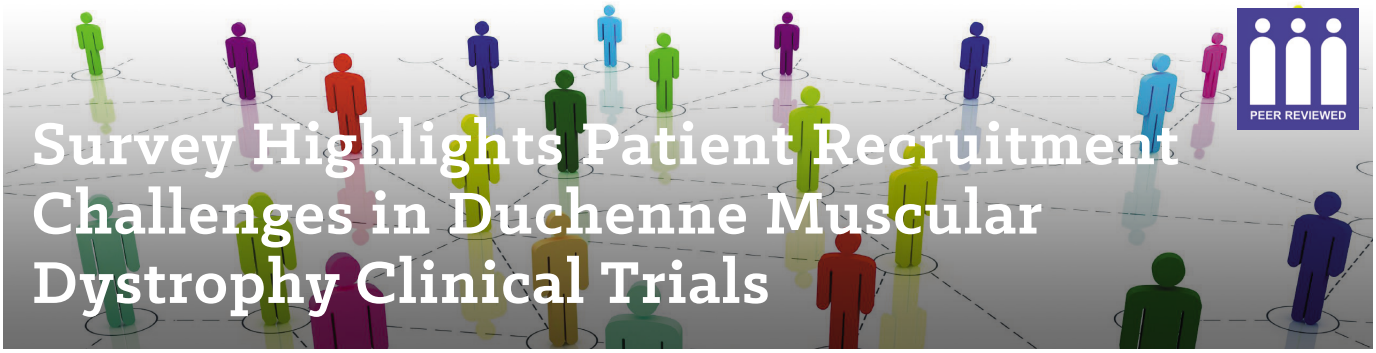


Survey Highlights Patient Recruitment Challenges in Duchenne Muscular Dystrophy Clinical Trials

Abstract

Although Duchenne Muscular Dystrophy (DMD) is a rare disease, multiple targets are being pursued to find treatments. As a result, DMD patients have several options when considering enrolling in clinical trials, which can contribute to the challenges when recruiting DMD patients for specific clinical trials. Additionally, trial sites are selected based on a myriad of factors, which may include sponsor choice (for business or rapid enrolment considerations), the physical location of the clinical sites (based on feasibility and capability), the site's principal investigator, marketing considerations and ease of access. These complexities must be balanced against the risk of conducting trials in countries/regions that may lack the ability, expertise, or capacity to participate. This paper describes the results of a proactive, global DMD feasibility study conducted by IQVIA with the objective of obtaining insights from investigators currently providing DMD patient care. The survey asked 23 questions regarding physician interest in and motivation for DMD clinical trial participation. Of the 200 investigators polled, 128 investigators across 40 countries responded to the survey, yielding a 64% response rate. Despite the limited responses from some geographies, the survey yielded useful directional information for recruiting DMD patients for clinical trials and further highlights the challenges associated with DMD drug development.

Introduction

Muscular dystrophies (MD) comprise a group of multi-systemic diseases that are primarily clinically manifested as progressive muscle weakness, with associated loss of mobility, agility and body movements due to defects in genes for the production of muscle proteins. The proteins and structures involved in certain disease processes are increasingly being elucidated, boosting the number of potential pharmaceutical targets, and resulting in heightened interest in investment, partnership and collaboration.

Although the muscular dystrophies are rare in terms of individual disorders, when combined with other neuromuscular disorders, they are considered to have an enormous influence on the global economy. For example, the IQVIA Institute estimates that collectively, the neuromuscular disorders impact an estimated 250,000 patients and their caregivers in the US. Analysis of healthcare charges using IQVIA real-world data indicates that total annual charges across all neuromuscular patients exceed $46b.[1]

There is no consensus as to who was first to describe MD.[2] One account of MD appeared in 1830, when Sir Charles Bell (1774–1842) wrote about an illness that caused progressive weakness in boys. Other sources point to Giovanni Semmola's publication in 1834 and a Semmola publication in conjunction with Gaetano Conte in 1836. Another account was given by Conte and Gioja in 1836, describing two brothers with progressive muscle weakness. In 1852, Dr Edward Meryon (1809–1880) described a family with four boys, all affected by significant muscle changes. The French neurologist, Guillaume Benjamin Amand Duchenne, MD (1806–1875) wrote about his first case of MD in 1861. In 1868, he gave a comprehensive account of 13 patients with MD. One of the most severe forms of MD, Duchenne MD, now bears his name.

