PEER REVIEWED

Exploring the Limb Girdle Muscular Dystrophy Clinical Trial Landscape

With the recent advent of adeno-associated, virus-based gene therapy treatments, limb girdle muscular dystrophy (LGMD) is currently attracting the attention of the biopharmaceutical industry, especially with the goal of restoring full or partial proteins that are otherwise dysregulated. Because of the multiplicity of LGMD subtypes (greater than 35 subtypes identified to date – each with a number and unique letter to identify it), is it likely that not all subtypes will be targeted simultaneously for drug development in the short term. For example, in contrast to Duchenne muscular dystrophy (DMD), where a dysregulation of the protein dystrophin is deemed to be the mechanism of action, LGMD presents as a complex of multiple subtypes of disease with sarcoglycan and dysferlin as the primary dysregulated proteins.

Several sponsors are developing potential gene therapies for LGMD patients. Therefore, LGMD patients have a choice of clinical trials, which can raise new challenges for recruitment. Additionally, trial sites are selected based on a myriad of factors, which may include sponsor choice (for an individual company's business purposes or rapid enrolment considerations), the physical location of the clinical sites (based on feasibility and capability), the site's principal investigator, regional marketing considerations, and ease of patient 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 article describes the results of a proactive, global LGMD feasibility study conducted by IQVIA in 2019, including insights from investigators currently providing LGMD patient care. The feasibility study asked 32 questions about physician interest in and motivation for LGMD clinical trial participation and solicited data regarding the investigator-estimated numbers of LGMD patients available for clinical trials by age group and for subtypes of LGMD identified by Nigro and Savarese. Over 200 investigators were polled in 48 countries with a response from 116 investigators across 36 countries.

Overview of the Muscular Dystrophies and US Impact

Muscular dystrophies (MD) comprise a group of multi-systemic diseases caused by defects in genes for the production of muscle proteins. These diseases manifest clinically as progressive muscle weakness, with associated loss of mobility, agility and body movements. Ongoing elucidation of the proteins and structures involved in certain disease processes has boosted the number of potential pharmaceutical targets, with significantly heightened interest in investment, partnership and collaboration as a result. The research community could benefit from tools to identify where patients are eligible and willing to participate in clinical research and where trial sites have adequate experience and resources to conduct the complex protocols that will be forthcoming.

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

Overview of the Limb Girdle Muscular Dystrophies

The LGMD group contains heterogeneous autosomal muscular dystrophies under the phenotype of progressive proximal weakness at the hip and shoulder girdles. There are multiple forms of LGMD due to mutations in different genes (such as CAPN3, DYSF, SGCA, SGCB, SGCG, SGCD, TTN and ANO5).[2]

Determinants of specific diagnoses include the distribution of weakness; ethnicity; family history; age at onset; rate of disease progression; presence of contracture, rigidity, rippling muscle, muscle hypertrophy or atrophy; and systemic involvement including cardiac, pulmonary, and skin complications.[3,4] By definition, the term "limb girdle muscular dystrophy" usually excludes other defined types of muscular dystrophies such as Duchenne and Becker MD, myotonic dystrophies, and facioscapulohumeral muscular dystrophy.[5] Ethnicity and family history may reveal recessive vs. dominant variants endemic to certain regions, e.g., LGMD 2A in southern Europe. In some families, the inheritance pattern and the exact gene mutation cannot be determined. Complicating the diagnostic process are substantial overlaps, as mutations in different proteins that share similar cellular functions can result in almost identical clinical phenotypes.

There is no standard of care for patients with LGMD,[6] though as with Duchenne MD, physicians often prescribe corticosteroids. In addition, supportive therapy is often prescribed for those patients with cardiopulmonary issues and cognitive issues. Many LGMD patients take various vitamin supplements, although little is known or proven about vita min supplementation in patients with LGMD.[7]

Increasing Number of Clinical Trials in LGMD

In addition to the heterogeneity of LGMD, the ultra-rare characteristics of each subtype add to clinical trial recruitment challenges. This article addresses the global LGMD landscape for a better understanding of patient distribution, aimed at overcoming these challenges.

LGMD clinical trial success relies upon site selection, which may include sponsor choice (for business purposes or rapid enrolment considerations, based on feasibility and capability), advice from patient advocacy groups specific for the subtype (e.g., Jain Foundation, Coalition to Cure Calpain 3, Family Group of Beta-sarcogylcanopathy, etc.), locations of natural history studies (e.g., Defining Clinical Endpoints in Limb Girdle Muscular Dystrophy or GRASP study),[6] the physical location of the clinical site, the site's principal investigator's speciality, regulatory requirements, marketing considerations and ease of access. These complexities must be considered when considering conducting trials in countries/regions that may lack the ability, expertise, capacity or willingness to implement LGMD studies.

It is worth highlighting that some sponsors of LGMD treatments hesitate to work in certain markets and geographies because of access and reimbursement challenges. Also, some sponsors are hesitant to partner with trial sites outside of traditional and known facilities, which could be due to long start-up timelines (e.g., in Eastern Europe and Latin America), lack of knowledge of the local environment and lack of previous rare disease clinical trial experience, especially when conducting first-in-human (FIH) clinical trials.

According to clinicaltrials.gov, a database of privately and publicly funded clinical studies conducted around the world, a total of 33 current trials mention the term "limb girdle muscular dystrophy" as of December 3, 2019 – although some are specified by the exact subtype (e.g., 2E, 2C, 2 and 2B). This compares with 266 DMD trials (search term "Duchenne muscular dystrophy"). Some of the postings on clinicaltrials.gov reflect the fact that LGMD clinical trial development is at an early stage, such as those seeking to identify clinical trial endpoints as well as those seeking to understand the natural history of a specific LGMD subtype. The number of LGMD clinical trials is expected to increase with cell and gene therapy development on the rise.

This paper will describe the results of a proactive LGMD 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 2019 with the objective of obtaining unique and current insights from global investigators currently providing LGMD patient care.

Methods

Our 32-question survey for LGMD clinical trial "readiness" – defined here as physician interest/motivation in LGMD clinical trial participation – was sent to more than 200 physicians treating LGMD patients across 48 countries.

The objective was to evaluate investigator access to LGMD patients, research experience, and challenges in recruiting and

treating the LGMD patient population, and to gain an awareness of access to equipment and diagnostic capabilities in different geographies.

