Neuromuscular Disorders 33 (2023) 339–348

Contents lists available at ScienceDirect

Neuromuscular Disorders

journal homepage: www.elsevier.com/locate/nmd

Workshop report

266th ENMC International Workshop: Remote delivery of clinical care and validation of remote clinical outcome assessments in neuromuscular disorders: A response to COVID-19 and proactive planning for the future. Hoofddorp, The Netherlands, 1–3 April 2022

Lindsay N. Alfano[a,b,*], Meredith K. James[c], Gita M. Ramdharry[d,e], Linda P. Lowes[a,b], on behalf of the ENMC 266 Workshop Study Group

[a] The Abigail Wexner Research Institute at Nationwide Children's Hospital, Center for Gene Therapy, Columbus, OH, United States
[b] The Ohio State University College of Medicine, Department of Pediatrics, Columbus, OH, United States
[c] The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom
[d] Queen Square Centre for Neuromuscular Diseases, National Hospital for Neurology and Neurosurgery, University College London Hospitals NHS Trust, London, United Kingdom
[e] Department of Neuromuscular Diseases, UCL Institute of Neurology, London, United Kingdom

ARTICLE INFO

Article history:
Received 16 February 2023

Keywords:
Clinical outcome
Assessment
Care
Remote
Video
Neuromuscular disorders
Function

1. Introduction

The organizers of this 266th European Neuromuscular Center (ENMC) workshop welcomed 24 additional participants from 10 countries across five continents (Argentina, Australia, Denmark, France, Greece, Ireland, Italy, South Africa, the United Kingdom, and the United States of America), comprising experts in physical therapy and outcome measure development, speech-language pathology, psychology, biostatistics, as well as industry and patient advocacy representatives. Due to COVID-19 restrictions and travel challenges approximately half of the participants were in virtual attendance. The other half of the study group gathered in Hoofddorp from 1–3 April 2022 to discuss progress in remote delivery of clinical care, validation of remote clinical outcome assessments (COA) for persons with neuromuscular disorders and plan future directions.

Deficits of muscle strength and function are hallmark features of neuromuscular disorders (NMD) and have been associated with sequelae including pain; musculoskeletal anomalies; decreased function and loss of independence in daily activities as well as inability to access their home, community, school and occupational environments; respiratory and/or cardiac complications; psychological distress and reduced health-related quality of life. Standardized assessments of strength and function are used to track disease trajectory to prospectively advise the need for equipment, home and work modifications, and other assistive devices. Given the significance and impact of progressive muscle weakness, strength and functional outcomes are often featured as primary and secondary endpoints for studies investigating natural history and therapies aiming to alter the progression of NMD. It is crucial that data representing key functional endpoints are obtained via highly controlled and standardized methods by individuals, primarily physical therapists (PT), who are qualified and trained to collect them.

The COVID-19 pandemic presented unprecedented challenges to the delivery of clinical care and the use of COA for people living

* Corresponding author at: 700 Children's Dr, Rm AB7036
E-mail address: lindsay.alfano@nationwidechildrens.org (L.N. Alfano).

https://doi.org/10.1016/j.nmd.2023.02.011
0960-8966

with NMD. Due to the frequent comorbidities seen in NMD and often the chronic use of immunosuppressive treatments, and thus the potential for severe disease from COVID-19 infections, it was considered a significant risk for many individuals with NMD to leave their homes for clinic/hospital visits during the height of the pandemic and subsequent waves; this was also exacerbated by heavily restricted travel in some areas of the world. To ensure the continuation of clinical care and clinical trials, COVID-19 mitigation strategies were urgently required to accommodate circumstances where clinical service users and research participants were unable to travel to clinics and hospitals.

In March 2020, with several trials and natural history studies underway, including trials collecting data on primary endpoints during lockdown, a fast response, and alternative strategies were required to protect study efficacy endpoints and ensure ongoing evaluations for patients and data collection for clinical trials. Remote testing of existing outcome measures had not yet been validated in individuals with NMD and clinical trials, therefore, did not include remote evaluations. Exploring the feasibility and suitability of adapting current COA as part of remote evaluations was critical to ensuring ongoing data collection in clinical trials, natural history studies and for healthcare service delivery.

Several study sponsors introduced amendments to enable remote evaluations, supported by video streaming of the visit with their trial PT or clinical evaluator (CE), which has raised discussions around the validity and reliability of remote evaluations and their correlation to clinic-based testing. Additionally, the model of training a PT to conduct specialized COA needed to evolve to overcome COVID-19 restrictions to ensure trained staff were available for clinical evaluations. A group of expert PT in the field of NMD, working across clinics, countries, and clinical trials developed initial guidelines for the suitability, feasibility, and acceptability of performing remote COA commonly used in clinical trials [1].

Remote evaluations have the potential to change traditional trial design paradigms and increase access to trials and expert clinical care, if deemed feasible, valid, and reliable. It is thus critical to understand the comparability of clinic/hospital-based evaluations and those live-streamed from an individual's home. The experts assembled for this workshop aimed to address the following goals:

- Evaluate the utility of remotely collected COA for both clinical and research purposes to advise best practice for continuity and access to expert clinical care and maintain the integrity of clinical trial design
- Document experiences of conducting remote COA from a wide range of stakeholders (including clinicians, patients, families, researchers, and industry).
- Identify limitations to using remote COA and other assessment tools and the impact for future trial design
- Evaluate the quality of remote training and reliability testing for PTs new to the NMD field.
- Develop an action plan to address identified knowledge gaps and areas of future research

To achieve these workshop goals, participants presented their area of expertise, recent experiences, as well as published and unpublished research. The shared information was used in the discussions to develop an action plan.

2. Current experiences using telemedicine around the globe

2.1. Utility of telemedicine from the patient perspective (Alessandra Gaeta, Director of Research at Duchenne UK, United Kingdom)

The workshop began with a perspective on how innovative technologies, including digital health technologies, and holistic assessments of disease progression can support the development of outcomes measures, interventions and treatments that are meaningful to people living with NMD. Dr. Gaeta elaborated on applications of digital technologies that the NMD community would particularly like to see implemented in the future, such as: encourage exercise (e.g., standing); help coordinate care (e.g., appointments and test results, reminders to take medication; monitor mental health through questionnaires); help access support networks and communicate with peers; and home-based Duchenne Muscular Dystrophy (DMD) assessments (also in the context of clinical trials). Validated outcome measures that can capture patient-generated data, and their systematic validation and adoption in clinical drug development will provide much needed evidence for regulatory, health technology assessment and payer decision making. Innovative technologies, including digital health technologies, have the potential to enable and accelerate research advancement.

2.2. Global experiences using telemedicine (Ulla Werlauff, Physical Therapist, Denmark; Robert Muni-Lofra, Physical Therapist, United Kingdom; Kristy Rose, Physical Therapist, Australia; José Corderí, Physical Therapist, Argentina)

Dr. Ulla Werlauff described the experience of the Danish National Rehabilitation Centre for Neuromuscular Diseases (RCFM). As a tertiary primary referral hospital, RCFM works as a facilitator of cross-sectoral collaboration with individuals, families, hospitals, and local communities about the person's rehabilitation. The RCFM includes clinical services where health professionals from multiple disciplines (i.e., physical therapists, occupational therapists, doctors, psychologists, and social workers provide counseling, information and education about neuromuscular diseases often in the individual's home and local communities; and a research service, where people with NMD are invited to participate in various studies. The delivery of actual physical therapy is for instance performed by local physical therapists with advice from physiotherapists from RCFM.

