Workshop report

Facilitating orphan drug development: Proceedings of the TREAT-NMD International Conference, December 2015, Washington, DC, USA

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1. Introduction

The bi-annual TREAT-NMD International Conference was held in December 2015 in Washington DC, with the theme of 'growing the drug pipeline for neuromuscular diseases: optimizing resources for clinical development of new therapies'. There is a perception, particularly in the patient/parent community, that there are many failures and few successes in drug development programmes in neuromuscular disease. A goal of the meeting was to address challenges facing the neuromuscular community regarding developing new therapies for patients, with key opinion leaders providing their perspectives, with ample time for discussion with the participants.

2. Session description

2.1. Patient and family involvement in drug development

It is increasingly recognized by regulatory authorities and drug developers that the input of stakeholders (patients and families) is important throughout the drug development process. Patients and families provide first-hand information on the burden of disease, relevance of outcome measures to quality of life, and acceptable risks. Whether and how patients and their families are engaged in the drug development process, and the level of communication throughout clinical development, should play a pivotal role in success or failure of a therapy development programme. Feasibility of clinical trial design hinges on early and frequent patient engagement, while attitudes about acceptable benefits versus risks are becoming an important factor in regulatory approvals.

This session provided concrete recommendations for active participation of patients and caregivers in drug development,

with three perspectives presented. Pat Furlong, from the viewpoint of patient advocacy, discussed the importance of patient/care provider views and active participation from the early stages of clinical trial design through marketing approval. Marc Boutin, from a patient advocacy perspective, discussed how patients connect to and help drive biomedical breakthroughs through regulatory approval. Finally, Cathy Turner and Olav Veldhuizen discussed the outcomes of the TREAT-NMD workshop, "Participants not Subjects: Engaging Patients and Families in Paediatric Clinical Research." The key message of this session was that success in development of novel therapeutics for neuromuscular diseases is best facilitated through a partnership with patients and families, where their voice is heard in decisions and planning rather than simply serving as subjects in clinical trials.

The National Health Council is at the forefront of shifting the focus of health care toward an approach that places the patient at the centre of the discussion. Using the reauthorization of the Prescription Drug User Fee Act (PDUFA) as an example, Boutin walked through the public policymaking process highlighting the importance of the patient perspective in ensuring the development of high-value products. Next Boutin addressed the need for health care systems to address both population and individual health. The health care system is shifting from focusing on acute to chronic conditions and from addressing the needs of the "average" patient to addressing personal preference and increasingly at the genetic level. Having a comprehensive and inclusive picture of patients for a given disease that recognizes their desired clinical outcomes, experiences, and life goals/aspirations is essential in the progress toward patient centricity.

Engagement of stake holders in drug development becomes more complicated when the research involves children – how and why should they be told about their condition and the clinical trial in which they are enrolled? How can their views and preferences be taken into account when planning and conducting research – trials in particular? What if children's preferences were different from their parents'? What is the

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[1] Appendix A.

purpose and importance of taking a child's formal 'assent' before enrolling on a clinical trial? Cathy Turner and Olav Veldhuizen addressed these questions through video interviews with different stakeholders giving their views on the questions. Focusing on rare paediatric neuromuscular diseases, experts included patient representatives (including parents) patients themselves, clinicians and ethicists – all with experience of clinical trials. Their responses were grouped into themes: Benefits and advantages of patient engagement in research, Barriers to engagement and possible solutions, How important is a child's assent?

2.2. Preclinical efficacy trials in mouse models

Animal models have long been used as a means of assessing safety of a new drug under development. In orphan drugs, animal models are increasingly utilized to assess efficacy, particularly in genetic disease where the same gene abnormality in human patients can also be studied in mouse models. EMA now suggests two independent efficacy trials in pre-clinical models when considering orphan drug status. Many of the key features of human clinical trials that are felt to build a compelling case for efficacy (blinded, placebo-controlled, robust outcome measures) are also now viewed as relevant to pre-clinical efficacy trials. Speakers were Jonathan Kimmelman (McGill University, Canada), Annamaria De Luca (University of Bari, Italy), and Arthur Burghes (Ohio State University, USA).