The broad categories of questions included: investigator interest, patient population (including age [3–6 years old, 7–17 years old, 18 years and older], subtype, and how patients are identified), diagnosis and treatment, and site experience and logistics.

The main physician specialities this survey interviewed were neurologists, paediatric neurologists, neuromuscular specialists, and paediatric neuromuscular specialists (see Figure 1).

The survey was launched in two phases: the first survey was distributed to treating physicians in 12 countries (the US, France, Italy, Spain, UK, Germany, Denmark, Finland, Malaysia, Korea, Japan and Brazil); while the second phase included physicians in 36 additional countries (Argentina, Belgium, Bulgaria, Czech Republic, Hungary, India, Mexico, New Zealand, Poland, Romania, Turkey, South Africa, Australia, Bosnia, Canada, Chile, China, Colombia, Costa Rica, Croatia, Greece, Israel, Latvia, Lithuania, Netherlands, Norway, Peru, Philippines, Portugal, Russia, Serbia, Slovakia, Slovenia, Sweden, Taiwan and Ukraine). Responses were summarised descriptively and by region.

Results

IQVIA received completed surveys from 166 investigators across 36 countries (see Figure 2) over a three-month period. There was no difference in the response rate between the two phases of the survey.

In terms of general interest in participating in LGMD trials, a majority (70%) of physicians responded positively (see Figure 3). More than 50% of the physicians, identified largely as neurologists or paediatric neurologists, who had expressed their interest to participate in a LGMD trial, were found to be associated with an academic hospital (see Figure 4).

Sites in the United States, Canada, Brazil, Russia, Portugal, Ukraine, China and Spain were among those having the largest numbers of interested physicians. It is important to note that physician interest may not necessarily imply that there is the ability to conduct a clinical trial or the capacity to enroll patients.