During the pandemic, meetings with people living with NMD and health professionals in the clinic changed from physical meetings to online meetings where possible, and when it made sense. Dr. Werlauff described the benefits of digital meetings as being more flexible and less time-consuming; having a stricter meeting structure; and the experience that digital meetings were a suitable forum for sharing information. Some assessments (e.g., the Egen Klassification 2 (EK2) scale) were possible to perform as interviews and video demonstrations, and in some situations a pre-recorded video of walking or other functions could be used to estimate the patient's current functional level. Identified disadvantages and challenges included technological problems such as poor internet or computer skills; difficulties conducting meetings with several family members on one screen; inability to assess muscle strength and joint motion; difficulties in assessing or determining moods and emotions. For research, the RCFM used surveys and questionnaires (e.g., Brooke scale, Visual Analog Scale, validated questionnaires); conducted interviews, either online (computer) or via the telephone, and focus group interviews using digital meeting apps such as Microsoft Teams or Zoom. In some disease groups (DMD and Myotonic Dystrophy Type 1) physical interviews were a priority and had to wait until it was safe to meet again. In the future, both services will use a combination of physical and remote meetings, therefore a hybrid approach.

Dr. Robert Muni-Lofra presented the UK experience based on the National Evaluation of Remote Physiotherapy Services of the Chartered Society of Physiotherapy [2] but also the team experience at the John Walton Muscular Dystrophy Research Centre (JWMDRC), Newcastle upon Tyne NHS Foundation Trust.

At the national level, the results of the study which evaluated the impact of remote PT service delivery were presented. Over the period of July 2020 to April 2021, a three-stage analysis was performed starting with a scoping review, a national survey and finalized with a series of case studies. The study identified a number of topics related to the person receiving the service such as preference in service delivery, degree of satisfaction, role of the current clinical presentation on the experience, challenges related to communication, perception of risk and safety, convenience of reducing burden to travel and cost and challenges related to technology. At the organization level, the topics reported related to the overall figures of the evaluation, the resources required at technical level but also for training and ongoing support, the workload pattern and intensity, the impact of the implementation of a quick transition in the leadership at organization and service level (COVID has been a catalyst for change) and different challenges identified (related to governance, policy and regulation, guidance, costs, insurance and legal).

The experience at the JWMDRC was reported relating to the evolution of the service provision from the end of May 2020 to March 2022. This started with a fully remote provision to a hybrid model, combining face to face clinic with remote at equal proportion. The introduction of remote clinical assessment with online surveys and remote spirometry had been the main structural changes together with the introduction of "Attend Anywhere" as a video platform for remote consultations.

The conclusion of both experiences suggest that a hybrid PT service model can offer a personalized and flexible approach. This model can help to ensure that PT is safe, equitable, effective and responsive to individual needs and preferences. It is important to take into consideration the multiple interacting factors such as communication needs, resources and digital literacy that can influence what feels is the right type of service delivery at the right time for each individual.

Dr Kristy Rose presented experiences and lessons learned using telemedicine in Australia during the height of the pandemic. Australia was fortunate to experience relatively short periods of lockdown. As a result, telemedicine was largely used in an outpatient capacity as individuals could still access their local hospitals for essential clinical care and clinical trial visits. Family engagement using telemedicine was variable during this time. Knowing the lockdowns would likely be brief, many individuals and families opted to take a "break" from therapy and clinics, particularly if they were clinically stable. In Australia, individuals often travel to different states to access clinical trials. Due to state border closures during the pandemic, some clinical trial participants were therefore unable to cross state borders for their study assessments. In this instance, online platforms such as Zoom were utilized to facilitate remote delivery of clinical trial COA. This proved to be successful until theose participants were able to travel to the clinical trial sites again. While a full assessment using all the study COA was usually not possible remotely, it still allowed for the collection of some data and allowed the trials to continue during the pandemic.

José Corderí presented the Latin American experience with telemedicine and discussed the difficulties with the technology required, primarily internet access. While access is less of a concern in larger cities, few individuals and families in rural areas of have access to fast, uninterrupted internet connection and in many instances the connection doesn't support video streaming. However, in Argentina, even during periods of lockdown, people living in the capital could attend clinical care visits at the center, in-person. Many centers attempted some level of telemedicine with varying levels of success. Lic. Corderí described PT as traditionally being a very hands-on practice. For this reason, he found the use telemedicine difficult because he had to rely on caregivers to facilitate the activities he wanted to observe. The PTs attempted to guide and train caregivers, however, the level of success differed across patients. When individuals couldn't travel to clinic for assessments, some clinical care and follow up was lost. He reports that the LATAM community is still assessing the negative effects of the COVID-19 lockdown, for example reduced access to rehabilitation, lost follow up, and weight gain due to reduce mobility. He indicated possible benefits of changing to telemedicine included increased access to psychological and mental health therapy, increased involvement in patient advocacy groups, and increased community involvement via social networks. However, there is an ongoing need to standardize remote COA and implementation of home-based rehabilitation programs.

2.3. Opportunities for global outreach (Maha Elseed, Physician, United Kingdom/Sudan)

Dr. Elseed provided an overview of her experience utilizing technology to provide outreach care to individuals in Sudan [3]. She highlighted the use of smart phones and WhatsApp as an application to communicate with 200+ caregivers providing care and support to children with neurological disabilities. Caregivers reported great benefit from participation in the WhatsApp group and felt their questions were answered and communication was useful. In addition, the group served to connect families in similar situations providing a support group framework and structure. While these activities and use of technology were initiated well before the pandemic, this study highlighted using commonly available technologies to expand access to high-quality care outside of tertiary academic centers.

3. Current experiences in clinical trials

3.1. Utility of remote testing from the patient perspective (Annette Costello, Ireland)

Ms. Costello provided the patient perspective of participation in telemedicine versus in-person visits. Having a long-standing relationship with an expert neuromuscular center, Ms. Costello outlined the personal benefits of in-person clinic visits, including access to leaders in the field, high-quality evidence-based recommendations, and the opportunity to socialize with other participants and team members. While access to the team during periods of lockdown was the main benefit of telemedicine during the pandemic, Ms. Costello felt these visits were useful, but looked forward to the return to in-person clinic visits.

3.2. Patient advocacy's role in remote testing and monitoring (Nathan Peck, CEO Cure VCP Disease, United States)

Mr. Nathan Peck from Cure VCP Disease presented to the workshop on the role of patient advocacy organization-assisted research by highlighting collaborations at both Nationwide Children's Hospital (NCH) and Casimir, LLC using both in-clinic and remote functional COA and conducting natural history studies. Cure VCP Disease advocates for ultra-rare VCP-associated multisystem proteinopathy (MSP-1 or VCP-MSP) characterized by adult onset via an autosomal dominant inheritance. Cure VCP Disease shared how they collaborated with researchers by providing patient insight and perspective on COA selection, especially for remote measures. The group organized a proof-of-concept pilot project with NCH researchers to better understand potential challenges of remote testing in VCP-MSP. Furthermore, Cure VCP provided funding to support key research initiatives; drove recruitment efforts through advertising clinical trials/studies via their network and registry; organized, shipped, and explained standardized

equipment kits for remote assessments to participants; and provided feedback on study logistics and execution to maximize study efficiency. In short, a true partnership between patient groups and researchers expedited progress in key initiatives and hastened clinical trial readiness.

