

Patient reported outcome measures were developed together with patients and caregivers, but so far no MCIDs have been established. The participants agreed to study current PROs in more detail and try to further improve these measures.

6.1.4. Real world data in DMD and novel trial designs

The use of natural history controls to compare with an intervention arm of a clinical trial or enrich the placebo arm requires sufficient quality control. Significant collaborative efforts have already assessed the consistency of certain functional outcome measures between placebo arm data and real world data [38,86]. The required level of quality control could be different for post marketing studies. Clinical/functional assessments may be relatively well standardized by now, but recording of treatment is more challenging and consensus on milestones is still required. Participants agreed that it should be defined what type of quality control is required to ensure observational studies and registries can conform to this.

Guidance on how to apply increased General Data Protection Regulation (GDPR) requirements would improve the process of sharing RWD, either via public-private collaboration or registries. Adding data longitudinally to cohorts we follow-up will not be possible in the same way we did this 10 years ago. The participants want to take this discussion forward and aim to receive guidance from regulatory authorities.

Patient representatives stressed the wish for shorter placebo arms, but not if this hinders the possibility to prove efficacy of new drugs and increases the chance of failed trials. Rescue protocols using an objective method to demonstrate a clear decline, potentially MRI, could be used to determine when to switch a patient from placebo to the active drug, potentially after 6–12 months.

The participants were interested in the option of a platform or master trial in which multiple drugs can be studied compared to a single placebo arm [82]. This is most likely to be successful for drugs with a particular mechanism of action, such as AAV mediated gene therapy or AON therapies. Representatives from sponsors added that these protocols need to be attractive for pharmacy to use them. The participants agreed that it would be useful to assess which of the current trials could have been combined in a platform trial and to discuss this option with sponsors.

Outcome measures and use of RWD on function should benefit from all developments on clinical meaningfulness and patient preferences in all phases of the disease. The participants agreed that it is worthwhile to discuss the use of real-world data and explore possibility of video technology or wearables to collect more frequent data in the real-world environment that may better reflect daily life and decrease trial burden. Additionally, agreement to better assess arm function related to clinical meaningfulness and PROs with EMA and FDA. The view on established functional assessments like PUL and their relation to clinical meaningfulness may not be similar in these agencies. This could be topic of separate workshops and regulatory discussions beyond the field of DMD.

6.2. Plan and action items for interacting with regulators to further discuss regulatory perspectives to guide upcoming clinical trial design and analysis

6.2.1. Trial outcome measures

A small brainstorm group will discuss composite endpoints and percent slowing of disease progression to explore this for use as outcome measures in DMD. The discussion on composite endpoints will range from combining scales to endpoints covering multiple outcome measure domains including biomarkers.

The participants agreed to try to expand the work on outcome measures in ambulant DMD to the non-ambulant phase focusing on outcome measures of arm function. This could be a topic of a separate workshop and regulatory discussion, potentially gaining insight from beyond the field of DMD.

The participants agreed that it would be valuable to conduct an analysis on muscle biopsies taken at baseline to show which standard values can be expected to demonstrate the redundancy of baseline biopsies especially in case of exon skipping studies, or now when recruiting patients on AAV micro-dystrophin therapies where it is possible to measure both the endogenous protein production, and the micro-dystrophin produced by the transgene.

Following on from the previous actions on outcome measures, the participants would like to organize and take part in a multi-disease (probably degenerative disorders) meeting with the EMA on outcome measures. Topics to discuss include completeness of data, clinically meaningfulness, percentage slowing of disease progression, composite endpoints, and biomarkers.

6.2.2. Heterogeneity in DMD and the effect on study protocols

In the discussions with regulatory agencies, the participants also want to raise concerns for the requirement of multiple endpoint clinical trials and discuss alternatives.

The participants agreed to discuss the protocols that are followed by regulators to assess feasibility and likelihood of