Jonathan Kimmelman discussed the issue of 'reproducibility'. There are many examples of where a drug showing promise in a mouse model did not show efficacy in a subsequent human trial. Indeed, the vast majority of new interventions fail to vindicate promise shown in preclinical studies or early phase trials. Some unsuccessful development trajectories are due to unavoidable properties of drug development, such as the fact that base rates for discovering useful interventions are exceedingly low. Many other failures in therapy development are due to avoidable problems with the design, reporting, and uptake of preclinical studies. To address design problems, researchers can draw on consensus recommendations for addressing threats to the internal, construct and external validity of their preclinical studies. Reporting deficiencies can be corrected by adhering to reporting guidelines like ARRIVE [1], and redoubling efforts to register preclinical studies and publish informative "negative" studies. Uptake of evidence can be improved by requiring systematic review of preclinical evidence before launching trials. Unsuccessful translation trajectories provide valuable feedback about pathophysiological mechanisms driving therapeutic development, and also about the properties of model systems and surrogate outcomes. However, only a fraction of the information generated in unsuccessful translation trajectories is ever reported. Capturing this information will require major improvements in the reporting of both preclinical and clinical research.

Arthur Burghes discussed the preclinical testing of treatments in SMA mice including the Delta 7 SMA mouse model [2]. In SMA there is an excellent target, the *SMN2* gene,

for development of treatments [3]. The key aspect of this target is that increasing SMN in man and mouse improves the SMA phenotype. Furthermore, humans with more copies of intact *SMN2* that produce more full-length SMN have milder phenotypes, or even no phenotype at all [4–6]. The same is true in mice [7,8]. The initial molecules that were developed to increase SMN levels from *SMN2* resulted in a weak increase in SMN or no effect at all in mice [9]. In the case of small molecules one must always consider the actual levels of drug obtained in the tissue before performing efficacy tests. As such, if sufficient levels of drugs are not achieved then the efficacy test is unlikely to show an improvement. In testing weak inducers it is important that the vehicle treated SMA mice do not show decreased survival when compared to untreated SMA. The survival in Delta7 mice should be significantly above 13 days (a survival curve composed of 89 SMA mice has a mean and median survival of 13 days) [2,10]. It is also preferable to have weak inducers duplicate in different laboratories or even different mice lines [11]. A series of well documented behavioural tests have been used in SMA, and the number of animals required for sufficient power has been determined [12,13]. Two of the simplest measures include weight and survival of SMA animals. In all studies, it is good practice to randomize the animals and have the testing investigator blinded. Various treatments including scAAV9-SMN gene therapy, antisense oligonucleotide therapies directed against ISS-N1 and small molecules that enhance incorporation of SMN exon7 have a major impact on SMA mice with survival increase from 13 days to well over 100 days [14–18]. In this case the investigator will always become unblinded to some extent in regard to genotype of treated SMA mice as rescued SMA mice are typically smaller compared to control mice. Furthermore, unintentional unblinding of treatment group will occur with very effective therapies due to decline of weight and death of untreated SMA mice.

The single most important criterion in evaluating the efficacy of a potential therapeutic is the size of the effect on the outcome (i.e. greater than 100 days extension of SMA mouse survival). Incredibly, effect size is not even listed in the NIH Rigor Guidelines. A large effect is much more likely to be reproducible and show efficacy in the clinic. Indeed, a lot of failures are linked to very small effect sizes in the original studies. Best practice suggests identifying treatments with large effects in the preclinical model before moving forward to expensive clinical trials.

The fundamental biology of the disorder is important to consider when developing therapeutics. Data from SMA clinical trials show that introduction of scAAV9-SMN early in the disease appears to have a major impact on the SMA phenotype (AveXis.com). This is consistent with the results from mouse studies that showed decreased therapeutic impact of SMN restoration after motor neurons are lost [19–22]. For the treatment of symptomatic SMA patients, it will be necessary to develop combinatorial therapeutics such that the remaining motor neurons are preserved with SMN directed therapies but other means of muscle enhancement will be required to optimize physical function. In conclusion a large

impact on the SMA phenotype in mice will help increase the likelihood of a significant impact in clinical trials. Furthermore, during the development and testing of potential therapeutics it is critical to consider the timing of treatment administration for the development of optimal therapeutic interventions.