3.3. Agile implementation of remote assessments in response to the pandemic (Meredith James, Physical Therapist, United Kingdom)

In reaction to the unexpected lockdowns, there was discussion surrounding the agile response of specialist physical therapists in ensuring high quality remote assessments be completed for both clinical and research purposes [1]. Ms. James described the global collaborative effort of expert physical therapists to develop initial guidelines and methods to perform valid and reliable remote assessments via live video conferencing. Experiences across clinical trials were presented with a focus on lessons learned and a framework to adapt current in-clinic evaluation for remote applications, as well as considerations for ongoing and future validation of these methods and COA.

3.4. Impact of travel restrictions on collection of key efficacy endpoints in clinical trials (Maria Mancini, VP, Head of Clinical Development Operations Edgewise Therapeutics, United States; Julie Coats, Senior Manager - Clinical Sciences Astellas Gene Therapies, United States)

Ms. Mancini and Dr. Coats contributed real-world experience from the industry perspective on the challenges of managing an ongoing clinical trial during the early days and months of the pandemic. While global lockdowns made traveling to sites impossible due to safety concerns, trial sponsors had to quickly adapt to gather data needed for future regulatory discussions and ensure that key endpoints were gathered to move clinical trials forward. The U.S. Food and Drug Administration (FDA) and European Medical Association (EMA) provided regularly updated guidance on best practice and considerations for conducting clinical trials throughout the pandemic [4]. Both presenters discussed updates to study protocols to enable high-quality, standardized, remote assessments and to monitor treatment safety, document any adverse or serious adverse events, and capture efficacy endpoints. While these modifications were enacted in response to an unexpected event, discussion focused on ways to better prepare for any future disturbances in clinical trial operations to maintain clinical trial integrity.

4. Ongoing validation and improvement

4.1. Efforts underway in Charcot Marie Tooth (CMT) disease (Gita Ramdharry, Physical Therapist, United Kingdom)

This session highlighted work on developing, validating and improving remotely delivered outcome measures. Dr. Ramdharry introduced the work of the National Institute of Health funded by the Rare Disease Clinical Research Network Inherited Neuropathy Consortium (RD-CRN INC) and the current studies validating the CMT Functional Outcome Measure (CMT-FOM)[5,6]. Similarly, evaluation of the utility of activity monitoring as a COA for individuals with CMT was presented. The challenges of the COVID-19 pandemic led to a collaborative effort between the Allied Health Professional research team to develop a remote version of the CMT-FOM. This COA consists of five functional items to be observed via video conferencing software and simultaneously timed by an assistant at home and the PT viewing the assessment. A study to test the feasibility, reliability and validity is currently underway.

4.2. CMT examination score (Valeria Prada, Physical Therapist, Italy)

The CMT Examination Score (CMTES) was previously devised and validated by the RD-CRN INC and was presented by Dr. Prada [7]. A virtual version of the CMTES (vCMTES) was developed starting from the validated CMTES, changing primarily the two items which required the use of a pinprick for sensation testing and a tuning fork for assessing vibration sense. A light touch and a proprioception test that could easily be administered in the home environment replaced these two items. The items on symptoms and strength remained the same. Two centers participated in the validation process, testing the participant in person with CMTES and vCMTES and then, after 3 weeks, testing the participant remotely using a Zoom platform [8]. Reliability was tested by two different professionals, evaluating the participant twice a week. Results are positive and statistically significant, showing that this is a reliable and valid scale.

4.3. Ongoing validation efforts to compare clinic-based assessments to live-streamed in home assessments in valosin-containing protein multisystem proteinopathy (VCP-MSP) (Lindsay Alfano, Physical Therapist, United States)

Dr. Alfano presented the ongoing clinical trial readiness study being conducted at the Abigail Wexner Research Institute at Nationwide Children's Hospital to evaluate the suitability of COA to quantify disease progression in VCP-MSP. A core aim of this study is to evaluate the feasibility and validity of assessments completed remotely via live-video conference with a trained physical therapist to those completed in-clinic. Cross-sectional data from the baseline visits were presented which indicated all COA (with the exception of the 9-hole peg test) and patient-reported outcomes (PRO) demonstrated excellent reliability within each testing environment. Some COA demonstrated slight increases in variability due to need for standardized equipment or administration considerations unique to the home environment such as the need for an appropriate height table. Some testing could not be completed within the home environment due to space constraints like the 10m walk/run test or concerns about safety with implementation such as 4-stair climb. Longitudinal data collection is ongoing.

4.4. Reliability of remote testing in young boys with Duchenne muscular dystrophy (Linda Lowes, Physical Therapist, United States)

Dr. Lowes presented the results of a study aiming to evaluate the congruence between remote and in- clinic administration of the North Star Ambulatory Assessment (NSAA). This validation study was completed as part of an ongoing gene therapy program to ensure 1) continued collection of efficacy data at key study endpoints and 2) to compare COA feasibility and scoring across both traditional, in-clinic assessments and remote assessments conducted by a highly trained and reliable PT with expertise in the administration and scoring of COA in individuals with DMD. Children with DMD completed remote assessments within two weeks of an in-clinic assessment. They completed the NSAA, 10-meter walk/run (if possible, in the home environment), and timed rise from the floor. Preliminary results indicated remote and in-clinic assessment scores and times were highly correlated (preliminary Pearson and Spearman correlation coefficients >0.90), although the 10-meter walk/run was only feasible in a small percentage of homes due to space constraints. Study findings support remote functional assessments as there was no statistically significant or clinically meaningful difference in performance across environments. Given the significant burden that treatment and monitoring places on individuals with DMD and their

caregivers, remote evaluation may also be beneficial in future clinical trials and for clinical management.

5. Alternative ways of monitoring patients with neuromuscular disorders

5.1. Remote monitoring using sensor-based platforms (Hara Pylarinou, CEO SystServ, Greece)

Dr. Pylarinou discussed a telemedicine ecosystem developed to support remote monitoring, remote clinical diagnosis, telemetry and other needs to connect patients and doctors within the home environment. The platform connected a healthcare team with patients to diagnosis and monitor conditions. Participants discussed the use of technology and future implications for clinical practice and research applications. Furthermore, access and privacy within the home environment and finding the balance between these as well as navigating the regulatory requirements which differ across regions were discussed.

5.2. Use of wearable devices to monitor progression (Charlotte Lilien, Physical Therapist, United Kingdom)

Over the last ten years, home-based digital assessment has been increasingly investigated, especially in the field of NMD, including DMD [9–11], spinal muscular atrophy (SMA) [12,13], and facioscapulohumeral muscular dystrophy (FSHD) [14] for both ambulatory and non-ambulatory patients. These measures allow continuous assessment over a period of time and are therefore less dependent on a day-to-day performance.

Despite the increased interest in using wearable devices in NMD in the recent years, the number of digital endpoints used as primary of even secondary endpoints remains low. Ms. Lilien discussed her experience in digital endpoint and wearable device development based on the only digital endpoint currently approved by the EMA [15], which is the 95th centile of stride velocity. An application as primary endpoint is currently under full consideration by EMA, and a Letter of Intent has been filed at the FDA level.