Duchenne MD (DMD) and Becker MD (BMD) are both dystrophinopathies and allelic disorders caused by mutations of the DMD gene located on Xp21, which encodes for the dystrophin protein.[3] DMD is among the most common forms of muscular dystrophy in childhood, with an estimated US incidence of one per 4600–5600 live-born males age 5–24 years. Becker's MD is a generally milder and more variable form of dystrophinopathy, with an incidence of one in 7250 male births age 5–24 years.[4]

Diagnosis is based on careful review of the clinical features and confirmed by additional investigations including genetic testing and less frequently, muscle biopsy. Suspicion of the diagnosis of DMD is usually triggered in one of three ways: (1) most commonly, the observation of abnormal muscle function with signs of proximal muscle weakness; (2) the detection of elevated serum creatine kinase as part of routine screening; or (3) the presence of elevated liver enzymes including aspartate aminotransferase and alanine aminotransferase. Current supportive strategies include promoting proper nutrition, delaying onset of complications, and optimising health outcomes through ongoing support. Current pharmaceutical interventions include corticosteroids for skeletal muscle weakness and symptomatic management of cardiomyopathy. Early recognition and precise genetic diagnosis will allow for new therapeutic options for DMD. Even though there is currently no cure, corticosteroids are considered an advancement as these appear to extend time to loss of ambulation. Respiratory intervention and other supportive strategies have led to improved survival and better health-related quality of life for many affected individuals. Novel treatment approaches are currently being actively tested, including dystrophin replacement/restoration approaches (e.g. genetherapy approaches to exon-skipping; stop codon readthrough; utrophin up-regulation); skeletal and cardiac muscle protection (myostatin inhibitors, and cell-based [cardiospheres] approaches for dilated cardiomyopathy); and compounds acting on mitochondrial dysfunction, inflammation and fibrosis.

DMD Clinical Trials are Ramping Up

According to *clinicaltrials.gov*, a database of privately and publicly funded clinical studies conducted around the world, a total of 238 trials are ongoing using the fully spelled out search term "Duchenne Muscular Dystrophy."[5]

Several companies are pursing potential treatments for MD and have advanced to the Phase II and III stages of clinical drug development, although only two products, eteplirsen (Exondys 51™) and deflazacort (Emflaza™), have been approved for the treatment of DMD in the US. Deflazacort is available in the EU and ROW under other trade names; however, Emflaza is only approved in the US. As such, corticosteroids – in various forms and under a range

of trade names – are considered the standard of care for DMD in the EU. Ataluren (Translarna™) is conditionally approved in the EU for the treatment of DMD. These are considered disease-modifying treatments; however, more treatments which cover all types of DMD mutations, and a cure, are desperately needed.

Although DMD is a rare disease, multiple targets (and mechanisms of action) are being pursued to find treatments. As such, DMD patients have multiple choices and opportunities to enroll in clinical trials. However, recruitment of DMD patients for clinical trials can be challenging for several reasons. For example, a sponsor of a new treatment may wish to target only a subset of DMD patients, as Sarepta did with Exondys 51, an exon-skipping therapy which targets only approximately 13% of boys and girls (extremely rare cases). Trial sites are also selected based on a myriad of selection criteria, which may include sponsor choice (for business or rapid enrolment considerations), the physical location of the clinical sites (based on feasibility and capability), the site's principal investigator, marketing considerations and ease of access. These complexities must be balanced against conducting trials in countries/regions that may lack the ability, expertise, capacity or willingness to act as sites for the DMD studies.

This paper will describe the results of a proactive DMD feasibility study which was conducted by IQVIA (a leading provider of advanced analytics, technology solutions and contract research services to the life sciences industry) in the second half of 2018, with the objective of obtaining unique and current insights from global investigators currently providing DMD patient care.

Methods

DMD clinical trial "readiness" – defined here as physician interest/motivation in DMD clinical trial participation – was sent to 200 physicians treating DMD patients across 48 countries globally. The survey was initially launched in two phases; the first survey was distributed to treating physicians in North American (NA) and Europe, Middle East and Africa (EMEA) countries only, while the second phase was more widespread and included physicians in Asia Pacific (APAC) and Latin American (LATAM) countries. Responses were summarised descriptively and by region. The primary physician specialities this survey interviewed were neurologists, paediatric neurologists, paediatricians, paediatric rehabilitation physicians, neurologist and medical geneticists, paediatric nephrologists, paediatric cardiologists, neuropaediatricians and neurosurgeons (see Figure 1).

Results

IQVIA collected completed surveys from 128 investigators across 40 countries in a three-month period (see Figure 2). It is not known why only eight US physicians responded, but this may be related to sites being very challenged for time with ongoing DMD trials or having less interest to answer a general proactive feasibility survey not linked to a proposed clinical trial. More than 50% of the physicians, identified largely as paediatric neurologists or neurologists, were associated with an academic hospital. In terms of general interest in participating in DMD trials, a majority (>75%) of physicians responded that they would be interested in participating in a DMD trial.

Sites in Brazil, China, Colombia, India, Portugal and Spain were among those having the maximum number of interested physicians. It is important to note that physician interest is different from being able to conduct a clinical trial and having the capacity to enroll patients. It should also be noted that some sponsors of DMD treatments hesitate to work in some of these markets because of access and reimbursement challenges.

