Patient-Centered Therapy Development for Myotonic Dystrophy: Report of the Myotonic Dystrophy Foundation–Sponsored Workshop

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Abstract
Myotonic dystrophy (DM) is an autosomal dominant, repeat expansion, progressive disorder with no drug therapies. Consequently, to better define a regulatory pathway in anticipation of new treatment strategies under investigation, the Myotonic Dystrophy Foundation convened a workshop entitled “Patient-Centered Therapy Development for Myotonic Dystrophy” in September 2015. Participants included representatives from academia, industry, the patient community, the National Institutes of Health (NIH) and the Food and Drug Administration (FDA). Presenters described the symptom burden of the disease, and existing data on DM biomarkers, endpoints, natural history, and benefit-risk considerations. FDA participants helped clarify the regulatory requirements for new drug treatment approvals and DM-specific issues such as variability, slow progression, and low prevalence. Workshop attendees gained a better understanding of DM and the current status of existing data and tools to support therapeutic drug research and development.

Keywords
myotonic dystrophy, PFDD, MDHI, biomarker, endpoint

Myotonic Dystrophy Patient-Centered Therapy Development Workshop
Myotonic dystrophy (DM), an inherited disorder characterized by myotonia, progressive muscle weakness, excessive daytime sleepiness, cardiovascular complications, and early cataract development, affects more than 45,000 people in the United States, and many more may be undiagnosed. Although DM is one of the most prevalent neuromuscular disorders in adults, there are currently no FDA-approved disease-modifying pharmacologic treatments. Recognizing the need for alignment among patients, clinicians, basic and applied scientists, drug developers, industry, and regulators, the Myotonic Dystrophy Foundation (MDF) convened a workshop on September 17, 2015, in Washington, DC, entitled Myotonic Dystrophy Patient-Centered Drug Development Workshop. This report summarizes selected Workshop findings.

DM Symptoms and Pathology
Nicholas E. Johnson, MD, University of Utah, provided an overview of DM symptoms and disease pathology. Patients with DM exhibit a variable array of symptoms and concerns. There are 2 types of DM, type 1 (DM1) and type 2 (DM2), which are due to distinct genetic mutations. Both conditions are inherited in an autosomal dominant manner. DM1 typically

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DM Disease Burden, Natural History, and Biomarkers

Findings from several studies on patient concerns, attitudes, and preferences describing DM disease progression and heterogeneity were presented at the workshop. Disease heterogeneity presents a particular challenge in studying DM1, one of the most variable genetic disorders. For rare diseases in particular, observational natural history studies represent one of the most valuable tools to gather reliable data about these aspects of disease. In addition, natural history studies of DM have led to the development of new outcome measures to better assess disease progression, which may represent useful tools for clinical trials.

Patient-reported outcomes (PROs) are based on reports coming directly from the patient about how he or she feels or functions. FDA has encouraged investigators and sponsors to use relevant and appropriate PRO measures as endpoints in clinical trials as they can potentially provide information that is meaningful to and only observable by patients.

Biomarkers are critical in drug development for multiple reasons. In early-stage drug development, biomarkers may provide early objective evidence of target engagement. They can also be useful for diagnosis, prognosis, demonstrating disease progression and predicting response to therapy. When validated, they can also sometimes be used as endpoints in clinical trials.

PRISM-1

Richard Moxley III, MD, University of Rochester, provided an overview of the Patient-Reported Impacts of Symptoms in DM1 study (PRISM-1). PRISM-1 was a 2-phased study designed to identify what symptoms and issues have the greatest impact on DM1 patients' lives. In phase 1, qualitative interviews with DM1 patients were used to identify and characterize symptoms that potentially are of highest relevance to DM1 patients. In phase 2, a survey of each of the issues identified in phase 1 was sent to a national cross-sectional group of individuals with DM1 to determine the prevalence and relative impact of 235 individual symptoms (representing 14 themes).