Annamaria De Luca discussed international efforts to standardize outcome measures in the mouse model for Duchenne muscular dystrophy (DMD) – the *mdx* mouse. She noted the importance of rigorous design of tests in animal models, and reduction in the heterogeneity of experimental approaches. The TREAT-NMD network has taken an active role in establishing standard operating procedures (SOP) as state-of-art experimental approaches for assessing hard end-points in pathology progression and drug study. Over the years several SOPs have been prepared, continuously upgraded and made freely available to the scientific community (http://www.treat-nmd.eu/research/preclinical/dmd-sops/). A converging attention is also on the lack of transparency, rigour and reproducibility in pre-clinical research, along with the confusion between explorative studies, for definition flexible and innovative, and confirmatory studies aimed at providing compelling evidence of efficacy [23,24]. For clinical translation, robustness of preclinical results, possibly independently validated by different laboratories, is critically important in rare diseases. These aspects are often underlined by TREAT-NMD Advisory Committee for Therapeutics (TACT) when providing guidance on submitted developmental paths of therapeutics in rare neuromuscular diseases. Unfortunately many of the published preclinical studies are conducted as exploratory studies but are then used to promote a clinical trial, based on the urgency in finding a therapy. Another possible bias is that results of pre-clinical tests need publication and that journals are keener to publish novel, impressive results with suggestive titles in a need to attract readers and citations. A novel study, even when based on a strong rationale and an important hypothesis, will hardly be published if results are negative. Impressive confirmatory results that lack novelty may encounter similar problems.

The improvement of translational research requires then a concerted effort of many stakeholders, including scientists, journal editors, funding agencies, patient's association and clinicians. Only a wide consensus on best approaches may actually lead to the desired change. In parallel, the issue of investing time and funding to define best practices and standard protocols for animal models of diseases definitely deserves more attention.

2.3. Innovative clinical trial designs and outcome measures

The number of drugs in clinical development programmes for rare neuromuscular diseases is rapidly expanding. While this represents a success in broadening the drug development efforts, this success also is accompanied by new challenges. The number of patients and clinical trial centres can become limiting to trial recruitment. Carrying out clinical trials with hundreds of patients, but with insensitive or unreliable outcome measures not only compromises the data from that trial, but also removes those patients from consideration in other clinical

trials that may be better designed. This session addressed how recent advances in the utilization of natural history, novel biomarkers and statistical methods are evolving clinical trial design, with presentations by Craig McDonald (University of California, Davis, USA), Susan Ward (The TAP Collaboration), Chris Coffey (University of Iowa, USA), Charles Mohan (The United Mitochondrial Disease Foundation, USA), and Joyce Kullman (Vasculitis Foundation, USA).

Susan Ward described the cTAP initiative to combine natural history, registry, and clinical trial data for Duchenne muscular dystrophy into a centralized resource. To date, natural history longitudinal data have been shared on over 1250 de-identified patients representing over 5000 patient-years. An initial goal is to query the diversity of longitudinal patterns of disease progression in Duchenne, possibly clustering into groups of patients that share similar rates of disease progression. To accelerate the adoption of historically controlled trials in Duchenne, the collaboration platform includes analysis tools that enable 'apples to apples' descriptions of both natural history and placebo arm outcomes – a prerequisite to gaining regulatory support for use of natural history in open label follow-on studies and prospective trials.

Charles Mohan described roles of Patient Advocacy Groups (PAGs), and the responsibility of these groups to adequately prepare patient or family member candidates for participation in drug development programmes, not simply by representing themselves and their own situation, but by representing the more general experience of all patients with a particular disorder. It is vital that PAGs provide accurate and clear information and not contradict themselves, while conveying the value of clinical trials and that without the patients there will be no trials, and no treatments leading to cures. There are many safeguard systems built into clinical development programmes, such as Institutional Review Boards, Data Safety Monitoring Boards, and the regulatory authorities. PAGs can provide the perfect liaison in connecting the various dots between clinical trials and patients. One initiative to support this is the Clinical Trials Transformation Initiative (CTTI). This initiative has five recommendations/best practices for all stakeholders. These include:

- Engage the "patient voice" by establishing partnerships from the beginning of the research and development programme to improve trial design and execution.
- From the start, clearly define the expectations, roles, and responsibilities of all partners, including the resources being committed, data being shared, and objectives of the programme.
- Build the trust required for successful partnerships by being transparent and trustworthy, following through on commitments, and honouring confidentiality.
- Involve the expertise of multiple partners for a broader perspective to mitigate risk and enrich pipeline development.
- Manage real or perceived conflicts of interest by establishing policies that require full disclosure, transparency, and accountability.

Through this approach, and with good coordination, communication and collaboration, mutual trust can be achieved, which will ultimately result in approved therapies for the benefit of patients by engagement and empowerment of those same patients.