Although the primary physician speciality of principal investigators for DMD clinical trials is typically neurology, other specialities are either already part of the DMD medical care team or may be added on to the DMD patient's management team as the disease progresses. For example, physical therapy is essential for DMD patients and is typically started very young to maintain flexibility of the tendons. When the DMD patient is young, there is less concern with cardiopulmonary issues, but these issues will garner greater medical attention as the disease progresses and may require close follow-up by a paediatric cardiologist and/or pulmonologist. In addition, during the transition from ambulatory to non-ambulatory status, there will be an increasing medical need for an occupational therapist and psychologist/neuropsychologist (as more than 30% of boys may have cognitive issues) to be added to the patient's DMD medical management team.

Patient Identification

In terms of numbers of DMD patients seen "in the last six months" and subsequent patient willingness to participate in DMD trials, investigators believe patients and caregivers across all three age groups would be evenly interested with slightly more patients coming from the seven-to-10-year age range (see Figure 3). Based on

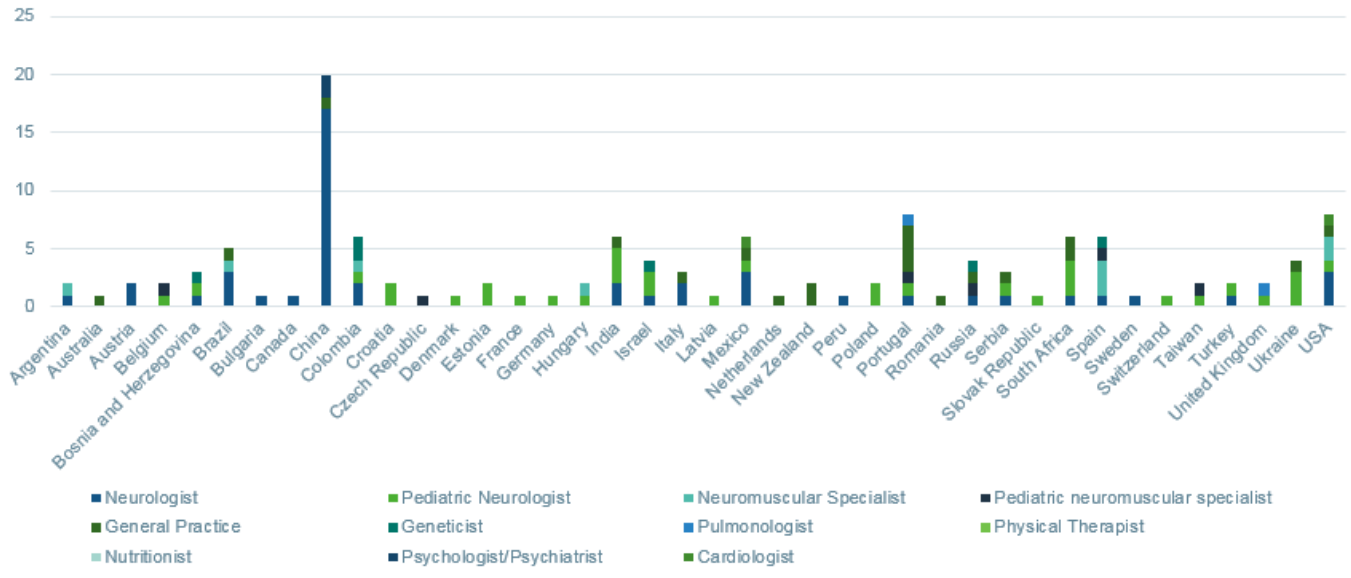
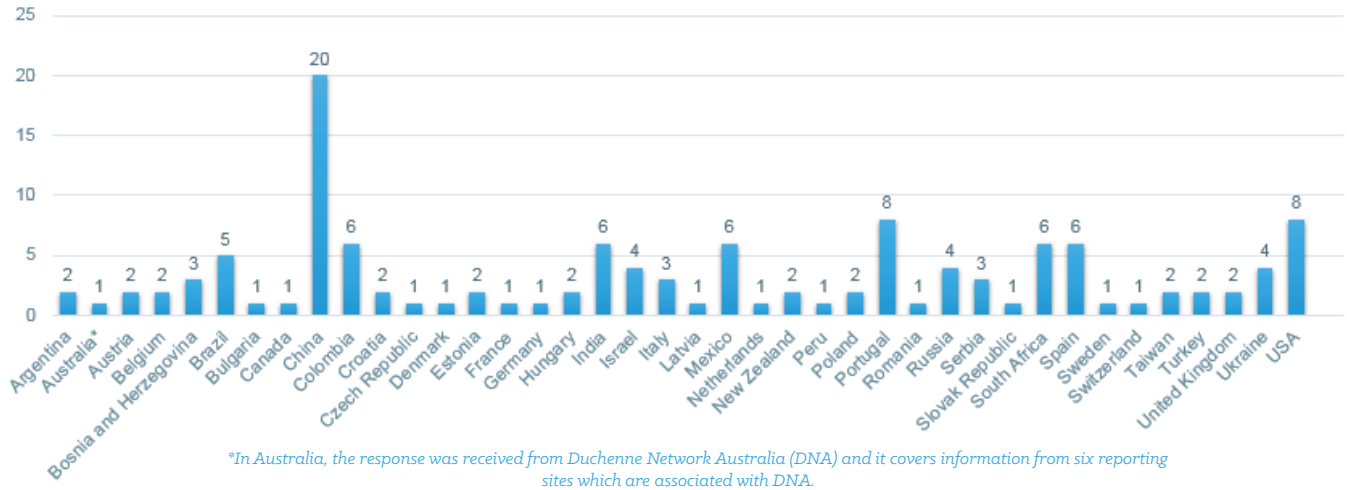