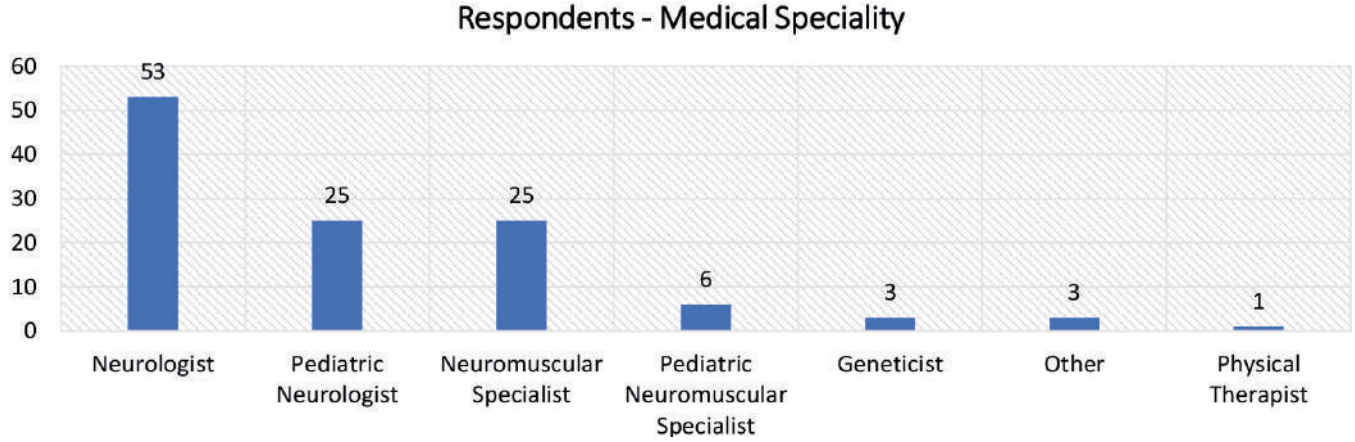

Figure 1 – An Overview of the Physician Specialities Responding

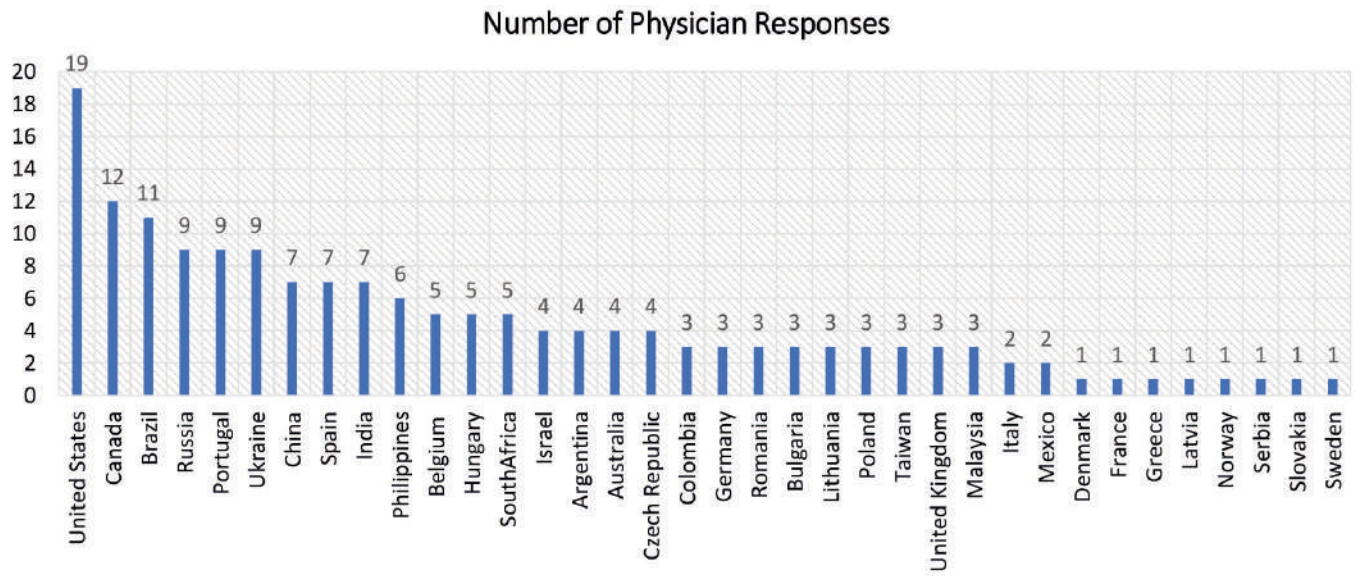

Figure 2 – Total Number of Survey Responses by Country

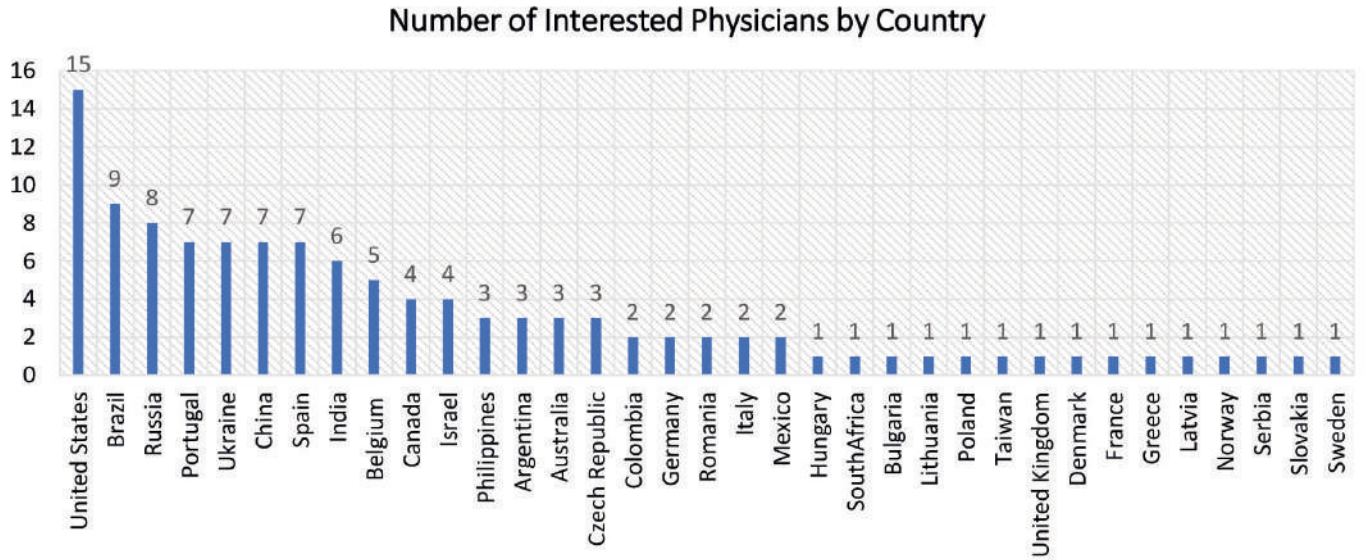

Figure 3 – Number of Interested Physicians by Country

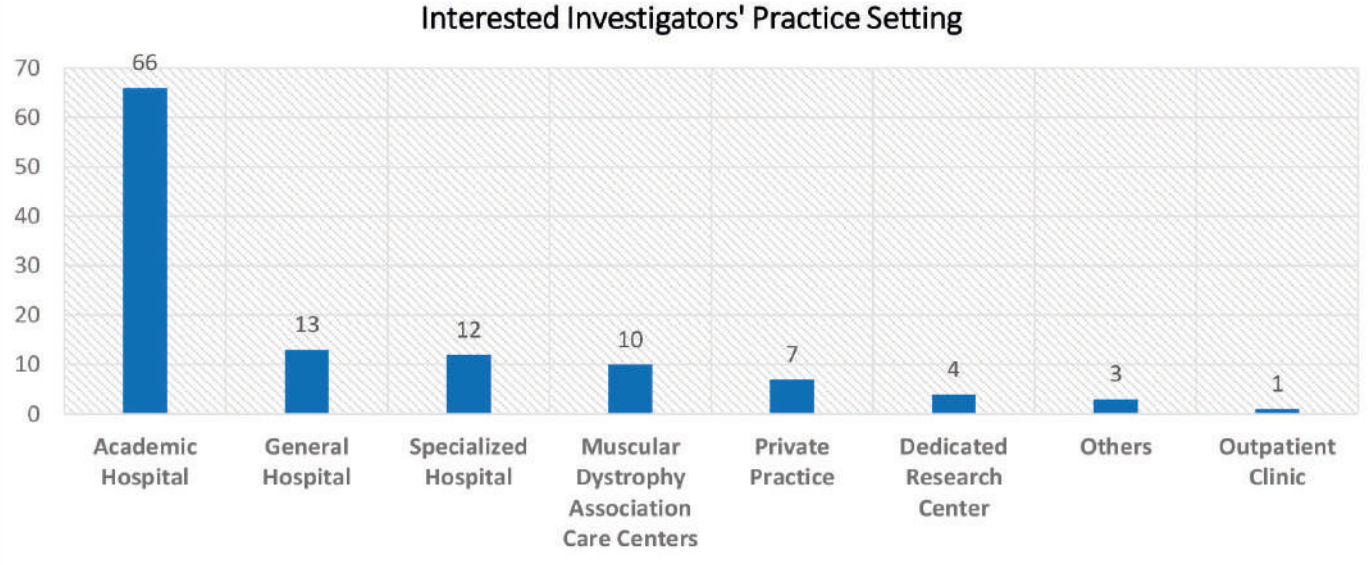

Figure 4 – Interested Investigators' Practice Setting

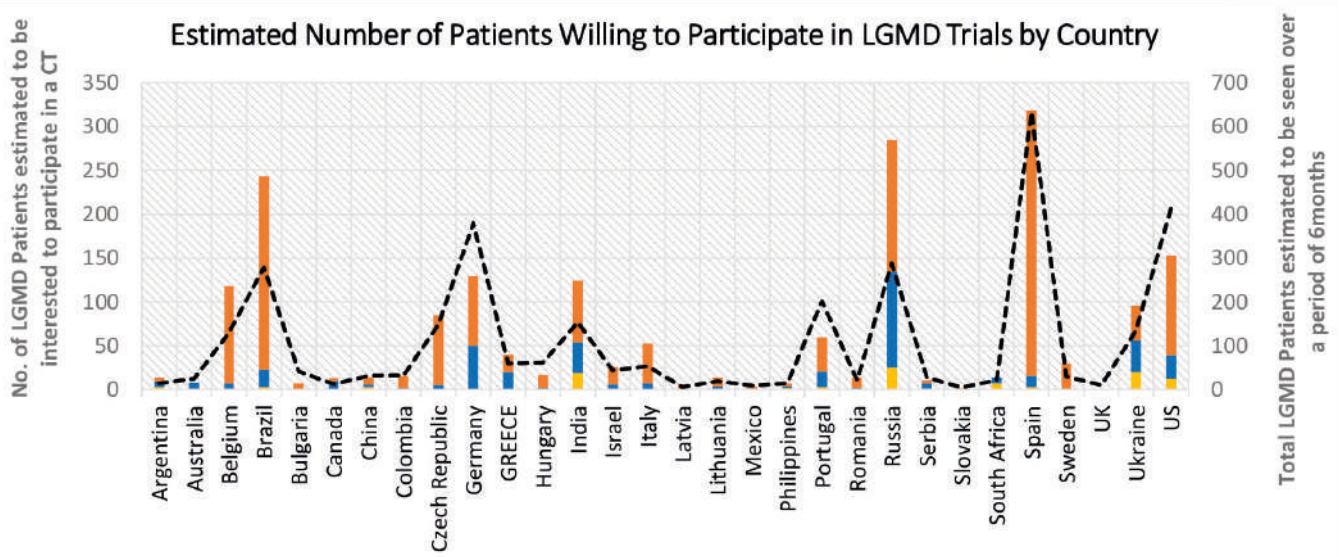

Figure 5 – Physician Estimates of Numbers of Patients Willing to Participate in LGMD Trials Based on Age Group – By Country

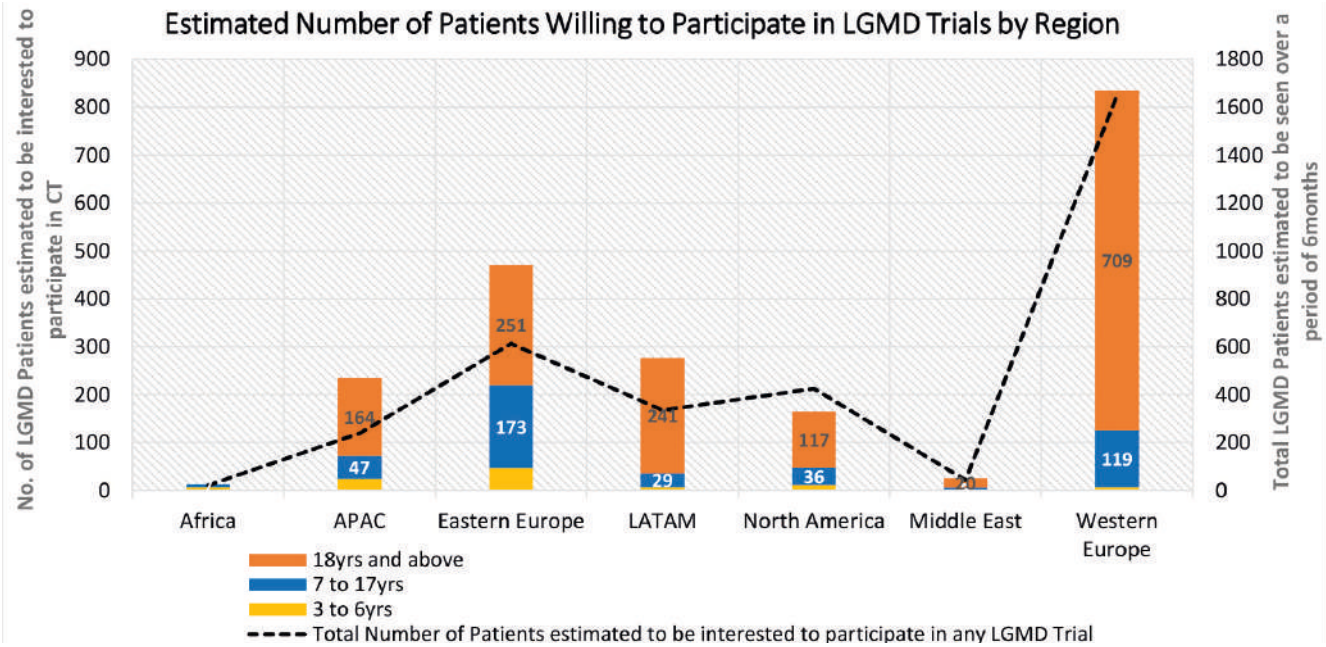

Figure 6 - Number of Patients Estimated by Physicians to be Willing to Participate in LGMD Trials Based on Age Group – By Region

Investigator Descriptions of Patients

Investigators who responded to the survey believe patients and caregivers treated in the last six months across all three age groups (3–6 years old, 7–17 years old, and ≥ 18 years of age) would be interested in being enrolled in LGMD clinical trials, with the largest number of patients coming from the adult (≥ 18 years) age group (see Figure 5 for country-by-country tallies).

In the 3–6-years age group, investigators from Russia, India, Ukraine and US reported the highest patient volume who may be interested in participating in a trial for LGMD. In the age group of 7-17 years, investigators from Russia, Ukraine, Germany and India reported a higher volume.

In the adult population, investigators from countries like Spain, Brazil, Russia and US have estimated ≥100 LGMD patients may be interested in participating in an upcoming LGMD trial (see Figure 5).

Figure 6 illustrates that investigators predict that a large number of LGMD patients would be willing to participate in an LGMD trial from Western Europe, followed by Eastern Europe, Latin America, Asia Pacific and North America. Regions/countries seeing a relatively smaller number of total / interested LGMD patients is mainly due to lack of access to appropriate genetic testing to confirm diagnosis and a lack of trial-ready infrastructure.

Across all regions, investigators reported that most of the patients in their clinical trials were identified through self-referral (34%), followed by patient registries / databases (23%) (see Figure 7). "Registries" referred to investigators' own patient databases, local registries or national/international neuromuscular disease registries.

It was also noted across regions that there was a variance in the distance travelled by the LGMD patients to reach their treating physician. In some regions, LGMD patients travelled long distances, some up to 75 miles (or more) to reach their treating physician (see Figure 8).

