iterative process to expand the current DMD dataset to 1) capture real-world safety and effectiveness of emerging therapies; 2) capture the patient voice; 3) understand the landscape for methodically capturing participation; and 4) align with the global TREAT-NMD expanded dataset. Initially, a survey framework based on the TREAT-NMD expanded DMD dataset was utilized to rank dataset items for inclusion in the CNDR. The survey was broadly distributed to health care providers within the CNDR network, as well as patient organization partners. The survey was then followed by a consensus meeting with the CNDR DMD working group to finalize the proposed dataset. In order to ensure the dataset aligned with stakeholder needs, patient organization partners were then re-engaged in discussions regarding data items. Lastly, the finalized draft dataset was circulated to pharmaceutical partners for feedback. Importantly, the DMD dataset was mapped across the ICF domains of body function and structure, activities, and participation to ensure a robust global picture of living with Duchenne in Canada. The CNDR captures a comprehensive DMD dataset to evaluate long-term real-world patient-focused experience with available and emerging therapies.

http://dx.doi.org/10.1016/j.nmd.2021.07.146

EP.122

Prognostic factors for pulmonary milestones in Duchenne muscular dystrophy (DMD)

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Knowledge of prognostic factors for pulmonary outcomes in DMD serves a general understanding of natural history and can help facilitate externally controlled studies and the long-term evaluation of novel therapies. We assessed prognostic factors for time to forced vital capacity (FVC) %-predicted < 80% (among n=368 boys free of this outcome at first assessment, 121 of whom eventually had the outcome) and time to FVC %-predicted < 50% (among n=488, 51 of whom eventually had the outcome) using Cox proportional hazards analyses. Data originated from three natural history databases (UZ Leuven, PRO-DMD-01 data provided by CureDuchenne, and Cincinnati Children's Hospital Medical Center) Average follow-up time was ~3 years. Being ambulatory at baseline and having higher baseline FVC %-predicted were significant predictors of longer time to pulmonary milestones. Prognostic accuracy was also compared between models based on age, data source, ambulatory status, and FVC %-predicted and models further incorporating steroid type, height, weight, BMI, and timed 10-meter walk/run velocity in ambulatory boys. The additional prognostic factors increased the pseudo-R2, a measure of the proportional of variability explained, from 0.20 to 0.31 for FVC %-predicted < 80% and from 0.17 to 0.19 for FVC %-predicted < 50%. Stratification of boys based on risk score tertiles produced groups with 2-year risks of reaching FVC %-predicted < 80% of 37%, 15%, and 4%, respectively; median times to FVC %-predicted < 80% in these groups were 2.4, 7.6 and 8.5 years, respectively. A prognostic score incorporating ambulatory status, level of 10MWR function for ambulatory boys, and baseline FVC%-predicted identified patients at significantly different levels of near-term risk of pulmonary decline.

http://dx.doi.org/10.1016/j.nmd.2021.07.147

EP.123

Functional trajectories of upper limb and pulmonary function before and after loss of ambulation in Duchenne muscular dystrophy

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Characterization of disease progression in DMD patients around loss of ambulation (LoA) is needed to inform selection criteria and choice of endpoints in clinical trials including these patients. We analyzed upper limb and pulmonary function in the years immediately before and after LoA (defined as inability to walk 10 meters) using data from 51 boys with DMD from the PRO-DMD-01 natural history study (data provided by CureDuchenne). Included boys were ambulatory at their first study assessment and non-ambulatory at a follow-up assessment. Mean age at LoA was 12.7 years (range: 7.1-18.6 years). Based on longitudinal mixed effects models, average annual declines for before vs. after LoA were 5.6 vs. 10.3 percentage points for forced vital capacity percent predicted (FVC-%p) and 2.3 vs. 3.8 points for Performance of Upper Limb (PUL version 1.2) total score. Neither difference was statistically significant, and there was substantial variability in function across individuals and within individuals over time. The proportion of patients with FVC-%p < 80% and PUL entry score <6 started increasing approximately two years before LoA. About 50% of patients experienced FVC-%p <80%, and ~75% experienced PUL entry score <6 by the time of LoA; all patients reached these milestones within two years after LoA. Among patients with 10 meter walk/run time > 10 seconds, median subsequent time to LoA was ~1 year and all reached LoA within 2 years. Overall, there is heterogeneity in the ordering and magnitude of deficits in upper limb and pulmonary function before and after LoA. Enriching trials for patients with declining upper limb or pulmonary function is achievable without restricting to non-ambulatory patients. Design of composite outcomes, or multi-outcome trial designs, that are sensitive to changes in multiple functional domains before and after LoA should be investigated.

http://dx.doi.org/10.1016/j.nmd.2021.07.148

EP.124

Actimyo®: Normative data in a non-controlled environment

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Duchenne muscular dystrophy (DMD) is a rapidly progressive X-linked disorder characterized by a muscle weakening responsible for the loss of ambulation around the age of 12. One if the limiting factor of clinical development is the sensitivity and the reliability of the current outcomes. Recently, the 95th centile of stride velocity (SV95C) was qualified by the European medicines agency as a valid secondary outcome for clinical trials in subjects with DMD. Gathering normative data is crucial to pursue validation process. For this purpose, 91 healthy volunteers aged from 6 to 85 years were enrolled in the ActiLiège study. Eighty-four were assessed at baseline and 12 months later. They performed the 6-minute walk, 4-stair climb, rise from floor, and the 10-metre walk tests. For one month at baseline and at 1-year, participants were also asked to wear ActiMyo®, a wearable device designed to accurately and passively capture limb movements in daily living. Afterwards, stride length, stride velocity and the distance walked per hour were calculated over each recording period. At baseline, SV95C was 2.6 m/s ± 0.4 in children and 1.6 m/s ± 0.3 in adults. It was not correlated

with height or age in children, and did not significantly change over a 1-year period. It was not correlated with 6MWT, 4SC or 10MWT as it is in DMD. In children, we observed significant correlations of stride length (50th and 95th centile) with age (ρ=0.869, ρ=0.312) and with height (ρ=0.876, ρ=0.274). These measures increase in children over 1-year, as did the timed tests (6-minute walk, 4-stair climb, 10-metre walk tests). Those normative data permit to identify variables with important confounding factors and help to interpret the longitudinal evolution of the SV95C over time in patient populations.