The group discussed difficulties associated with the development of digital endpoints and wearable devices such as high costs and the long time it takes from developing prototypes to validation of the variables and finally to regulatory approvals. The group discussed the need for a strong collaboration between the technology team and medical team, as well as the need for dedicated teams to manage deployment and support. The last area of discussion revolved around techniques to keep individuals engaged and compliant with wearing the device. Interest in wearable devices, as an efficacy outcome for clinical trials, is growing as it may have the potential to reduce clinical trial duration or the number of participants required per trial [11].

5.3. Development and validation of a standardized video-based software tool in Duchenne muscular dystrophy (Mindy Leffler, President, Chairman Casimir, United States)

Work on the development of the Duchenne Video Assessment (DVA), a novel DMD outcome measure developed for remote assessment of individuals across the spectrum of disease progression, was presented. The DVA was developed as a video-based tool that could complement traditional in-clinic assessments by enabling in-home evaluation of standardized activities and reduce patient burden associated with traveling to a clinic for follow-up visits. The goal of the DVA was to capture movement patterns reflective of daily life (i.e., habitual performance) in the comfort of one's home. Recording partners (i.e., parents, caregivers) recorded individuals performing standardized movement tasks at home using a secure mobile application. PTs, certified in the DVA, scored the videos using standardized scorecards with predefined compensatory movement criteria as a measure of disease progression. An update regarding Casimir's FDA COA qualification pathway and plans to conduct an investigator-initiated study known as ARISE were discussed. The ARISE study will recruit 180 participants with DMD at any stage of disease progression for a 24-month study in which they will remotely capture the DVA and other traditional COA. The ARISE study will assess the DVA's validity, reliability, and sensitivity to change over time to evaluate how the DVA coupled with DMD functional assessments may provide a comprehensive picture of a participant's progression.

5.4. Digital technology and assessments in neuromuscular disorders (Elin Haf Davies, CEO Aparito, United Kingdom)

Dr. Davies presented an update on the development of a DMD home platform which enables home-based assessment of disease progression. The tool includes digital outcomes to analyze movement and quantify compensations in individuals with DMD, with a primary focus on the transfer and transition phase. The video-based approach, delivered through an iOS or Android mobile application, collects video of individuals completing certain motor function tasks within their home environment and then applies pose estimation for analysis of movement quality and quantification. A pilot study in a small number of individuals has given early indication that this approach, when further validated, may be used to capture and quantify voluntary or compensatory movements in patients with DMD [16]. The current strengths of digital technology were discussed in the context of home monitoring and reduced burden of traveling. Dr. Davies also discussed the lessons learned throughout the development process including the need for standardization of the video capturing and to improve the widespread adoption of this approach beyond a research context.

5.5. The importance of monitoring respiratory function (Anri Human, Physical Therapist, South Africa)

Dr. Human discussed the timely topic of respiratory problems among people with NMD and that the pandemic likely presented an additional risk. Respiratory muscle weakness and ineffective cough as well as diminished lung volumes can further lead to, dyspnea; sleep disturbances (e.g., nocturnal hypoxia and hypercapnia); restrictive lung disease and decreased exercise tolerance and subsequently influence the health-related quality of life (HRQoL) of individuals and their families [17–19]. The COVID-19 pandemic led to numerous challenges, but also opportunities for alternative methods of assessment, treatment innovations and reaching all individuals with NMD within different socio-economic contexts. There was discussion about options to remotely monitor respiratory function as well as discussion of online strategies to preserve or improve respiratory muscle strength, optimize ventilation, improve cough ability, reduce respiratory morbidity, and potentially improve HRQoL. Considerations for mitigating the effect of limited resources, knowledge, and infrastructure such as electricity and availability of internet were discussed including assessing upper limb function, vital signs, or oxygen saturation as a proxy [20]. Dr. Human discussed the use of low cost, portable pulmonary function equipment that can measure expiratory flows and peak cough flow as an option for countries with limited resources. The COVID-19 pandemic has provided us with the opportunity to explore surrogate assessment techniques to monitor

respiratory function and to ensure timely intervention, when required.

5.6. The psychological impact of the pandemic and considerations (Lone Knudsen, Psychologist, Denmark)

Dr. Knudsen presented results from a national survey on the biopsychosocial health and quality of life of individuals with NMD during the COVID-19 pandemic with a special emphasis on the patient perspective of the changes in healthcare delivery [21]. Eight hundred and eleven adults with NMD and 67 parents of children with NMD participated in the survey. Twenty-five percent of adult patients and 47% of parents of a child with NMD reported anxiety. Nearly half of all the participants stated the pandemic had contributed to anxiety. For depression, 20% of adults patients and 28% of parents fulfilled the criteria. The majority of all participants said the pandemic had contributed to depression. Quality of life was negatively affected by the pandemic in approximately 80% of adult patients and children. A small group of adult patients (5.5%) and children (8.6%) experienced improved quality of life.

The decreased access to health care appointments had a negative impact on physical function (i.e., loss of muscle strength, poor balance, increased pain and fatigue, less mobility, weight gain, increased need for personal assistance) with few patients using other means (e.g., exercising on their own, buying training equipment or making use of the help of personal assistants to train at home) to maintain activity. Only 4% had received physical therapy via remote means such as virtual sessions or telephone calls. On such grounds, Dr. Knudsen discussed whether remote delivery of PT could have prevented some negative consequences of the pandemic by providing patients with the opportunity to access therapy. However, she acknowledged that face-to-face interventions contain social elements (e.g., informal socializing both with the PT and, in the case of group PT, fellow patients) that may promote rehabilitation, and that these aspects may not as easily be facilitated in the remote delivery of health care. Thus, considerations of continuing remote delivery of health care will need to take this into consideration in addition to the resources of the individual and family. In the end, what is important is what type of delivery will cause least strain and provide the best outcome and rehabilitation for people with NMD and their families.

5.7. Remote monitoring of bulbar physiology and function (Katlyn McGrattan, Speech-language pathologist, United States)

Dr. McGrattan reviewed clinical and research methods of monitoring an individual's bulbar integrity including their ability to verbally communicate and orally consume nutrition. One advantage of remote monitoring of bulbar integrity is that it often places a greater importance on the person's ability to perform functions of daily living that are meaningful to the individual, such as consume a meal with their friends without coughing and choking. Less emphasis is placed on physiologic imperfections that may not be causing clinically significant deficits. However, remote monitoring may not detect small physiological changes that may not be significant enough to cause a change in the individual's immediate bulbar function but can be optimized through treatment to prevent future complications. With this differentiation in mind, the literature highlighting methods of evaluating functional and physiological communication and deglutition outcomes was reviewed. Given the limited number of remote monitoring devices within this realm, the literature review was not restricted to methods tested in NMD only.