2.4. Biochemical and imaging outcomes in clinical trials

Tests of specific proteins, metabolites, or nucleic acids in patient blood, muscle or urine (biochemical outcomes, or biomarkers), and imaging of patient tissues can be alternatives to clinical outcome measures. Biochemical and imaging outcomes may serve as more acute and objective read-outs of drug effects compared to clinical outcomes. The role of biomarkers in rare neuromuscular disease drug development includes: molecular diagnosis for entry into a mutation-specific clinical trial, acute read-outs of drug mechanism of action, monitoring of aspects of safety, and dose finding (highest safe dose and lowest efficacious dose). Biomarkers can offer an invaluable tool for monitoring disease progression, prognosis and response to drug treatment during clinical trials, but each biomarker must be placed into a specific 'context of use', and a robust and compelling dataset established showing that the biomarker is valid for that context of use, and that the tests utilized to detect the biomarker are sensitive and reliable. Speakers in this session were Pietro Spitali (Leiden University Medical Centre, The Netherlands), Yetrib Hathout (Children's National Health System, USA), Lee Sweeney (University of Florida, USA), and Giorgio Tasca (Catholic University School of Medicine, Italy).

Pietro Spitali of the Leiden University Medical Center described how different biomarker datasets can be integrated to have more in depth understanding of the biology behind neuromuscular disorders and especially Duchenne Muscular Dystrophy. As an example the statin pathway was identified as holding potential to mitigate symptoms based on data from both lipid and metabolite datasets in mouse models. This finding was further discussed in light of the recent publication that treatment with simvastatin improved muscular dystrophy in dystrophic mice [25]. While work is still ongoing to complete data collection, the presented approach already highlighted the potential of data integration to identify biomarkers and therapeutic targets.

Yetrib Hathout described his utilization of two complementary serum proteome profiling methods, mass spectrometry and somaSCAN aptamer panels, to query about 1500 serum proteins in both DMD patients and *mdx* mice. Biomarkers were classified into groups reflecting specific aspects of pathology, including myofibrillar biomarkers reflecting muscle fibre leakage, inflammation and fibrosis [26,27]. Different biomarkers were seen to respond to different pharmacological treatments. Membrane leakage biomarkers were sensitive to dystrophin replacement therapy [28] while inflammation and immune associated biomarkers were sensitive to glucocorticoid treatment [29]. These data set the stage for integration of these biomarkers into drug development programmes, particularly in Phase 2 dose-finding studies.

The use of MRI as an imaging outcome was described in DMD by Dr. Sweeny, and in Facioscapulohumeral dystrophy (FSHD) by Dr. Tasca. Facioscapulohumeral muscular dystrophy (FSHD) is one of the most frequent muscle diseases, characterized by a unique, non-conventional genetic mechanism. Using MRI to characterize muscle involvement and follow patients up, a picture has emerged in which sequential bursts of degeneration involve individual muscles in an asynchronous manner [30]. This peculiar radiological progression is in line with results obtained with multidisciplinary approaches, thus configuring FSHD as a "muscle by muscle" disease.

In this context, a common feature of FSHD is the presence of areas of hypersignal on STIR (short-tau inversion recovery) sequences, which represent areas of muscle oedema/inflammation. Imaging and molecular evidence have accumulated, pointing toward the fact that these STIR+ lesions mark a different phase of disease at single muscle level. Consequently, even though the exact role of inflammation is not fully understood, the detection of these abnormalities is surely important to monitor disease evolution.

Relevant for clinical trials, muscle imaging can be useful for choosing the patients who are in an "active" phase of the disease, as well as for correctly stratifying patients, accurately following muscle involvement over time and choosing the targets for quantitative studies. Longitudinal, large cohort imaging studies using both standard and quantitative MRI are definitely needed to move forward in our understanding of FSHD natural history and disease pathophysiology. Improving our knowledge about mechanisms that lead to muscle damage will also facilitate the discovery of tissue and circulating biomarkers.

2.5. Standards of care

Therapeutic developments in neuromuscular disorders have highlighted the impact of care and management on the outcomes currently measured in clinical trials. If there is wide variability in standards of care, then patients may show different onset and progression of disease. Such variability significantly complicates interpretation of clinical trial data regarding efficacy and safety of new drugs. The session gave an update on the standards of care and guidelines for different neuromuscular disorders in the context of clinical trial readiness. Speakers were Bernard Brais (Université McGill, Canada), Nicholas Johnson (University of Utah, USA), Cynthia Gagnon (Université de Sherbrooke, Canada), Richard Finkel (Nemours Children's Hospital, USA), and Michela Guglieri (Newcastle University, UK).