http://dx.doi.org/10.1016/j.nmd.2021.07.149

EP.125

Minimal detectable changes in functional measures in Duchenne muscular dystrophy (DMD): A study of multiple centers, networks and trial arms

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Design of clinical trials and evaluations of treatment efficacy in DMD require an understanding of the meaningfulness of changes in functional measures. An important concept is the *minimal detectable change* (MDC), i.e., the minimal magnitude of measured change indicative of true changes due to acquisition or loss of motor function related to the disease, rather than transient variation or measurement error. We used data from six real-world/natural history data sources (RWD/NHD) and eight clinical trial arms to obtain MDC estimates for North Star Ambulatory Assessment (NSAA) total (n=1,012), 4-stair climb (4SC) completion time and velocity (n=1,029), and 6-minute walk distance (6MWD; n=625). For 4SC time, completion times were truncated at 12s in all data sources to mitigate differences in recording of completion times between RWD/NHD and clinical trial arms. Patients aged ≥4 to <18 years, receiving steroids, and with at least minimal baseline ambulatory function (NSAA > 12, 4SC time < 12 seconds, or 6MWD > 75 meters) were analyzed. Variation around patient-specific fitted trajectories, based on longitudinal mixed effects models, was used to estimate MDCs and thresholds that provide >80% confidence that observed changes reflect underlying definitive functional change. Minimal important difference estimates based on 0.5 standard deviation (SD) of baseline values were also calculated. Estimated thresholds for >80% confidence in true change were 2.8 units for NSAA, 1.3 seconds for 4SC time, 0.36 stairs/second for 4SC velocity and 36.3 meters for 6MWD. MDC estimates were similar across RWD/NHD sources and trials for all measures. Thresholds for minimal detectable change in NSAA were similar across different age groups. MDC estimates were smaller than 0.5 SD estimates. The identified thresholds can be used to inform endpoint definitions, as inputs into power calculations, or as benchmarks to contextualize individual and group-level changes due to treatment.

http://dx.doi.org/10.1016/j.nmd.2021.07.150

EP.126

DMD Hub: Preparing the field for gene therapy trials

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Funded in 2015, the DMD Hub, a collaboration between Duchenne UK and the two UK neuromuscular centres of excellence, is an established network of Duchenne muscular dystrophy (DMD) clinical trial sites in the UK (www.dmdhub.org). With the arrival of advanced therapy trials for DMD, the DMD Hub is supporting the neuromuscular community to facilitate the setting up and running these trials in the UK. In November 2019, the DMD Hub held the first gene therapy meeting with over 100 key stakeholders including clinical experts, patient representatives, industry, regulators and payers to discuss existing barriers to gene therapy access through clinical trials and as approved treatment in the UK. We present the results of two collaborative DMD Hub projects, which were identified as two of the main deliverables of the 2019 meeting. 1. Patient Preference Survey - a unique collaboration between the DMD Hub, Parent Project Muscular Dystrophy (PPMD) and 6 industry partners. The survey builds on the *DMD* gene therapy patient preferences information and methodology previously published by PPMD and RTI International. The results of the survey will help inform the community, facilitate regulatory submissions and manage patient expectations. 2. Institutional Readiness Survey - UK neuromuscular sites have participated in a detailed survey to better understand how prepared sites are to run gene therapy trials and deliver licenced products. The results will be used to drill down on the true capabilities and facilities at sites and to help identify areas for development and training. The DMD Hub will work with established infrastructures to create and deliver work plans to address the identified needs. The collaborative work has increased the knowledge of the DMD community and will ensure we are in a strong position to effectively and efficiently deliver the gene therapy trials and when appropriate, as ready as possible to implement gene therapy in a clinical setting. The outputs will be shared so that other countries and other diseases may benefit and duplicate the models developed.

http://dx.doi.org/10.1016/j.nmd.2021.07.151

EP.127

The Dutch multicenter Duchenne and Becker register: facilitation of trial readiness and effective use of patient data

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Trial readiness and reduction of burden is of utmost importance in view of the number of compounds currently in development for Duchenne and Becker patients (DBMD). National registries play an essential role as they facilitate patient recruitment and are able to give insight in population's characteristics. The Dutch dystrophinopathy database (DDD), a DBMD register, has been updated and now functions as a multicenter database of the Duchenne center NL (DCN) able to capture a cohesive and extensive standardized dataset. DCN is a collaboration between three academic partners (LUMC, Radboudumc, Kempenhaeghe) and two patient organizations (Duchenne Parent Project, Spierziekten NL). The main goals of the DDD are 1) the ability to approach patients for study participation, 2) the description of epidemiology and natural history using a yearly questionnaire and 3) reduce of burden for patients by storing clinical data in the registry that have been obtained within the DCN healthcare centers. To achieve this