Communication remote monitoring was discussed as it related to monitoring the cumulative effects of the voice, articulation, and language subsystems. Dr. McGrattan highlighted several devices for home monitoring such as the Language Environment Analysis (LENA) remote monitoring device that can record an individual's verbal communication for up to 16 hours of the day [22]. The majority of LENA research focuses on home monitoring of child language development, however, work has been conducted demonstrating its validity and reliability in other populations such as those with autism spectrum disorders [23,24] and aphasia [25]. Other systems have been developed and utilized to enable more refined assessment of voice attributes that require a controlled environment where the user takes part in volitional voice assessment tasks. These are primarily isolated to phone applications such as GRABASZero, that enable the objective analysis of vocal attributes that contribute to an individual's communicative effectiveness and aesthetics including frequency, jitter, shimmer, ceptral peak prominence, harmonic-to-noise ratio [26,27], as well as typically subjective analyses such as grade, roughness, breathiness, asthenia, and strain [28]. A limitation of this method to date, however, has been in the ability to specifically evaluate voice loudness due to the many environmental variables that influence this outcome [29].

Remote monitoring of deglutition is an area with building scientific and clinical interest, but to date, there are not commercially available tools. Research has primarily focused on the adult population where users place an adhesive composed of an accelerometer and microphone on their throat to enable identification of when swallowing occurs [30,31] and thus provide a measure of swallow integrity including the risk for aspiration [32]. While the promise of such tools is tremendous in monitoring not only mealtime function, but also spontaneous swallowing rate of saliva, further development is needed for these to be readily available for clinical use and commercial markets and specific investigation into their reliability and validity in NMD.

6. Needs and future considerations

6.1. Considerations for inclusion of remote testing in trial design (Heather Gordish-Dressman, Biostatistician, United States)

Dr. Gordish-Dressman discussed several statistical considerations that need to be addressed when considering the use of remote outcome measures. While these considerations are necessary for the statistical analysis of data from any type of study, they are particularly important for data from clinical trials: 1) Variability: It is possible that a COA measured remotely will have greater variability than one measured in-clinic which can have strong statistical consequences; because greater variability in an outcome will affect the ability to detect a statistically significant effect. Most studies, and all clinical trials, are designed around a sample size that is adequate to detect a statistically significant effect based on an estimated effect size and variability. If the study outcome is assessed remotely, and yields a greater variability than expected, the study will require a larger sample size (or be underpowered) to detect a significance difference. 2) Missing data: All datasets have a degree of missing data points and, while we often see that missing data is simply ignored, there are statistical methodologies to appropriately assess and account for it. If we determine that the data is missing completely at random (MCAR) or missing at random (MAR), easily implemented methods can be applied. However, remote data collected by the individual may be more likely missing not at random (MNAR), that is, the reason for the missingness is related to the value of the missing outcome. For example, a remotely collected functional assessment that is difficult and missing for more severely affected patients but easily and routinely collected for milder patients would be considered MNAR as the reason the assessment is missing is related to the

functional value of the assessment. And though the methods appropriate for MNAR data can be very complex, simply ignoring the issue can lead to very biased conclusions and should be avoided. 3) Monitoring devices: Many remote outcome measures are under development for measurement with a home monitoring device which often measure outcomes in a continuous manner and over an extended period, yielding a very large number of data points. The challenges in analysis of these data sets need to be considered before they can be a viable choice. The format of the data available from a home monitoring device can differ considerably between devices and there remains a gap between the data created and a way to interpret that data in a statistical and clinically meaningful way. When data is received from a monitoring device, it has to be considered if there was any pre-processing of the data or if the data consist of raw measurements. Other questions to consider are: Does the researcher or clinician have access to the data as measured, or must they rely on the device or the device manufacturer's choice of data to share? What is the correct and appropriate summary measurement to use to reflect the intent of the outcome? These are all questions that need to be answered so that a clear understanding of what the collected data represents is possible. 4) Validation: Validation of any outcome requires several considerations [33,34]. The outcome must be appropriate for the population and meaningful to the person for whom it is measured. It must be feasible to both assess the outcome and to process and analyze the data. The outcome must be interpretable, measured precisely, and measure the characteristic that it claims to measure. Lastly, the outcome must be responsive to change. All these considerations must be addressed before an outcome can be deemed useful in a clinical trial setting as a primary outcome.

6.2. The role of patient registries (Allison Peck, Treasurer Cure VCP Disease, United States; Jennifer Levy, Scientific Director Coalition to Cure Calpain 3, United States)

It is well-established that patient registries are valuable tools in patient identification, collection of evidence to better understand a disease or condition, clinical study design, and standard of care development; however, the COVID-19 pandemic highlighted their value as a remote monitoring tool. Allison Peck shared insights from designing an international patient registry and utilizing a patient-led registry as a building block for research. As a new, ultra-rare disease patient organization, Cure VCP Disease considered the following factors as critical for their registry platform: low cost, accessibility, international reach, patient data-protection, customized surveys, and data-sharing with the community.

Ms. Peck reported that 90 patients with VCP-MSP have enrolled in the Cure VCP Disease Patient Registry with 10 countries represented. The Cure VCP Disease Registry has been used to integrate the patient voice into several research projects, including 1) a research study comparing patient insights with clinical observations [35], 2) the clinical study design of a natural history study [36], and 3) the development of a standard of care guideline [37]. Similarly, a patient registry can reveal gaps in current clinical care. Comparison of the age of symptom-onset and age of diagnosis revealed that diagnosis lags symptom-onset in VCP-MSP, with 48% reporting symptoms prior to age 41 but only 27% of those receiving a diagnosis prior to that age. Patients with VCP-MSP often reported experiencing fatigue, pain, and depression, but few patients received medical care to address these symptoms due to reduced awareness of these co-morbidities. Prospective collection of these symptoms in the Cure VCP Disease registry raises awareness of the broad existence of increased tiredness (reported in 76% of patients), pain interfering with health-related quality of life in 45%, and depression in 29%. Well-designed, remote, open-access patient registries elevate the patient voice and can provide critical disease insights when designing clinical trials and establishing standards of care without the requirement of travel.

Dr. Levy presented on the international LGMD2A/R1 registry administered by Coalition to Cure Calpain 3 (C3), a nonprofit patient foundation. The registry, which can be accessed at www.lgmd2a.org, allows individuals with limb girdle muscular dystrophy 2A/R1 (LGMD2A/R1, a form of calpainopathy) to self-report their contact information, year of diagnosis and genetic testing results, neurologist and clinic information, disease symptoms, and current medications and adaptive equipment used. Questions are in plain English without medical jargon, and the estimated time to complete is approximately five minutes. At the time of the ENMC workshop, the registry had over 1250 submissions. The registry has been successfully utilized for clinical study recruitment and to distribute research questionnaires. C3 will soon launch a new registry on the IAMRARE platform, a program of the National Organization for Rare Diseases. This will allow for longitudinal data collection using data elements informed by TREAT-NMD's Limb girdle muscular dystrophy Core Dataset project. Dr. Levy expects the new registry to launch within the next 12 months.

7. Current experience with virtual training and reliability

7.1. Global lessons learned from remote training and reliability (Michelle Eagle, Managing Director ATOM International, United Kingdom; Kristy Rose, Physical Therapist, Australia; Lindsay Alfano, Physical Therapist, United States)

Dr. Eagle, managing director of the ATOM International consortium which provides standardized training of trial PTs, presented the lessons learned and challenges of implementing remote training in response to the pandemic lockdowns. In this role, Dr. Eagle was instrumental in developing training and quality control policies to ensure high-quality trial data despite the challenging circumstances. There was discussion around the development of procedures to ensure site PTs continued to have access to standardized training through use of videoconferencing, but also allowed flexibility to transition to in-person training when deemed safe by regional, local, and institutional governing bodies. Dr. Eagle discussed cultural and geographical differences in response to the remote training transition as well as considerations for hybrid training options moving forward. One important consideration is understanding patient privacy rules/policies among different countries to determine if live streaming video to an individual in a different region is legally allowed. A benefit of the pandemic was a push toward and quick acceptance of videoconferencing as a suitable training modality. Utility of this modality has continued to supplement in-person training throughout the progression of the pandemic with fluctuating lockdowns or travel restrictions across regions persisting.