Nicholas Johnson discussed the management of congenital and childhood onset myotonic dystrophy. Congenital myotonic dystrophy should be defined as onset of symptoms (hypotonia, respiratory failure, or feeding difficulty) in the first month of life. Childhood onset myotonic dystrophy is onset of symptoms after the first month of life. There are currently no standards of care for this disorder. However, there are best practices for each stage of development. In infancy, children's respiration should be supported with ventilation as needed. Parents should be

informed that nearly all children are able to wean from the ventilator. Similarly, feeding difficulties may require a gastrostomy tube, which nearly universally improves. During childhood, children benefit from exercise and rehabilitation. Cardiac arrhythmias may develop at any age and should be screened for as early as possible. Intellectual impairment, autism spectrum disorder, and ADHD may accompany myotonic dystrophy and benefit from early intervention programmes. A high fibre diet is the first line treatment for diarrhoea or constipation. In adolescence, fatigue and myotonia develop and may require treatment with stimulants or anti-myotonia medications (e.g., mexiletine). In one study, 86.7% of adults with childhood onset myotonic dystrophy were unemployed [31]. Care should be taken early to prepare for a transition to independence with vocational counselling.

Cynthia Gagnon further elaborated on the great clinical variability of myotonic dystrophy. She noted that the Food and Drug Administration has issued recently a roadmap to patient-focused outcome measurements in clinical trials emphasizing the need to have clinical care standards in order to reduce potential bias. In DM1, clinical care standards have been produced in 2010 by an international panel of experts in regard to global management of the disease [32]. It emphasized the importance of a multidisciplinary team with a focus on impairment, activity limitation and participation restriction in regard to daily activities and social roles. More recent initiatives are currently ongoing for management in neurology by the American Academy of Neurology and the Myotonic Dystrophy Foundation. Current challenges have been discussed including: (1) the presence of executive functions impairment often present among DM1 patients which may impede their abilities to implement the recommendations; (2) the number of healthcare providers to be consulted each year; (3) the poor socio-economic environment of several patients which affects their access to care and services. Several steps were underlined to increase trial readiness including the development of clinical standards of care for each member of the multidisciplinary team and the mapping of care organization to facilitate standardization of care in regard to key elements such as cardiac follow-up.

Richard Finkel focused on spinal muscular atrophy (SMA). He noted that SMA is a monogenic disorder that causes motor neuron loss and dysfunction, and causes progressive weakness. There is a broad range of phenotypes: approximately 60% of patients present with early infantile onset type I (Werdnig–Hoffmann disease), 25% with late infantile type II (intermediate form, "sitters"), and 15% early childhood onset type III (Kugelberg–Welander disease, "walkers"). Each type has its own profile of motor impairment, morbidity, and mortality. This is especially pronounced in the type I infants who struggle with bulbar related impairment of feeding and handling oral secretions, hypoventilation, and lack of motor development. Survival is uncommon after 2 years of age without nutrition and ventilation support. While pro-active care with feeding tubes and non-invasive ventilation support have become increasingly available over the past several years, and do prolong survival, it remains ethically necessary to offer parents a palliative care option in the absence of a proven treatment for SMA. This creates a quandary for the design and conduct of clinical trials for SMA type I. Having a homogeneous group of infants who receive similar care would likely reduce the variability in survival and motor function among these participants. A more efficient clinical trial could then be designed. Type II infants also struggle with nutrition and ventilation issues, but to a lesser degree, and also have significant musculoskeletal issues that impair their function and well-being. Standards of care are evolving, with earlier use of prophylactic non-invasive ventilation and with the advent of growing rods to allow surgical correction of scoliosis at a younger age. As a consequence, clinical trials have needed to address the impact of these interventions on the ability to capture the child's motor performance effectively. As such, inclusion and exclusion criteria have had to define parameters that often exclude patients with more substantial musculoskeletal complications or who have had scoliosis surgery. Type III children who are still ambulant are at risk of significant decline in function at the time of puberty. This observation has led to discussion of how to design an effective clinical trial that includes a broad range of type III children and adults, yet avoids pitfalls of including patients who are likely to undergo significant decline within the next year or two. The SMA Standard of Care guidelines are being updated in 2016 and will assist in focusing the care of individual patients and in the design and conduct of clinical trials.