Figure 1 – An Overview of the Physician Specialities Surveyed



In Australia, the response was received from Duchenne Network Australia (DNA) and it covers information from six reporting sites which are associated with DNA.

*Figure 2 – Total Number of Survey Responses Received by Country**

all the responses received, it was found that 63% of the investigators surveyed have not yet enrolled any patients in DMD studies in the past five years. This is because there are fewer DMD clinical trials available in specific countries. Indeed, our findings showed us that more than 50% countries surveyed have never enrolled DMD patients in a clinical trial. Taken together, this highlights a growing opportunity for patient recruitment in future DMD clinical trials.

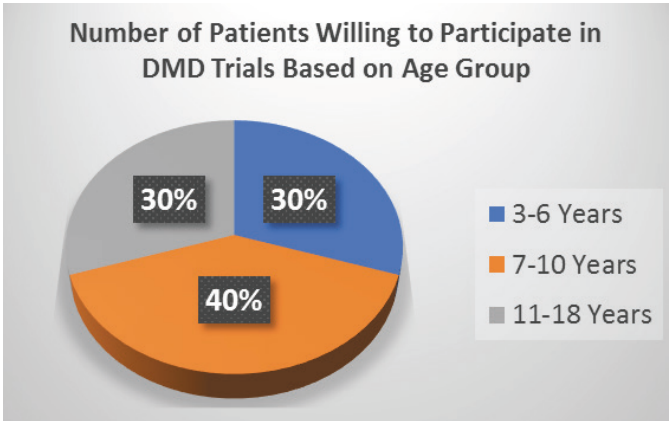


Figure 3 – Physician Estimates of Numbers of Patients Willing to Participate in DMD Trials Based on Age Group

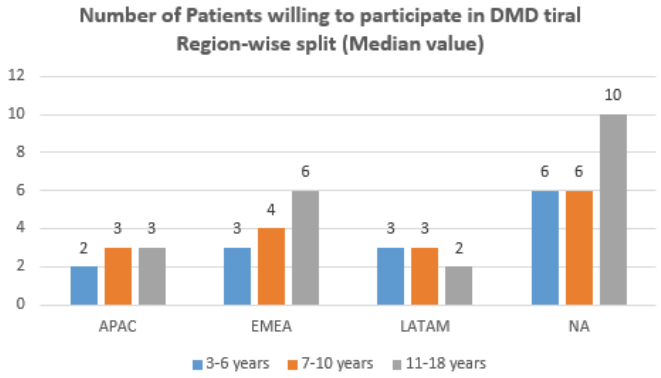


Figure 4 – Number of Patients Estimated by Physicians to be Willing to Participate in DMD Trials Based on Age Group by Region (Median Value)

As seen in Figure 4, investigators predict that the largest number of DMD patients willing to participate in a DMD trial would be from the North American (NA) region, followed by the Europe, Middle East and Africa (EMEA) region.

Across all regions, most of the patients that have participated in clinical trials were identified through self-referral, followed by identification via primary care physicians (PCPs) and patient registries/databases, respectively (see Figure 5).