Dr. Rose shared her experience conducting remote training and reliability methods across the Asia Pacific Region (APAC) during the global pandemic. She noted training across the APAC has always presented unique challenges. The APAC region is geographically vast and there is significant variation in the education, training, professional qualifications, and scope of work of medical professionals across the region who often serve as evaluators for clinical trials. Prior experience with industry sponsored trials is also variable, as historically, this region has had limited trials. The impact of the language differences cannot be overlooked as APAC evaluators are frequently asked to communicate with trainers and review documents in English rather than their primary language. During a video recording

the advantage of easy demonstration to supplement the verbal instruction is lost. There is also significant variation in local language and cultural practices across the region, which requires additional consideration. Compared to other regions, it was the experience of her and colleagues that many clinical trials sites across APAC require more input in terms of training and ongoing support to conduct assessments at the quality and consistency required from industry.

Remote training has required many alterations to the original robust face-to-face method of training. While the remote delivery of training enabled study sites to continue and trials to be run across APAC during the pandemic, she found it was not a substitute for robust face-to-face training, particularly for those evaluators who are new to clinical trials or having difficulty conducting standardized assessments.

Dr. Alfano discussed the quick implementation of virtual training and reliability methods in the United States. Training via virtual methods was feasible in most circumstances, though sessions were divided into multiple, shorter sessions to avoid 'Zoom fatigue' and maximize active engagement in learning. Traditional didactic training methods were adapted for use in virtual settings including the use of slide presentations via screen sharing capabilities and sharing of patient videos to practice scoring of assessments. Reliability testing via virtual platforms was slightly more challenging to implement though was successful in most instances. The burden of ensuring successful virtual reliability fell primarily on the site to provide appropriate visual clarity for the virtual trainer. This obstacle was overcome by using a second person to manage the laptop or camera to ensure an adequate view. Some COA required in-person reliability, such as handheld dynamometry or spirometry, and could not be completed virtually. However, the trainer could generally assess the evaluator's technique and provide feedback to improve consistency of administration.

7.2. Utilization of remote platforms for training and reliability (Anna Mayhew, Physical Therapist, United Kingdom)

Dr. Mayhew reminded the workshop group that the mode of training and utility of virtual platforms must begin with the purpose of training, its role, and who is being trained. Remote or virtual training likely does not replace in-person training in most instances, but can work very well in conjunction with or in preparation for face-to-face training. She stressed the importance of linking the expert NMD centers and community therapists to ensure continuity for individuals with NMD and their families; perhaps by making training material available directly to the community. Dr. Mayhew discussed an example of an online training portal, opentact.net, which was specifically aimed at PTs in the UK but is freely available to therapists outside of the UK as well. The portal includes information on assessment and management of several of the more common NMD and included virtual clinics where therapists could practice scoring COA such as the NSAA for patients with DMD [38,39], EK2 [40], North Star assessment for limb girdle type muscular dystrophies [41], and Revised upper limb module for SMA [42]. One advantage of this platform was its accessibility at any time of the day and across the globe so it could potentially reach more people than offering in-person training. It is very easy to add material to the opentact.net platform and provides easy access to existing links to other training material. She cautioned that the website was only successful because it had staffing and funding to maintain the website as well as develop new material.

Limitations to the opentact.net training portal were discussed: i) it does not include any translations. ii) It cannot replace the benefit of learning how joints or muscles feel, iii) it does not demonstrate how to facilitate movements or safe handling techniques that require hands-on training. The portal does, however, use a wide variety of different media techniques which include videos, podcasts, written material, and virtual clinics which can cover a large amount of complicated material. Dr. Mayhew pointed out that other training material exists such as the Scottish Muscle Network and exercise guidelines for people with NMD. However, she acknowledged that remote training needed to be expanded so that it is accessible regardless of global location, and would be user-friendly based on countries' access to internet or cellphone coverage, and most importantly kept up-to-date.

8. Workshop summary and call to action (Meredith James, Physical Therapist, United Kingdom)

Upon completion of the workshop, there was consensus among participants that remote testing has merit in both clinical and research contexts and is worth further investigating and refining. Use of telemedicine improves access to leading experts in the field of NMD clinical care and research both locally and expanding geographically to underserved populations with previously limited options for care. There are restrictions to provision of telemedicine that vary based on geographical location, for example many state licensures within the United States restrict the use of clinical telemedicine by only allowing service to patients residing in the same state in which the PT is licensed. The group agreed that some clinical testing can be completed within the home environment to assess an individual's function and abilities. A benefit to telemedicine is that it provides a window into the individual's true abilities at home in the environment in which they complete daily tasks. Providing guidance to individuals with NMD and their families within this context enables efficient incorporation into daily use. However, remote testing for clinical purposes is not without its challenges. Access to high-quality internet with sufficient bandwidth to permit dual video conferencing is not equitably accessible within countries and across the globe. Use of other methods such as smart phone applications or mobile hotspots are other options that can provide access to telemedicine, but are also not equally accessible. Furthermore, poor health literacy may prevent some patients from engaging in remote testing. Health professionals need to consider whether the patient and family have the abilities and resources to engage in remote health care. Poor physical and/or cognitive functioning as well as communication abilities may also be barriers. Also, one needs to consider if there are beneficial aspects of face-to-face health care and rehabilitation that may be missing in a telemedicine approach.

Use of remote testing for research purposes was also deemed to be useful and worth validating. However, first the method of remote testing must be determined as either 1) live testing using videoconferencing methods with a specialist, 2) use of home-based applications that collect information within the home environment to be processed or scored post-testing, 3) use of other technologies, such as wearable devices, that can assess movements and activities within the home or community environment over a specified period. While all the methods have value in their specific contexts, each requires a high level of development and validation to ensure data quality and reliability for use in clinical trials. Similarly, understanding sensitivity to change and meaningful change within the remote environment is critical for interpretation of trial results utilizing these methods. Validation efforts are ongoing for each of these methods and may provide further evidence to support their use and in which contexts they are most informative.

The vast acceptance and implementation of video conferencing methods in response to the pandemic opened additional options for training, reliability testing, and ongoing quality control. While remote training options may, in some circumstances, provide

more widespread access, via virtual meetings with experts or via internet repositories and platforms, there was consensus among workshop participants that in-person training opportunities were still highly valued and most effective in some circumstances. Because patient care and evaluation in clinical trials can include hands-on activities, training and reliability should also ensure a hands-on component. Virtual or hybrid training options can improve the efficiency of didactic training and may provide the opportunity for ongoing quality control or ensuring reliability in some instances. Having these methods available, in conjunction with in-person training will likely be the most readily adopted training method moving forward.

While there is significant work remaining to better understand and exploit the full potential of remote testing and training methods, workshop participants agreed that the benefits of improved access to individuals within their home environments, reduced burden of clinical care and/or trial participation through reduction of travel, and increased flexibility in scheduling visits and sessions was worth the time and effort. Further research is needed to specifically validate these methods within their appropriate context of use and much of this work is already ongoing.