Only one LGMD treatment guideline exists within the ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) countries. Dated 2014,5 this

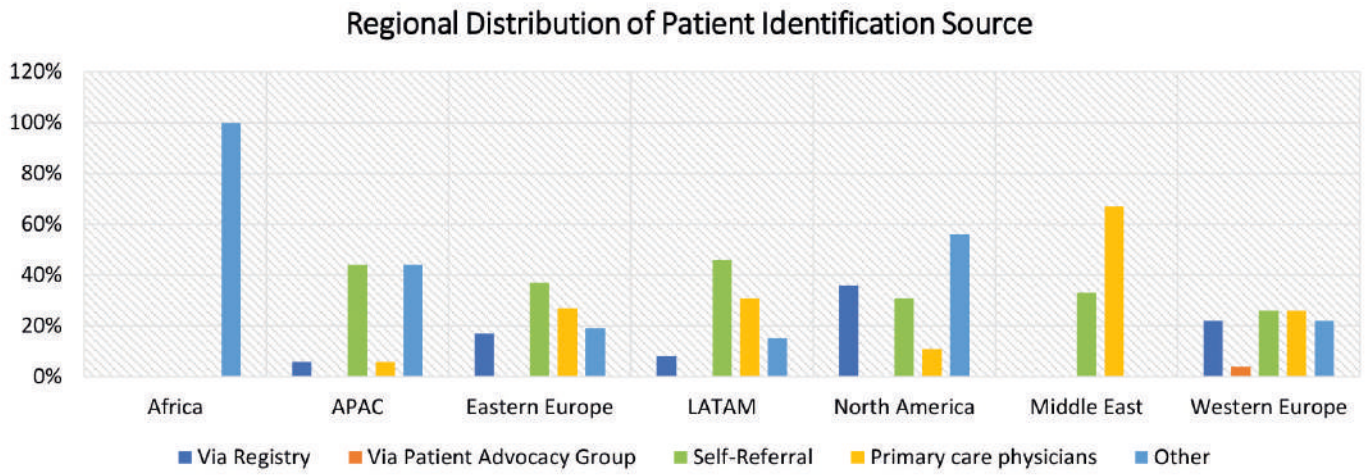

Figure 7 – Regional Distribution of Patients by Source of Identification

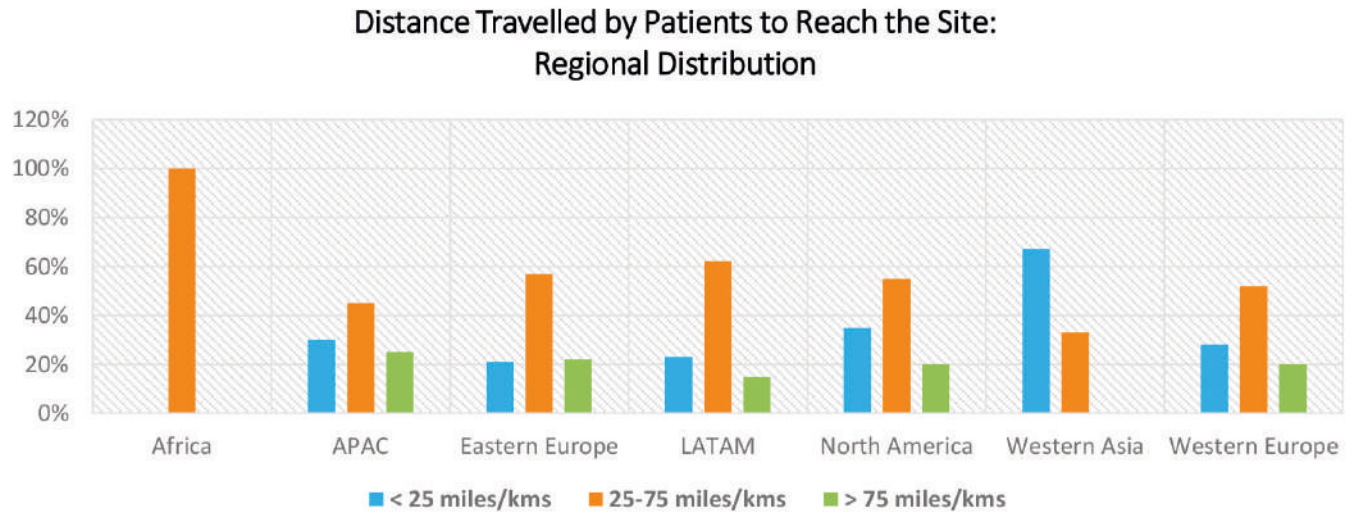

Figure 8 – Distance Travelled by Patients to Reach the Site

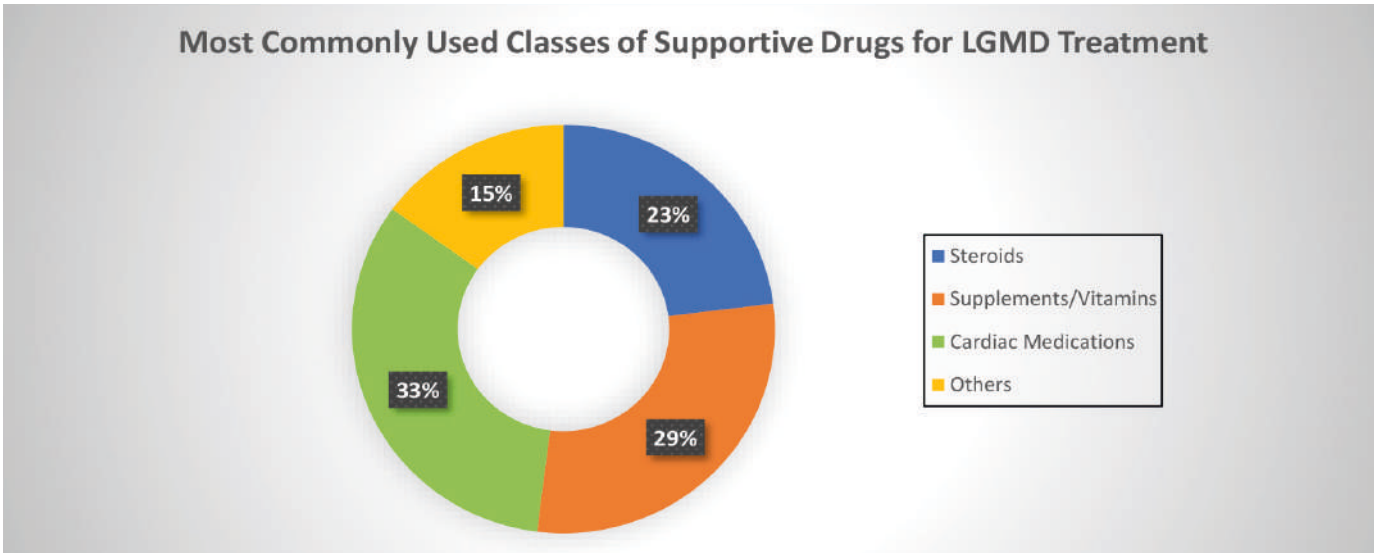

Figure 9 – Classes of Medications Used as Supportive Care for LGMD

states that any experimental treatment offered to patients with LGMD (e.g., myostatin, gene therapy, etc.) should be administered only within the clinical trial setting.