Michaela Guglieri summarized the progress in defining standards of care for Duchenne muscular dystrophy. Organized by the Centers for Disease Control (USA) through an act of Congress, care recommendations for Duchenne muscular dystrophy (DMD) were published in Lancet Neurology in 2010 [33,34] and an update is currently under review. In the UK these standards received NICE accreditation in 2011 becoming the national guidelines for the treatment and management of DMD patients.

Over the last two years, TREAT-NMD has supported two projects (CARE-NMD, led by Dr Janbernd Kirschner (Freiburg) and Burden of illness/Healthcare utilization study supported by GSK) to evaluate the key components of the care considerations against the experience of patients in a range of different countries [35,36]. The studies utilized the TREAT-NMD infrastructures, including patient registries and Care and trial site registry. The studies showed a significant discrepancy in age at diagnosis in the different countries ranging from 3.7 years (SD 2.0) to 6.4 years (SD 4.0) [35]. Corticosteroids remain an equipoise both in terms of prescription and type and regimes. Patients who regularly attend specialist neuromuscular centres are more likely to receive steroids. The provision of physiotherapy input and recommendations on home stretching were also discordant in the different countries but consistently adults seem to have less access to physiotherapy than the paediatric population.

Hopefully the FOR DMD study (Find the optimum corticosteroid regime for DMD) will help in the dissemination of the care standards and will provide robust evidence of the best corticosteroid regime. Moreover, initiatives such as

STRIDE-NMD (Strategic Targeting of Registries and International Datasets of Excellence in Neuromuscular Disorders) are currently in development to improve the link between clinical care and research projects.

2.6. The role of registries in orphan drug development

Registries provide a centralized data resource on patients that can be queried to answer basic questions such as the number of patients with a specific diagnosis, and their geographic location. TREAT-NMD has taken an international leadership role in standardizing and expanding registries internationally, including mutation data. Registries then become a critical tool in defining feasibility of clinical trials, especially in trials targeted to specific gene mutations (trial readiness). In orphan drug development, Phase 3 trials focused on quality of life are often moved to the post-marketing space, and registries can take key roles in post-marketing. Post marketing surveillance traditionally refers to the collection of patient data on safety of a drug that is marketed. More recently, accelerated approval mechanisms embraced by both FDA and EMA are moving phase 3 efficacy studies into the post marketing space. In the orphan disease space, it is increasingly recognized by regulators, patient organizations, and clinical investigators that a shared disease-focused infrastructure for post marketing of many or all drugs will be necessary. A coordinated approach will provide conservation of patient, family and physician resources.

An overview of the needs and existing resources developed in the neuromuscular space was presented. TREAT-NMD and the academic clinical trial network, the Cooperative International Neuromuscular Research Group (CINRG), have led these efforts respectively with global patient registries and regulatory compliant clinical studies and infrastructure. Activities from the European Patient's Academy on Therapeutic Innovation (EUPATI) were reviewed as well as probabilistic prevalence-based cost of illness model to estimate the economic impact of rare disease such as Duchenne muscular dystrophy.

Initiatives for patient registries with the EMA were presented and plan to facilitate the use of existing and new registries to collect and analyze high quality data informing regulatory decisions. Learning about the experience of another orphan disease: cystic fibrosis provided valuable information. Their programme, initially established in the mid-1960s, has been sustained with longstanding and ongoing commitment to care centres across the US and partnership with qualified and domain expertise in registries. Speakers were Hanns Lochmüller (Newcastle University, UK), Stefano Marini (President, European CRO Federation, Italy), Chris Dowd (Cystic Fibrosis Foundation, USA), Lawrence Korngut (University of Calgary, Canada), and Petra Kaufmann (NCATS, NIH, USA).