Declaration of Competing Interests

Lindsay N Alfano reports a relationship with Sarepta Therapeutics that includes: funding grants, speaking and lecture fees, and travel reimbursement; Astellas Gene Therapies that includes: funding grants; ATOM International, Ltd that includes: consulting or advisory fees, and travel reimbursement.

Meredith K James reports a relationship with Sarepta that includes: consulting or advisory. Meredith James reports a relationship with Pfizer that includes: consulting or advisory. Meredith James reports a relationship with ATOM Ltd that includes: consulting or advisory and travel reimbursement.

Gita M Ramdharry reports a relationship with Orphazyme ApS that includes: consulting or advisory. Gita Ramdharry reports a relationship with F Hoffmann-La Roche Ltd that includes: consulting or advisory.

Linda P Lowes reports a relationship with Sarepta Therapeutics Inc that includes: funding grants and travel reimbursement. Linda Lowes reports a relationship with ATOM International that includes: consulting or advisory and travel reimbursement.

Declarations of interests of members of the Workshop Study Group can be found online.

Acknowledgments

This Workshop was made possible thanks to the financial support of the European Neuromuscular Centre (ENMC) and ENMC main sponsors:

Association Française contre les Myopathies (France), Deutsche Gesellschaft für Muskelkranke (Germany), Muscular Dystrophy Campaign (UK), Muskelsvindfonden (Denmark), Prinses Beatrix Spierfonds (The Netherlands), Schweizerische Stiftung für die Erforschung der Muskelkrankheiten (Switzerland), Telethon Foundation (Italy), Spierziekten Nederland (The Netherlands) and Associated members:

Finnish Neuromuscular Association (Finland), Österreichische Muskelforschung (Austria), SMA Europe and the World Duchenne Organisation.

With thank the following members of the ENMC Company Forum for their support to the ENMC:

Sanofi Genzyme, Santhera Pharmaceuticals, Amicus Therapeutics, CSL Behring LLC, Ionis Pharmaceuticals, Perkin Elmer/Wallac Oy, AveXis Switzerland GmbH, Biogen International GmbH, Hoffmann-la-Roche, Lupin Atlantis Holdings SA

A special thanks to the Parent Project Muscular Dystrophy and Edgewise Therapeutics for their support to cover travel costs from non-ENMC member country participants.

Workshop participants:

Julie Coats, Astellas Gene Therapies, Raleigh, NC, United States.
José Corderí, Favaloro Foundation, Buenos Aires, Argentina.
Annette Costello, Patient advocate, Dublin, Ireland.
Michelle Eagle, ATOM International, Ltd, Newcastle Upon Tyne, United Kingdom.
Maha Elseed, The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom.
Alessandra Gaeta, Duchenne UK, Hammersmith, United Kingdom.
Heather Gordish-Dressman, George Washington University School of Medicine and Health Sciences, Pittsburgh, PA, United States.
Elin Haf Davies, Aparito, Wrexham, United Kingdom.
Anri Human, Physiotherapy Department, University of Pretoria, Pretoria, South Africa.
Lone Knudsen, The National Rehabilitation Centre for Neuromuscular Diseases, Aarhus, Denmark.
Mindy Leffler, Casimir, Seattle, WA, United States.
Jennifer Levy, Coalition to Cure Calpain 3, Westport, CT, United States.
Charlotte Lilien, University of Oxford, Department of Paediatrics, Oxford, United Kingdom.
Maria Mancini, Edgewise Therapeutics, Boston, MA, United States.
Anna Mayhew, John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne, United Kingdom.
Katlyn McGrattan, University of Minnesota, Minneapolis, MN, United States.
Robert Muni-Lofra, The John Walton Muscular Dystrophy Research Centre, Newcastle University and Newcastle Hospitals NHS Foundation Trust, Newcastle Upon Tyne, United Kingdom.
Allison Peck, Cure VCP Disease, Americus, GA, United States.
Nathan Peck, Cure VCP Disease, Americus, GA, United States.
Valeria Prada, Fondazione Italiana Sclerosi Multipla, Rome, Italy.
Hara Pylarinou, Systserv SA, Patras, Greece.
Kristy Rose, The University of Sydney Discipline of Physiotherapy, Sydney, Australia.
Ulla Werlauff, The National Rehabilitation Centre for Neuromuscular Diseases, Aarhus, Denmark.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2023.02.011.

References

[1] James MK, Rose K, Alfano LN, Reash NF, Eagle M, Lowes LP. Remote delivery of motor function assessment and training for clinical trials in neuromuscular disease: a response to the COVID-19 global pandemic. Front Genet 2021;12:735538.
[2] Chartered Society of Physiotherapy. Final report: understanding the opportunities and challenges of remote physiotherapy consultations and rehabilitation during the Covid-19 pandemic. 2022 [cited 2023 15Jan]; Available from: https://www.csp.org.uk/system/files/documents/2022-02/csp_remote_pt_evaluation_final_report.pdf.
[3] Mohamed IN, Elseed MA. Utility of WhatsApp in healthcare provision and sharing of medical information with caregivers of children with neurodisabilities: experience from Sudan. Sudan J Paediatr 2021;21:48–52.
[4] U.S. Department of Health and Human Services: Food and Drug Administration. Conduct of clinical trials of medical products during the COVID-19 public health emergency: guidance for industry, investigators, and institutional review boards. 2020.