Figure 9 shows supportive care for LGMD under treatment by the responding investigators. Figure 10 summarises the types of treatments used as "standards of care" by country.

Some regions are currently conducting clinical trials either for LGMD or other types of muscular dystrophies as seen in Figures 11 and 12.

Antisense oligonucleotides (ASOs), such as nusinersen, inotersen and drisapersen) were the most commonly used class of drugs for trials in treatment of LGMD globally (24%), followed by small molecules such as edasalonexent and risidiplam (20%), others (which

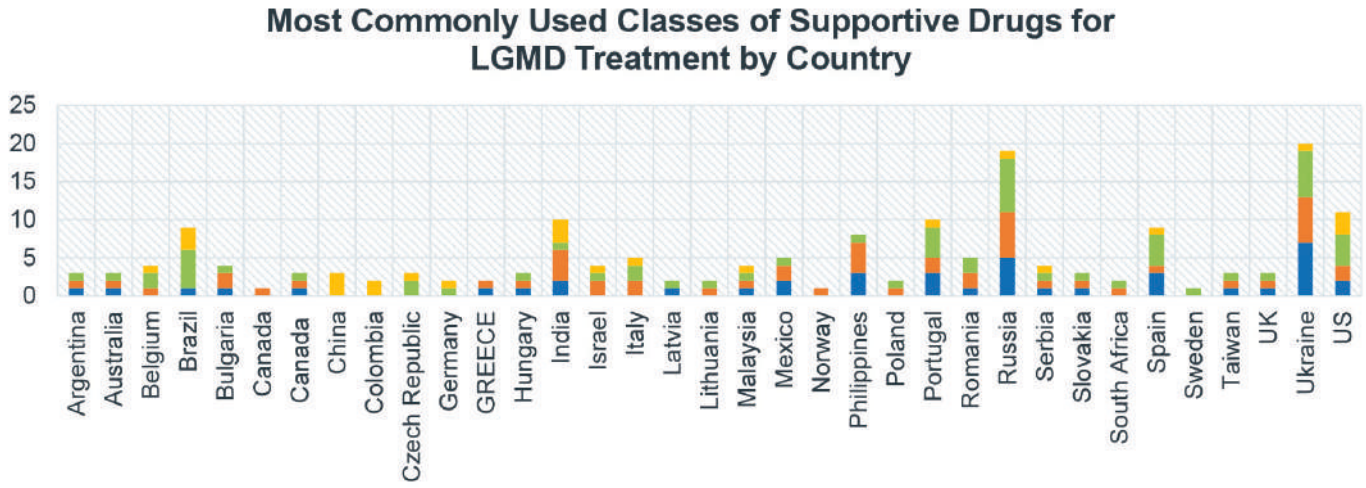

Figure 10 – LGMD Standard of Care by Country

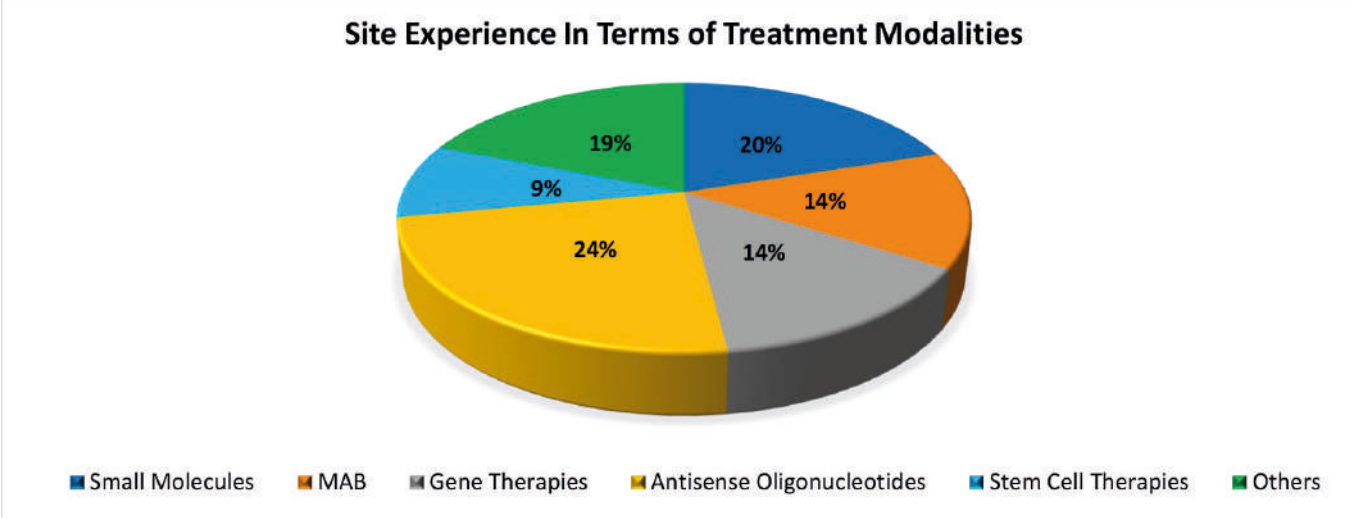

Figure 11 – Site Experience with Investigational Products for LGMD and Other Muscular Dystrophy Clinical Trials