Lawrence Korngut provided a summary regarding the barriers to the conduct of clinical trials and research in Canada focusing on geographic barriers. The Canadian Neuromuscular Disease Registry (CNDR) was launched in 2011 to mitigate these barriers. The CNDR is currently located in 24 clinical centres in 7 provinces. The CNDR currently has 2663 individuals with NMD registered with over 90 different diagnoses. The funding model includes dedicated sponsors for each index disease on which a detailed dataset is collected along with contributions from each sponsor for central office operating costs. To date, the CNDR has facilitated 28 data inquiries, mailed study notification to over 900 patients, and has helped attract at least three clinical trial opportunities to Canada. In 2014, the Canadian Neuromuscular Diseases Network (CAN-NMD) was launched and consists of over 130 members from the basic science, clinical research, and clinical and patient care communities in Canada. Task forces have been established addressing clinical care, research, education and knowledge translation. CAN-NMD has 22 activities across the three broad themes and over 100 project milestones to be accomplished by March 2017. To date, CAN-NMD has launched English and French websites, the Neuromuscular Now Blog, a monthly newsletter; a Knowledge Translation Framework has been implemented; National Interdisciplinary NMD rounds were launched; and the network is now open to international NMD personnel who can join as Affiliate Members.

Chris Dowd described alternative uses for patient registries from the perspective of the Cystic Fibrosis Foundation – a leader in coordination of care and facilitation of orphan drug development. He noted that patient registries are powerful tools to uniformly collect data on specific patient populations in order to study specific outcomes for a particular disease. The Cystic Fibrosis Foundation Patient Registry (CFFPR) is one such example. While its initial intent was to better understand the pathogenesis of cystic fibrosis, the CFFPR evolved over time to expand its uses to broaden its impact for the CF community. In the late 1990s, the CFFPR began to be used for quality improvement purposes with the intent of yielding high-quality standardized care for all patients with CF. In the 2000s, those uses expanded further to help test promising new therapies by establishing a framework for clinical trials and to promoting evidenced-based clinical decision making through the conduct of comparative effectiveness research. Most recently, the CFFPR has been used in post-marketing surveillance studies to ensure the safety and effectiveness of approved products. The CFF provided three examples where it has worked with the pharmaceutical industry and regulatory agencies, in both the United States and European Union, to meet post-marketing requirements (PMR). The examples demonstrated that patient registries can be flexible to meet the varying needs of pharmaceutical sponsors and their data do have credibility with the regulatory agencies.

2.7. International trial readiness and access to emerging therapies

Increasing numbers of drug development programmes in neuromuscular disease put increasing demands on patients, families and the clinical teams, as well as companies working to meet demands for post-marketing programmes and early/ expanded access (compassionate use). It is important to ensure that these resources are efficiently utilized to bring the most

drugs to market to the most patients in the fastest time. The session discussed emerging innovations in clinical trial design and conduct, in both pre-marketing and post-marketing spaces, as well as expanded access programmes. Speakers were Hiroki Morizono (Children's National Health System, USA), Emil Kakkis (Ultragenyx, USA), Lori Reilly (Executive Vice President, Pharmaceutical Research and Manufacturers of America, USA), Nabarun Dasgupta (Harvard Medical School, USA), Michelle Eagle (Newcastle University, UK) and Tina Duong (Stanford University, USA).

Hiroki Morizono described progress in the development of a mobile health toolbox for outcomes in the community setting using the Microsoft Band wrist device. Efficacy of drugs in neuromuscular disease is typically tested by timed function tests or other motor skill tests, and these are conducted in a hospital clinic setting. Such tests can be reliable and sensitive, but may not reflect changes of patient ability to carry out tasks related to quality of life in the community and home setting. Emerging mobile health devices include very sensitive and reliable sensors that can collect large amounts of data on mobility and certain limited aspects of health. The Microsoft Band has an optical heart rate monitor, accelerometer/gyrometer, barometer, GPS, microphone, ambient light sensor, galvanic skin response sensors, and UV sensor. These devices are being implemented as exploratory outcome measures in drug development programmes where the number and speed of steps taken in the community setting is compared to the timed function test (4 step climb) in the clinic setting. In the future, validated Band outcomes could be very useful in post-marketing studies, enabling some reliable testing of drug safety and efficacy in the community setting.

Lori Reilly described the economics and policies surrounding pricing and access to orphan drugs. The biopharmaceutical industry is deeply committed to developing medicines to treat rare diseases, including neuromuscular disorders. In the U.S. alone, there are more than 450 medicines in development for rare diseases, including 33 medicines in development for multiple sclerosis, 31 for Parkinson's disease, and 19 for muscular dystrophy, among many others. One of the major drivers of the treatment innovation we are witnessing in neuromuscular diseases is the Orphan Drug Act (ODA), which created important incentives that have spurred research and development in rare diseases. In the decade prior to ODA passage in 1983 10 orphan drugs were approved, but in the decades since about 500 more have reached patients.