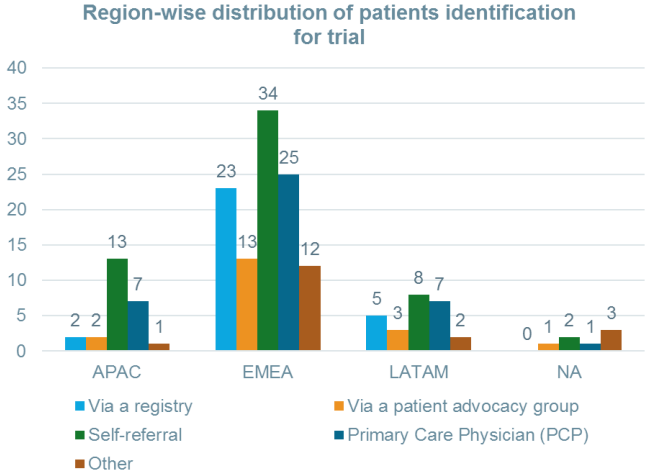


Figure 5 – Regional Distribution of Patients Identification for a Clinical Trial

In the case of registries, most of the investigators referred to either their own patient databases, local registries or national/international NMD registries for identifying patients. In addition, travel requirements for the patient and caregiver need to be addressed, with the majority of DMD patients from EMEA countries as well as Russia and Ukraine, travelling long distances, some up to 75 miles to reach their treating physician.

The most commonly used class of drugs for treatment of DMD globally is corticosteroids (aka "steroids") with 59% patients globally starting treatment from three to six years of age (see Figures 6 and 7). This complements US MD STARnet data which estimates steroid use at around 60%. Unexpectedly, steroid use was reportedly the sole DMD treatment in the US, however the authors believe this number is underestimated due to the small number of responding investigators in the US. It is well known that there have been multiple cases with US DMD patients taking more than 20 different vitamins and supplements daily in addition to medications like human growth hormone and medications in an effort to combat osteoporosis and cardiorespiratory issues.

Supplements/minerals and cardiac medications were also reported in other regions, as well as alternative forms of treatment including physical rehabilitation and non-invasive ventilation procedures in Serbia and Czech Republic or traditional Chinese medicine from some of the responding Chinese sites.

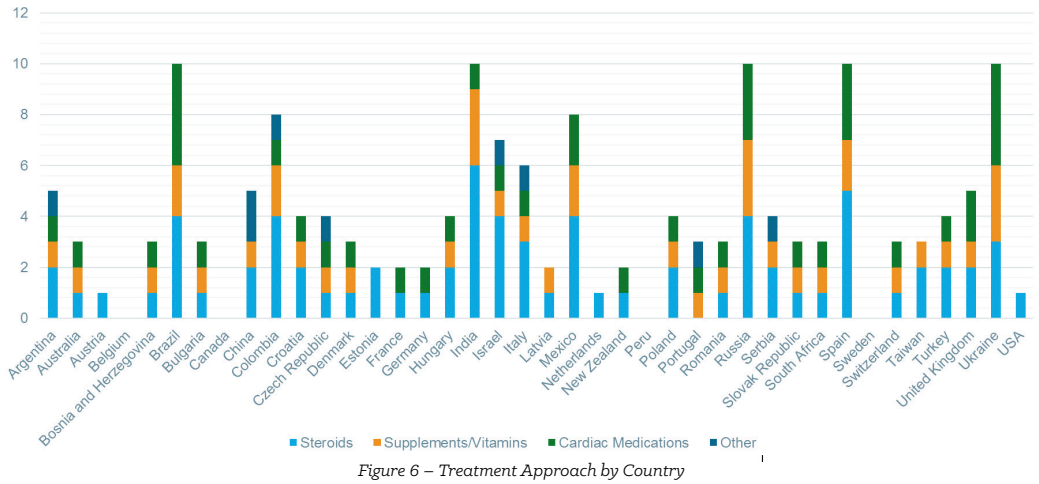


Figure 6 – Treatment Approach by Country

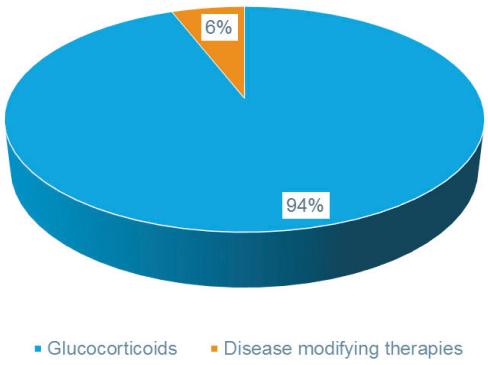
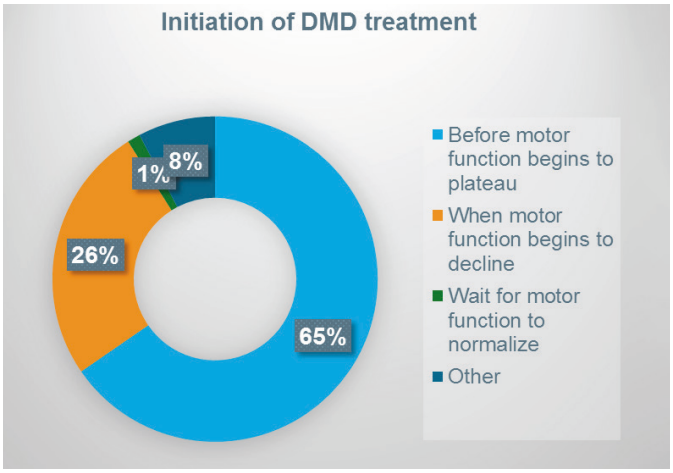