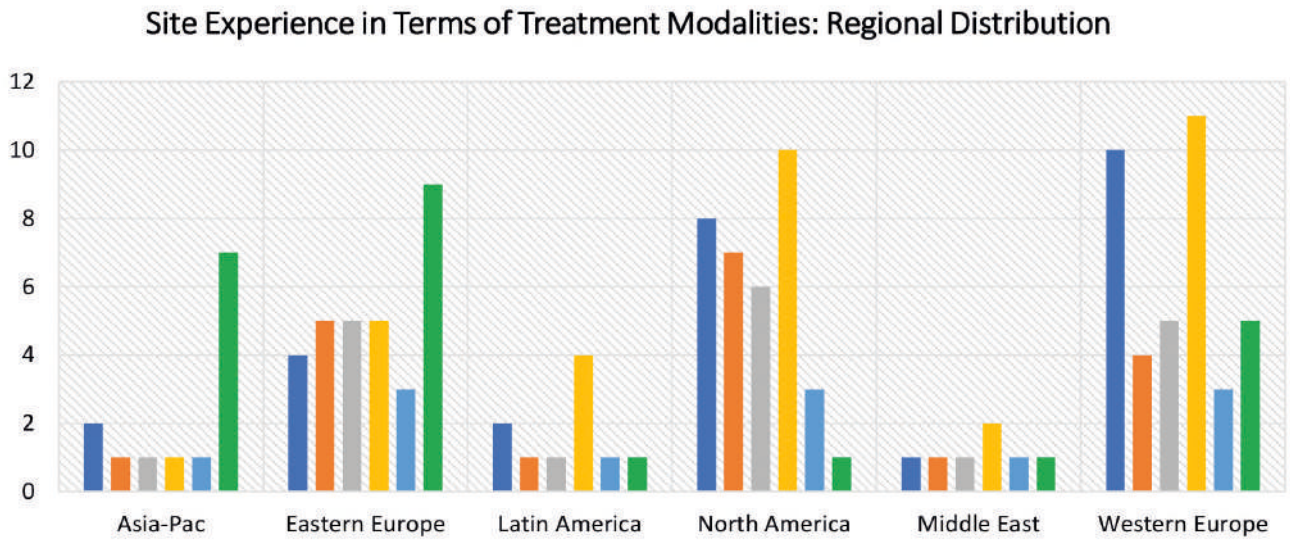

Figure 12 – Site Experience in Terms of Treatment Modalities: Regional Distribution

include enzyme replacement and adrenocorticotropic hormone or ACTH therapy) (19%), gene therapies (14%) and monoclonal antibodies (14%).

Most investigators started LGMD treatment before the motor function plateaued, with some preferring to start the treatment when the motor function begins to decline.

Conclusions

In summary, responses to the global proactive feasibility study from 116 investigators treating LGMD patients in 36 countries yielded the following findings:

- In terms of general interest in participating in LGMD trials, a majority (70%) of physicians responded positively.

- The typical speciality of principal investigators for LGMD clinical trials is neurology.
- More than half of the physicians – identified largely as neurologists or paediatric neurologist – who had expressed their interest in participating in a LGMD trial, were found to be associated with an academic hospital.
- Sites in the United States, Brazil, Russia, Portugal, Ukraine, China and Spain were among those having the largest numbers of interested physicians.
- There is an opportunity to enroll more LGMD patients in global clinical trials, beyond North America and Western Europe.
- Investigators rely on self-referral, LGMD patient registries and site databases to identify patients for clinical trials.
- Travel distance for LGMD patients may be an important barrier for recruitment.

LGMD is one of the most severe forms of muscular dystrophy with currently no available cure and no approved disease-modifying treatments. Since LGMD can be life-threatening and severely debilitating due to progressive muscle weakness, new disease-modifying therapies aiming to slow or halt disease progression – as well as curative treatments – are desperately needed.

LGMD in all of its forms represents a formidable challenge for drug developers. Due to the disparity of subtypes, some forms might not be amenable to all types of currently proposed therapies (e.g., gene therapies using AAV vector technology). Although advanced / precision therapy use is currently a small part of the LGMD treatment regimen, this is expected to increase considerably in importance if disease-modifying therapies are approved.

As the pathology of each of the subtypes becomes more elucidated, additional targets will be available for study. As the number of clinical trials rises, so will the need for patients with certain subtypes. Given the small size of the clinical trials, as shown in the clinicaltrials.gov postings, concierge services (including reimbursement for travel costs, and vouchers for meals and accommodations) 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.

The speciality of principal investigators for LGMD clinical trials is typically neurology; although other specialities are either already part of the LGMD medical care team (respiratory pathologist, cardiologist, physical therapist, speech pathologist, etc.) or may be added to the patient's management team as the disease progresses.

Based on all global investigator feedback received, the authors believe that while LGMD patient enrolment will be challenging in certain geographies (such as the US and Europe), other regions are not yet fully explored (including Eastern Europe, Latin America, China and India).

As clinical research is still at an early stage in LGMD, some expert sites have never participated in industry-sponsored clinical trials, especially in FIH studies. LGMD clinical trial expertise and knowledge could be provided to investigative trial sites by the pharmaceutical companies and/or designee, directly. Once a trial has been identified and initiated, LGMD training should be provided from the early stages and throughout the study.

It is hoped that with further LGMD feasibility analyses, we will gain a better grasp on investigator interest and experience with the potential to allow all patients with LGMD – regardless of subtype or geography – to enroll in a clinical trial to explore products that could provide desperately needed disease-modifying treatments or a cure.

Diagnostic Approach to LGMD

The diagnosis of limb girdle muscular dystrophy is often challenging because of significant disease heterogeneity. Historically, the muscular dystrophies were classified as either type 1 (dominant) or type 2 (recessive) depending on the mode of inheritance. According to Nigro and Savarese (2014), there are currently eight subtypes of autosomal dominant (type 1) limb girdle muscular dystrophy.

Calpainopathies or LGMD type 2A, are the most common form of LGMD, and are caused by mutations in CAPN3. LGMD type 2B, also known as dysferlinopathies, are caused by mutations in the DYSF gene. While sarcoglycanopathies, also known as LGMD types 2D, 2E, 2C, and 2F are caused by mutations of the following genes: SGCA, SGCB, SGCG, and SGCD genes. Mutations of the ANO5 gene cause type 2L LGMD. Several other gene mutations cause LGMD forms called dystroglycanopathies, including types 2I, 2K, 2M, and 2N. The disorders are labelled alphabetically according to when the individual genes were identified. The main classes of proteins involved in these conditions include extracellular matrix and external membrane proteins, enzymes or proteins with putative enzymatic function, sarcolemma-associated proteins, nuclear membrane proteins, and sarcomeric proteins.

The differential diagnosis of limb girdle muscular dystrophy is broad which, at least in the past, has led to misdiagnoses. For example, the authors have met several patients with LGMD who had previously been diagnosed with DMD or another dystrophy before their LGMD and specific subtype diagnosis. The differential diagnosis spectrum includes other muscular dystrophies such as congenital muscular dystrophies, myotonic dystrophy, facioscapulohumeral muscular dystrophy, and Emery-Dreifuss muscular dystrophy, as well as congenital myopathies, myofibrillar myopathies, distal myopathies, metabolic myopathy (such as Pompe or lipid storage disease), channelopathies, inflammatory myopathies, neurogenic disorders, and neuromuscular junction transmission disorders.