Getting these medicines to patients is crucial. We must ensure that everyone has access to adequate, affordable insurance with benefit designs that meet their needs. Although insurance is crucial, patient assistance programmes provide a safety net for un-and under-insured patients. It is also important to recognize the total financial burden patients face including all medical expenses and reduced ability to work.

The science has never been more promising, but the challenges have never been greater as we learn more about the complexities of these diseases and work through increasing regulatory requirements and reimbursement pressures. Thoughtful policies are necessary to accelerate advances in and

patient access to orphan medicines. These include strong intellectual property protections, regulatory requirements that keep pace with the changing science, and coverage and payment policies that foster innovation.

Nabarun Dasgupta described his development of Epidemico – a software tool that enables social media reporting of adverse events. It is estimated that 350 million people worldwide, or 1 in 10 Americans, suffer from a rare disease. Most rare diseases do not have an FDA-approved treatment or a treatment in development. For there to be successful treatments developed for rare diseases patient involvement is crucial through the entire process; more so than traditional large scale development efforts. Social media listening can assist this process by amplifying the patient voice. As more patients post their disease and medication experiences publicly in social media, this data source can provide insight into the needs of patients in a low-burden manner. Advanced machine learning (i.e., artificial intelligence) and natural language processing tools can efficiently make sense of voluminous amounts of social data in an automated way. For example, a Bayesian classifier which automatically identifies posts with resemblance to adverse events during off-label use among rare disease patients can help these patients' voices come to the fore. With 88% sensitivity and 68% precision these posts become a wealth of knowledge for any individual involved in the drug development process with the unique ability to track patient reported adverse events in real-time. In addition, private social media-style communication tools (e.g., patient diaries) can help rare disease patients record experiences and communicate with their physicians without the need to travel to clinic. Automated tools reduce the burden on both patient and clinician. The hope is to use this technology to give patients a collective voice during the drug development process and beyond.

Michelle Eagle and Tina Duong discussed the development of International clinical evaluator certification to improve reliability of clinical trials. A critical component of successful evaluation of clinical outcome assessments (COAs) in multisite clinical trials and clinical practice includes having standardized training and documented reliability of collection of COAs. It is apparent that varying experiences of evaluators, maturational and disease differences may be widely divergent among clinical centres. The reliability of commonly used measurements is fundamental to clinical research and our ability to have confidence in the data we collect and to draw rational conclusions from the data.

The purpose of establishing a Clinical Evaluator (CE) Certification process is to establish a standard guideline of practice and recommendation for ensuring quality assessments in DMD specialty clinics and clinical trials. Thirteen experts in clinical outcomes training provided input and consensus on this guidelines document for CE certification.

As part of clinical trial readiness, the CE Certification programme will help expedite study start up with a CE readiness pathway with CEs who have shown to be reliable and knowledgeable in clinical assessments typically used in DMD clinical trials. The CE Certification process will include roles and responsibilities of individuals who are experts in DMD

outcomes development and training such as Master Physiotherapists (MP) and site CEs. Certification of CEs will be performed by MPs. This document also includes guidelines for ensuring quality and consistency in MP training and certification.

Implementation of this certification process would provide pharmaceutical and academic institutions with information that would be comparable across studies and programmes. This type of model will ensure more efficient, reliable, consistent results from outcome measures tested by certified CEs. Future project goals include establishment of a steering committee and database to monitor and track CE Certification trainings.

3. Final comments

This latest conference organized by TREAT-NMD again addressed the challenges facing the community in bringing care and new treatments and therapies to patients. The talks described the varied and intense work that is going on to address these diseases and the progress that is occurring across more and more specific neuromuscular diseases. The pivotal role of the patient in the drug development process was acknowledged by all at the conference, not only in participating in research but contributing to the decisions and planning of such research. Design of clinical trials was also a key feature of the conference with many speakers contributing to the discussions on relevant endpoints, innovative trial designs, and biomarkers. The first therapies are reaching patients, the issue of drug approval and how to capture post-marketing data was a new and exciting area for the audience to discuss, and this also brought up issues around access and pricing of these new novel therapies. The ever increasing number of drugs in the development pipeline for neuromuscular diseases has never been greater and there is renewed optimism, as well as challenges, for us to face, but through the collaborative approach of the community, we will face these together and provide that all important benefit to the patient.

Acknowledgements

Appendix A

Workshop participants

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