Figure 7 – Corticosteroid Use Versus Disease Modifying Therapy Use



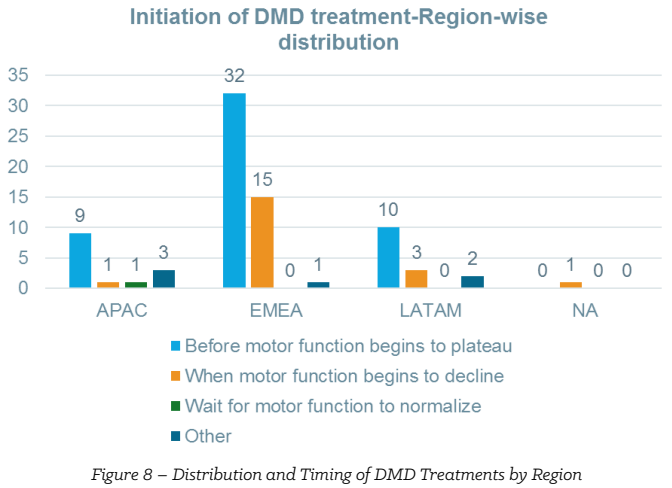


Figure 8 – Distribution and Timing of DMD Treatments by Region

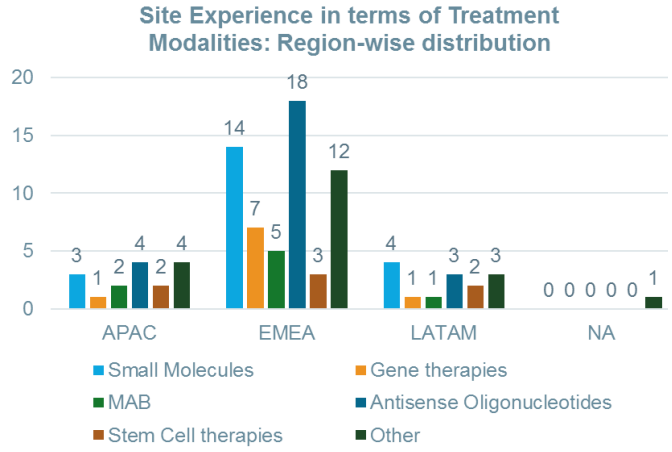


Figure 9 – Site Experience with Treatment Modalities for Ongoing or Completed Clinical Trials by Region

Although advanced/precision therapy use is currently a small part of the current DMD treatment regimen, it is expected to rise considerably as more DMD disease modifying products are approved.

Most investigators start DMD treatment before the motor function begins to plateau, with some preferring to start the treatment when the motor function begins to decline (see Figure 8).

Antisense oligonucleotides (ASOs) were found to be the most widely used treatment modalities within clinical trials, closely followed by small molecules. The majority of ASOs are exon-skipping therapies, such as drisapersen. Although this drug candidate's clinical trials were ultimately terminated, the fact that the study was global and had many sites led to widespread exposure to this treatment modality.

In the case of small molecule clinical trial experience, ataluren and givinostat were the most familiar drugs being studied by the investigators that were interviewed. Interestingly, of all the sites we reached out to, the most experienced locations with treatment modalities such as ASOs and small molecules were in the EMEA region. This may be due to availability of the patients from these regions, capacity to conduct clinical trials, marketing authorisation or reimbursement issues, or a business decision made by the sponsor in terms of site selection at the time of clinical trial execution.

Conclusions

Duchenne MD is one of the most severe forms of muscular dystrophy with no cure, with only three, ICH-region approved

disease-modifying treatments currently available. Since DMD can be life-threatening, new disease-modifying therapies aiming to slow or halt disease progression, as well as curative treatments, are desperately needed.

As the mechanism of action is further elucidated regarding the dystrophin and the genes associated with dystrophin dysregulation, more biopharmaceutical companies, in conjunction with DMD patient advocacy groups, are turning their attention to advanced (regenerative) treatment approaches targeting RNA and DNA (e.g., phosphorodiamidate morpholio oligomers [PMO], peptide-conjugated PMO [PPMO], gene therapy, gene editing, etc.) meaning more patients will be needed in the DMD clinical trial space.