Similar to other muscular dystrophies, the approach to LGMD requires a detailed history, a thorough physical examination, and measurement of a serum creatine kinase level. Other genetic and acquired causes of proximal muscular weakness should be excluded. The diagnosis may be confirmed by molecular genetic testing, muscle biopsy, or a combination of both. Muscle biopsy will typically reveal the characteristic dystrophic features; further immunostaining may demonstrate the presence or absence of specific muscle proteins such as dystrophin, dysferlin, sarcoglycans, emerin, collagen VI, merosin, and glycosylated alpha-dystroglycan. The future of molecular testing may shift away from targeted genetic analysis toward whole genome or exome sequencing that will allow rapid and cost-efficient confirmation of the diagnosis. General treatment principles include offering genetic counselling for affected individuals and families; connecting them with patient organisations and disease registries; providing rehabilitation through multidisciplinary clinics to maximise function; supporting education, career, social, and financial needs; screening and treating the associated complications; and evaluating new treatment options for specific diseases when available.

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REFERENCES

1. Understanding Neuromuscular Disease Care: Current State and Future Prospects; Institute Report, October 30, 2018; https://www.iqvia.com/insights/the-iqvia-institute/reports/understanding-neuromuscular-disease-care, accessed November 12, 2019.
2. Nigro V, Savarese M. Genetic Basis of Limb-Girdle Muscular Dystrophies: the 2014 Update. Acta Myol. 2014 May; 33(10):1-2; https://www.ncbi.nlm.nih.gov/pubmed/24843229, accessed November 27, 2019.
3. Mercuri E, Muntoni F. Muscular Dystrophies. Lancet. 2013; 381:845-60.
4. Mah JK. Chapter 5: An Overview of the Other Muscular Dystrophies: Underlying Genetic and Molecular Mechanisms in Muscular Dystrophy: A Concise Guide (Huml RA, Editor), Springer Publishing (ISBN 978-3-319-17361-0), Copyright 2015.
5. Narayanaswami P, Weiss M, Selcen D, David W, Raynor E, Carter G, et al. Evidence-based guideline summary: Diagnosis and treatment of limb-girdle and distal dystrophies: Report of the guideline development subcommittee of the American Academy of Neurology and the practice issues review panel of the American Association of Neuromuscular & Electrodiagnostic Medicine. Neurology 2014;83:1453-63.
6. Evidence Based Guideline: Diagnosis and Treatment of Limb-Girdle and Distal Dystrophies; American Association of the Neuromuscular & Electrodiagnostic Medicine (AANEM) group: Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Issues Review Panel of the American Association of Neuromuscular & Electrodiagnostic Medicine at https://www.aan.com/Guidelines/home/GetGuidelineContent/672, accessed November 20, 2019.
7. Life Extension: The Source of a Healthier Life at https://www.lifeextension.com/protocols/neurological/muscular-dystrophy#, accessed November 27, 2019.
8. Defining Clinical Endpoints in Limb Girdle Muscular Dystrophy (LGMD) (GRASP); https://clinicaltrials.gov/ct2/show/NCT03981289, accessed November 20, 2019.

Raymond A. Huml

Raymond A. Huml, MS, DVM, RAC is Vice President and Head of IQVIA's Global Biosimilars Center of Excellence, 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 co-wrote eight chapters for the Springer book, "Muscular Dystrophy: A Concise Guide (2015)."

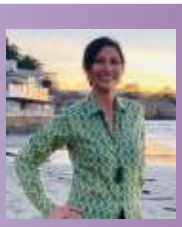
Email: raymond.huml@iqvia.com

Olja Tanjga

Olja Tanjga, MD is Director of IQVIA's CNS Biotech solution. Dr Tanjga is a neurologist with 17 years' combined industry and clinical research experience. Dr Tanjga is a board-certified neurologist with a special interest in MS, neuromuscular diseases, extrapyramidal disorders, stroke and pain with experience in many other neurology indications. She has served as both medical and scientific advisor on over 40 clinical trials including the following indications: multiple sclerosis, Parkinson's disease, Alzheimer's disease, ALS, epilepsy, stroke, acute / chronic pain (headache, low lumbar pain, neurogenic, herpetic pain, diabetic neuropathy, trigeminal neuralgia), and myasthenia gravis.

Email: olja.tanjga@quintiles.com

Tiffany Chow



Tiffany Chow, MD is Director and Medical Strategy Lead for IQVIA's CNS Center of Excellence. A neurologist by training, she is an experienced industry physician with over 20 years of clinical research in both academic neuroscience and research on elucidating the neurobiology of neurodegenerative disorders, applying PET imaging and functional neuroimaging methods, neuropsychiatric assessments and genomic testing in order to develop clinically meaningful therapies.

Email: tiffany.chow@quintiles.com

Siddharth Aras

Siddharth Aras, MS is a Clinical Planning Strategist and the Global Feasibility Manager 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 programmes. Siddharth has 12 years of industry experience in the areas of regulatory affairs and global feasibility.

Email: siddharth.aras@quintiles.com

Marie Trad

Marie Trad, MD is Vice President and Head of IQVIA's CNS Biotech division. Dr Trad has over 30 years of CNS experience, including 11 years as a clinical Neurologist / Neuroradiologist and 19 years of pharmaceutical industry experience as a Clinical Research Specialist / Consultant. She also has 19 years of CNS drug development and clinical trial management experience, providing medical, clinical and global strategic support to neurology and psychiatry trials in: epilepsy (both monotherapy and add-on therapy), idiopathic Parkinson's disease (early and advanced), Alzheimer's disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), chronic and acute pain, including diabetic neuropathic pain and post herpetic neuralgia, migraine, major depressive disorder, schizophrenia, bipolar disorders, generalised anxiety disorder, traumatic brain injury and stroke. She has significant experience in neuroradiology, including magnetic resonance imaging, magnetic resonance angiography, and computed tomography (e.g., scans of head, neck and spine).

Email: marie.trad@novellaclinical.com

Jill Dawson

Jill Dawson, PhD, is a medical writing consultant to IQVIA, and a co-author of multiple papers on muscular dystrophy, biosimilars, celiac disease and other topics. She has a BSc and a PhD in Life Sciences from Imperial College London.

Email: jilldawson100mac.com