The survey was mailed to 530 patients with clinically or genetically confirmed DM1. The response rate was 52%. Patients ranked fatigue as having the greatest impact on their lives, followed in order by mobility, inability to do specific activities, problems with hands or arms, and impaired sleep. They identified problems with hands and arms as the most prevalent theme, followed by fatigue, myotonia, impaired sleep or daytime sleepiness, and problems with physical health. This study also noted a marked increase in frequency and impact of mobility issues between the ages of 25 and 35.

PRISM-1 led to the development of the Myotonic Dystrophy Health Index (MDHI) as a disease-specific instrument designed to measure patient-reported disease burden and symptomatic severity in DM. Initial studies of the MDHI in the DM1 population, described below, suggest that this instrument is reliable, has low floor and ceiling effects, and shows good response.

The Christopher Project

Katharine Hagerman, PhD, Stanford University, provided an overview of The Christopher Project. The Christopher Project is a collaboration between patient advocacy organizations, health care providers, disease experts, and patients and families in North America that used a paper-based survey to understand the experience of living with DM, identify unmet needs and what matters most to patients and caregivers, and to improve outcomes for patients and families. Dr Hagerman presented data gathered from 457 DM1 patients who were contacted directly through patient advocacy registries and mailing lists. Among these respondents there was substantial diversity in symptoms reported, with muscle weakness being the most common and most impactful symptom, followed by fatigue. The study concluded that DM1 patients have significant unmet needs and a heavy disease burden. Data analysis from a complementary survey of the family member/caregiver perspectives was also under way.
MDF Benefit-Risk Considerations in Drug Development Study

Sharon Hesterlee, PhD, Myotonic Dystrophy Foundation, presented a project MDF undertook in conjunction with Silicon Valley Research Group to weigh benefit-risk considerations, as described by patients with DM. The quantitative methodology selected for this study—discrete choice methodology—forces participants to select among the most tolerable and least tolerable risks for a given benefit and produces a large amount of data with reduced bias. The survey created by MDF tested each of 8 benefits, including improving, stopping, or slowing loss of muscle strength; eliminating or reducing tiredness during the day; and reducing, stopping, or slowing myotonia; protecting against 6 levels of risk, including loss of appetite, nausea and vomiting, small or large increases in tiredness during the day, and 1:100,000 or 1:10,000 chance of liver failure. The survey was sent by email to individuals in the MDF database and the Myotonic Dystrophy Family Registry. Of those who had adult-onset DM1 or DM2, with symptoms for at least 15 years, 267 completed the survey by email or phone.

Dr Hesterlee reported preliminary results suggesting that patients placed the greatest value on a treatment that would improve muscle strength and the least value on one that improved fatigue. Participants who were more severely affected had a higher tolerance for fatigue and a lower tolerance for liver damage, but were willing to tolerate fatigue in return for a benefit related to slowing or reducing myotonia. A follow-up study and caregiver assessment are planned.

Although benefit-risk surveys can help answer questions about patient preferences for therapeutic benefit and tolerance of risk, workshop participants raised a number of concerns about this type of survey, including the need to obtain representative samples of responders that truly reflect the disease population, and the importance of gauging the impact of disease-related cognitive impairments on the accuracy of data. This latter concern may be partially addressed by obtaining responses from family members and caregivers as well as patients, although this approach also introduces additional challenges.

Saguenay Longitudinal Study

Cynthia Gagnon, PhD, Université de Sherbrooke, described a longitudinal study conducted by the Groupe de recherche interdisciplinaire sur les maladies neuromusculaires at the Saguenay Neuromuscular Disorders Research Center. Study participants were assessed on 2 occasions by trained healthcare professionals (200 participants in 2002 and 115 in 2011) using performance and/or clinician-reported outcomes for all affected systems as well as PRO measures. Decreased strength was observed in this cohort in all assessed muscle groups for most individuals, along with decreased performance in mobility, endurance, and balance. Patients themselves perceived clinically significant deterioration on 6 activities: nutrition, fitness, personal care, mobility, community life, and recreation.