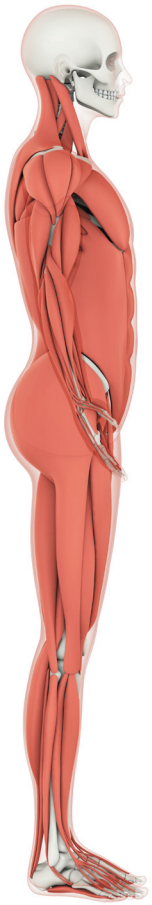
IQVIA's proactive feasibility study involving responses from 128 investigators across 40 different countries yielded the following findings with our interpretation (in *italics*):

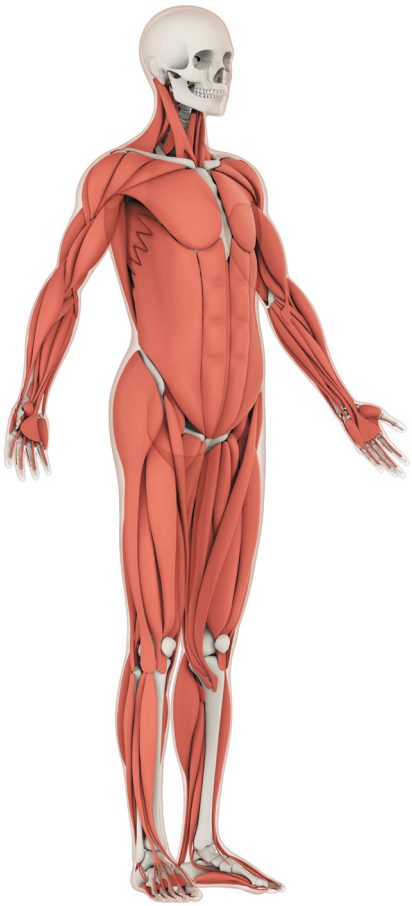
Most DMD patients at the surveyed sites have participated in clinical trials and came to the site after learning about studies through social media. *This provides an opportunity for patient advocacy groups and the biopharmaceutical industry to use social media (including exclusive sites) and internet sites as educational channels to raise patient and caregiver awareness about trends in research, likelihood of receiving active medication in clinical trials, the identification of sites that are actively enrolling, and currently used designs in the DMD. This is especially important to DMD patients because enrolment often depends on inclusion/exclusion criteria, such as ambulatory status, and given the current constraints with gene therapy (related to neutralising antibodies to viral vector which render gene therapy ineffective, and capsid specific CD8+ T cell driven immune response – decreasing efficacy and leading to safety concerns), DMD patients may only be eligible to enroll in one gene therapy trial in their lifetime (since following vector administration, neutralising antibodies are induced at high titers preventing vector re-administration).*

- There is an opportunity to enroll more DMD patients in global clinical trials. *Given the limitations of our survey (e.g., only 40 countries surveyed), many countries have not yet been explored, while other regions, such as sites in the US and Big 5 EU (including the UK, preBrexit), are likely to become severely competitive and congested. Challenges for patients crossing borders or countries need to be addressed, such as: long-term patient and caregiver accommodation while the trial is being conducted, and local language considerations, since the child must speak the language to sign the informed consent form and understand and follow the directions required for clinical trial evaluation and assessment.*

- Investigators rely on DMD patient registries and site databases to identify DMD patients for clinical trials. *In the case of registries, most of the investigators referred to either their own patient databases, local registries or national/international NMD registries for identifying patients. In the US, with more than 5000 patients and ten years of data, Parent Project Muscular Dystropy's (PPMD) Duchenne Registry is currently the largest database of Duchenne and Becker patients. PPMD has 24 Certified Duchenne Care Centers where most of the patients are seen. The Muscular Dystrophy Association (MDA) is also building a NeuroMuscular ObserVational Research (MOVR) Data Hub which will incorporate data from all of the group's MDA Care Centers.*

- Physician education regarding DMD is still needed. *For example, one of the reasons that investigators declined participation in a*





future DMD trial was because they lacked knowledge regarding DMD. In addition, 63% of the investigators surveyed have not yet enrolled any patients in DMD studies in the past five years. DMD clinical trial knowledge could be provided to investigative trial sites by regional patient advocacy groups or clinical trial organisations directly. Once a trial has been identified and initiated, DMD training should be provided at the investigator kick-off meeting prior to the start of a clinical trial and throughout the ongoing trial via the clinical research associates.

- *Travel distance for DMD patients may be a patient recruitment barrier. Given the small size of the clinical trials as per clinicaltrials.gov, concierge services (money for transport, vouchers for meals and accommodations, etc.) and language support services (e.g., a translator) should be considered to ease patient and caregiver burden after enrolling in a clinical trial and to ensure compliance.*

- *As expected, the most commonly used class of drugs for treatment of DMD globally is steroids. Although non-steroid disease-modifying therapy use is currently a small part of the current DMD treatment (4%), it is expected to rise considerably as more DMD disease-modifying products are approved. The most experienced locations with treatment modalities such as antisense oligonucleotides and small molecules were in the EMEA region. This is not surprising; however, it is important to note that Prosensa/GSK/Biomarin studies in antisense oligonucleotides have since been terminated.*[6,7]

Based on all global investigator feedback received, the authors believe that while DMD patient enrolment will be challenging in certain geographies, other regions are not yet fully explored. It is hoped that with further DMD feasibility analyses, that we will have a better grasp on investigator interest and experience with the potential to allow all patients with DMD – regardless of where they live – to enroll in a DMD clinical trial to explore biopharmaceutical products that could provide desperately needed disease-modifying treatments or a cure.