[5] Bray P, Cornett KMD, Estilow T, Pareyson D, Zuccarino R, Skorupinska M, et al. Reliability of the Charcot-Marie-Tooth functional outcome measure. J Peripher Nerv Syst 2020;25:288–91.
[6] Eichinger K, Burns J, Cornett K, Bacon C, Shepherd ML, Mountain J, et al. The Charcot-Marie-Tooth Functional Outcome Measure (CMT-FOM). Neurology 2018;91:e1381–4.
[7] Shy ME, Blake J, Krajewski K, Fuerst DR, Laura M, Hahn AF, et al. Reliability and validity of the CMT neuropathy score as a measure of disability. Neurology 2005;64:1209–14.
[8] Prada V, Laura M, Zuccarino R, Reilly MM, Shy ME. Virtual Charcot-Marie-Tooth examination score: a validated virtual evaluation for people with Charcot-Marie-Tooth disease. Neurol Clin Pract 2022;12:e98–e104.
[9] Le Moing AG, Seferian AM, Moraux A, Annoussamy M, Dorveaux E, Gasnier E, et al. A movement monitor based on magneto-inertial sensors for non-ambulant patients with Duchenne Muscular Dystrophy: a pilot study in controlled environment. PLoS One 2016;11:e0156696.
[10] Lilien C, Gasnier E, Gidaro T, Seferian A, Grelet M, Vissiere D, et al. Home-based monitor for gait and activity analysis. J Vis Exp 2019.
[11] Servais L, Camino E, Clement A, McDonald CM, Lukawy J, Lowes LP, et al. First regulatory qualification of a novel digital endpoint in Duchenne Muscular Dystrophy: a multi-stakeholder perspective on the impact for patients and for drug development in neuromuscular diseases. Digit Biomark 2021;5:183–90.
[12] Alfano LN, Miller NF, Iammarino MA, Moore Clingenpeel M, Lowes SL, Dugan ME, et al. ACTIVE (Ability Captured Through Interactive Video Evaluation) workspace volume video game to quantify meaningful change in spinal muscular atrophy. Dev Med Child Neurol 2020;62:303–9.
[13] Annoussamy M, Seferian AM, Daron A, Pereon Y, Cances C, Vuillerot C, et al. Natural history of type 2 and 3 spinal muscular atrophy: 2-year NatHis-SMA study. Ann Clin Transl Neurol 2021;8:359–73.
[14] Gidaro T, Gasnier E, Annoussamy M, Vissing J, Attarian S, Mozaffar T, et al. Home-based gait analysis as an exploratory endpoint during a multicenter phase 1 trial in limb girdle muscular dystrophy type R2 and facioscapulohumeral muscular dystrophy. Muscle Nerve 2022;65:237–42.
[15] Haberkamp M, Moseley J, Athanasiou D, de Andres-Trelles F, Elferink A, Rosa MM, et al. European regulators' views on a wearable-derived performance measurement of ambulation for Duchenne muscular dystrophy regulatory trials. Neuromuscul Disord 2019;29:514–16.
[16] Ferrer-Mallol E, Matthews C, Stoodley M, Gaeta A, George E, Reuben E, et al. Patient-led development of digital endpoints and the use of computer vision analysis in assessment of motor function in rare diseases. Front Pharmacol 2022;13:916714.
[17] Boentert M, Wenninger S, Sansone VA. Respiratory involvement in neuromuscular disorders. Curr Opin Neurol 2017;30:529–37.
[18] Chiang J, Mehta K, Amin R. Respiratory diagnostic tools in neuromuscular disease. Children (Basel) 2018;5(6):78. doi:10.3390/children5060078.
[19] Toussaint M, Chatwin M, Gonzales J, Berlowitz DJ. ENMC Respiratory Therapy Consortium. 228th ENMC International Workshop: airway clearance techniques in neuromuscular disorders Naarden, The Netherlands, 3-5 March, 2017. Neuromuscul Disord 2018;28:289–98.
[20] James M, Gordish Dressman H, Hilsden H, Rufibach L, Human A, Duong T, et al. P.162 Clinical outcome study of dysferlinopathy: performance of upper limb entry item to predict foced vital capacity in dysferlinopathy (LGMDR2). Neuromuscul Disord 2022;32:S114.
[21] Handberg C, Werlauff U, Hojberg AL, Knudsen LF. Impact of the COVID-19 pandemic on biopsychosocial health and quality of life among Danish children and adults with neuromuscular diseases (NMD)-Patient reported outcomes from a national survey. PLoS One 2021;16:e0253715.
[22] Ganek H, Eriks-Brophy A. Language environment analysis (LENA) system investigation of day long recordings in children: a literature review. J Commun Disord 2018;72:77–85.
[23] Burgess S, Audet L, Harjusola-Webb S. Quantitative and qualitative characteristics of the school and home language environments of preschool-aged children with ASD. J Commun Disord 2013;46:428–439.
[24] Jones RM, Plesa Skwerer D, Pawar R, Hamo A, Carberry C, Ajodan EL, et al. How effective is LENA in detecting speech vocalizations and language produced by children and adolescents with ASD in different contexts? Autism Res 2019;12:628–35.
[25] Suting LB, Mozeiko J. Analysis of real-world language use in a person with Wernicke's Aphasia. Perspectives of the ASHA Special Interest Groups 2021;6:553–65.
[26] van der Woerd B, Wu M, Parsa V, Doyle PC, Fung K. Evaluation of acoustic analyses of voice in nonoptimized conditions. J Speech Lang Hear Res 2020;63:3991–9.
[27] Lin E, Hornibrook J, Ormond T. Evaluating iPhone recordings for acoustic voice assessment. Folia Phoniatr Logop 2012;64:122–30.
[28] Kojima T, Hasebe K, Fujimura S, Okanoue Y, Kagoshima H, Taguchi A, et al. A new iPhone application for voice quality assessment based on the GRBAS Scale. Laryngoscope 2021;131:580–2.
[29] Schneider SL, Habich L, Weston ZM, Rosen CA. Observations and considerations for implementing remote acoustic voice recording and analysis in clinical practice. J Voice 2021.
[30] Shu K, Mao S, Coyle JL, Sejdic E. Improving non-invasive aspiration detection with auxiliary classifier wasserstein generative adversarial networks. IEEE J Biomed Health Inform 2022;26:1263–72.
[31] Kim MK, Kantarcigil C, Kim B, Baruah RK, Maity S, Park Y, et al. Flexible submental sensor patch with remote monitoring controls for management of oropharyngeal swallowing disorders. Sci Adv 2019;5:eaay3210.
[32] Coyle JL, Sejdic E. High-resolution cervical auscultation and data science: new tools to address an old problem. Am J Speech Lang Pathol 2020;29:992–1000.
[33] Boateng GO, Neilands TB, Frongillo EA, Melgar-Quinonez HR, SL Young. Best practices for developing and validating scales for health, social, and behavioral research: a primer. Front Public Health 2018;6:149.
[34] US Food and Drug Administration: Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, Center for Devices and Radiological Health. Guidance for industry patient-reported outcome measures: use in medical product development to support labeling claims. 2009 [cited 2022; Available from: https://www.fda.gov/regulatory-information/.
[35] Ikenaga C, Findlay AR, Seiffert M, Peck A, Peck N, Johnson NE, et al. Phenotypic diversity in an international cure VCP disease registry. Orphanet J Rare Dis 2020;15:267.
[36] Johnson MA, Klickstein JA, Khanna R, Gou Y, Consortium Cure VCP Disease Research, Raman M. The Cure VCP Scientific Conference 2021: molecular and clinical insights into neurodegeneration and myopathy linked to multisystem proteinopathy-1 (MSP-1). Neurobiol Dis 2022;169:105722.
[37] Korb M, Peck A, Alfano LN, Berger KI, James MK, Ghoshal N, et al. Development of a standard of care for patients with valosin-containing protein associated multisystem proteinopathy. Orphanet J Rare Dis 2022;17:23.
[38] Mayhew A, Cano S, Scott E, Eagle M, Bushby K, Muntoni F, et al. Moving towards meaningful measurement: Rasch analysis of the north star ambulatory assessment in Duchenne muscular dystrophy. Dev Med Child Neurol 2011;53:535–42.
[39] Mazzone ES, Messina S, Vasco G, Main M, Eagle M, D'Amico A, et al. Reliability of the north star ambulatory assessment in a multicentric setting. Neuromuscul Disord 2009;19:458–61.
[40] Werlauff U, Fynbo Steffensen B. The applicability of four clinical methods to evaluate arm and hand function in all stages of spinal muscular atrophy type II. Disabil Rehabil 2014;36:2120–6.
[41] James MK, Alfano LN, Muni-Lofra R, Reash NF, Sodhi J, Iammarino MA, et al. Validation of the north star assessment for limb-girdle type muscular dystrophies. Phys Ther 2022;102.
[42] Mazzone ES, Mayhew A, Montes J, Ramsey D, Fanelli L, Young SD, et al. Revised upper limb module for spinal muscular atrophy: development of a new module. Muscle Nerve 2017;55:869–74.