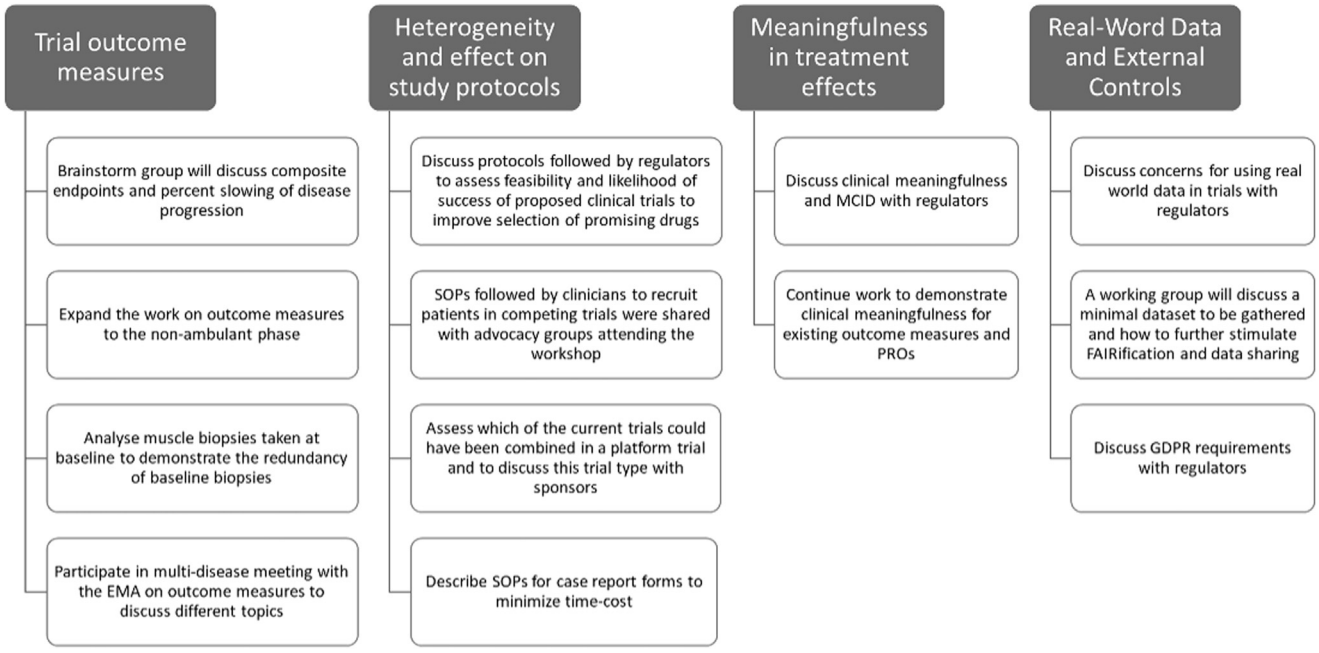

Fig. 1. Plan and action items resulting from the workshop.

success based on preclinical data of proposed clinical trials in order to improve the selection of promising drugs. The participants agreed that it would be useful to communicate which procedures are followed by clinicians to recruit patients in competing trials, and existing SOPs were shared with the advocacy groups attending the workshop.

The participants underlined the importance of studying objective outcome measures to use in rescue protocols. The participants decided to assess which of the current trials could have been combined in a platform trial and to discuss this trial type with sponsors.

The participants agreed to discuss with regulators/sponsors or put in writing what SOPs for case report forms should be to minimize time-cost.

6.2.3. Meaningfulness in treatment effects

The participants agreed to discuss the topic of clinical meaningfulness and MCID with regulatory authorities and continue the work to demonstrate clinical meaningfulness of existing outcome measures. A universal definition and registration of milestones would aid in the assessment of clinical meaningfulness.

The participants agreed to demonstrate clinical meaningfulness for PROs, study them in more detail and try to optimize these measures for use in clinical trials.

6.2.4. Real-Word data and external controls

The participants plan to discuss potential concerns for using real world data as historical controls or to enrich a placebo arm with regulators. These concerns will be studied using data from available real world data sources in close contact with patient representatives. The participants want to ensure that a clear definition of required quality control is produced and shared. Additionally, the potential bias induced by including external controls needs to be quantified. Regulatory guidance on this matter will be considered when identifying and prioritising these concerns, with an aim to understand the potential inclusion of external controls across the full scope of the clinical trials process. A small working group will discuss a minimal dataset to be gathered (Fig. 1).

The participants plan to discuss General Data Protection Regulation (GDPR) requirements with regulators and receive guidance on how to implement this into research practise. A small working group will discuss how to further stimulate FAIRification and sharing of data.

Participants

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Abbreviations

10MWR	10 metre walk run
4SC	4 stair climb
6MWD	6 min walking distance
AAV	Adeno-associated Virus
ACTIVE	ability captured through interactive video
ASO	Anti-sense Oligonucleotide
BMD	Becker Muscular Dystrophy
CHMP	Committee for Medicinal Products for Human Use
ClinRO	Clinician-Reported Outcomes
CTS	Clinical Trial Simulation
DMD	Duchenne Muscular Dystrophy
D-RSC	Duchenne Regulatory Science Consortium
DVA	Duchenne Video Assessment
EMA	European Medical Agency
FDA	Food and Drug Administration
FF	fat fraction
GC	glucocorticoids
MCID	minimal clinically identifiable difference
MDC	minimum detectable change
MHLW	ministry of health, labour and welfare of Japan
NHD	natural history dataset
NSAA	North star ambulatory assessment
OLE	open label extension
PPMD	parent project muscular dystrophy
PROs	patient reported outcomes
PUL	performance of upper limb
qMRI	quantitative MRI
QoL	quality of life
RFF	rise from floor
RWD	real world data
SMA	spinal Muscular Atrophy
SOP	standard operating procedures
SV95C	stride velocity 95th centile
VL	vastus lateralis

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Declaration of Competing Interest

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