Acknowledgement

The authors wish to thank Dr. Jill Dawson, consultant to IQVIA, for her editorial contributions, insights and support.

REFERENCES

1. Understanding Neuromuscular Disease Care: Current State and Future Prospects, IQVIA Institute, 64pp, published online 30 October 2018 @ https://www.iqvia.com/institute/reports/understanding-neuromuscular-disease-care.
2. Huml RA. Muscular Dystrophy: Historical Background and Types in Muscular Dystrophy: A Concise Guide, Springer Publishing, ISBN 978-3-319-17361-0, 2015, 191pp.
3. Mah JK. Duchenne and Becker Muscular Dystrophies: Underlying Genetic and Molecular Mechanisms in Muscular Dystrophy: A Concise Guide, Springer Publishing, ISBN 978-3-319-17361-0, 2015, 191pp.
4. Romitti PA, Zhu Y, Puzhankara S, James KA, Nabukera SK, Zamba GK, Ciafaloni E, Cunniff C, Druschel CM, Mathews KD, Matthews DJ, Meaney FJ, Andrews JG, Conway KM, Fox DJ, Street N, Adams MM, Bolen J; MD STARnet. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015 Mar;135(3):513-21.
5. Duchenne Muscular Dystrophy in Clinicaltrials.gov, accessed 13 November 2018.
6. BioMarin Ends Duchenne Program, Withdraws EU Application for Drisapersen, Biopharma Dive Website, 31 May 2016, , https://www.biopharmadive.com/news/biomarin-ends-duchenne-program-withdraws-eu-application-for-drisapersen/420094/, accessed 13 December 2018.
7. Two Years After Paying $680M, BioMarin Shelves Duchenne Drug, 31 May, 2016, Xconomy Website, https://xconomy.com/san-francisco/2016/05/31/two-years-after-paying-680m-biomarin-shelves-duchenne-drug/, accessed 13 December, 2018.

Raymond A. Huml

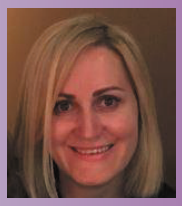
Raymond A. Huml, MS, DVM, RAC is IQVIA's Vice President of Global Biosimilars Strategic Planning, has a personal interest in MD and works with the IQVIA/Muscular Dystrophy Association (MDA) team on their national patient registry. Dr. Huml is a member of the FSH Society, co-founder and member of the North Carolina Chapter of the FSH Society, and a member of MD STARnet's NC Advisory Committee. He edited and wrote or co-wrote eight chapters for the Springer book, "Muscular Dystrophy: A Concise Guide (2015)."

Email: raymond.huml@iqvia.com

Sarah Richerson

Sarah Richerson, BSc, PhD is a Therapeutic Strategy Lead in the Therapeutic Sciences and Strategy Group of IQVIA and is responsible for developing customised project-specific execution strategies which meet all customers' unique development challenges. Sarah has over 18 years' experience within clinical research and has been involved in project leadership for numerous successful drug development programmes in psychiatry and neurology that have led to new treatments for patients. Sarah has also been the Deputy Head of the Neuroscience Center of Excellence, responsible for coordinating the enterprise-wide strategy for neuroscience, encompassing drug development and healthcare services.

Olga Uspenskaya-Cadoz



At the time of writing this paper, Olga Uspenskaya-Cadoz, MD, PhD was IQVIA's Senior Medical Director of CNS Center of Excellence. Olga is a board-certified neurologist with 11 years of experience in clinical medicine and eight years of experience in clinical research. Olga has a special interest in muscle diseases.

Akshay Kelji

Akshay Kelji, MS is a Clinical Planning Strategist and the Global Feasibility Lead at IQVIA. Some of his key responsibilities include overseeing and analysing business requests for designing, developing and delivering analytical solutions to support and enhance IQVIA R&D and RWI solutions opportunities and trial programme. Akshay has eight years of industrial experience in the areas of regulatory and global feasibility.

J Emilio Da Silva Neto

J Emilio Da Silva Neto, PharmD, MBA is the Head of the Therapeutic Strategy Lead group at IQVIA, a team dedicated to developing customised, project-specific execution strategies to meet customers' unique development challenges. Emilio has more than 17 years of experience, with two in academic research, including DMD, and over 15 years in operational strategy development, operational delivery and programme implementation in the clinical development space across multiple regions and in multiple therapeutic areas.