A follow-up study over 15 years is planned in 90 patients from this initial cohort, along with additional patients who will be newly recruited. The first phase of the study has improved understanding of the relations between impairments, physical limitations, and restrictions of participation. The longitudinal follow-up will provide a more comprehensive model to understand the progression of impairments, physical limitations, and restrictions of participation and their interrelations.

From this study, and those of several other centers around the world, emerged the Outcome Measures in Myotonic Dystrophy type 1 (OMMYD) initiative, which seeks to develop a core outcome measure set so that data can be pooled across multiple centers. Seven special interest groups within OMMYD have been organized to develop standard operating procedures to validate selected measures, as well as cultural translations of the measures so they can be used globally.

Rochester Natural History and Performance Measures Study

Charles Thornton, MD, University of Rochester, presented data from 58 subjects who are participating in a 3-year natural history study of DM1, with an emphasis on motor function and mobility. As expected, the study group was very heterogeneous in the initial extent of motor impairment, but also in the trajectory of disease progression over time. Some individuals had relatively stable muscle function for up to 3 years, whereas others showed impressive decline. From initial analyses, future progression was not deemed predictable by initial performance, age, or size of the CTG repeat expansion.

The 6-minute walk test (6MWT) has been a primary outcome measure in several pivotal studies of muscle disease, including trials for alpha-glucosidase deficiency and Duchenne muscular dystrophy (DMD). However, in the Rochester study, the annual percentage decline of 6MWT distance in DM1 was 20-fold lower than in DMD, highlighting the overall slow rate of progression. DM1 patients showed a larger fractional decline of 30-ft walk/run speed, an alternative test of mobility. It is possible that the 30-ft walk/run test may capture the effects of DM1 more effectively, especially in distal muscles that control ankle movement and acceleration.

Quantitative measures of muscle strength may offer advantages for measurement precision and reproducibility, but clinical meaningfulness needs to be established. The finger flexor muscles of the forearm are among the earliest-affected limb muscles in DM1, producing loss of grip strength. Measurement of grip strength is known to be highly reliable and was previously associated with many dimensions of human health, including survival. Grip strength was among the quantitative muscle tests showing significant 1- and 3-year declines. However, there may be floor effects for individuals starting with less than 20% of predicted strength.
Rochester Myotonic Dystrophy Health Index (MDHI)

Chad Heatwole, MD, University of Rochester, presented a disease-specific PRO measure for use in clinical trials that has emerged from the PRISM-1 study discussed earlier. The MDHI is composed of 17 subscales, including mobility, upper extremity function, ability to do activities, fatigue, pain, gastrointestinal issues, vision, communication, sleep, emotional issues, cognitive impairment, social satisfaction, social performance, myotonia, breathing, swallowing, and hearing. Taken together, the subscales are designed to measure the multifactorial patient-reported burden of disease. Dr Heatwole described the development of the MDHI and assessments of its reliability and validity, as well as comparisons to other assessments.

The MDHI showed excellent test-retest reliability (interclass correlation coefficient of 0.95) both overall and on each subscale. Internal consistency was demonstrated through factor analysis, which showed that fatigue links to other questions about muscle endurance. The MDHI has been shown to differentiate between patient groups in terms of employment status, CTG repeat status, education, and duration of symptoms. The MDHI showed high correlations with other functional tests and clinical measures, including those assessing strength, myotonia, motor and respiratory function, ambulation, and body composition. In addition, the subscales of the MDHI correlated well with functional measures designed to measure similar concepts.

Biomarkers

As presented by John Day, MD, PhD, Stanford University, myotonia may represent a biomarker of disease presence and response to treatment and can be assessed at multiple levels: clinical (muscle stiffness), functional (grip myotonia relaxation time), physiological (EMG myotonia quantification), structural/anatomical (muscle biopsy with chloride channel [CIC] immunofluorescence), biochemical (muscle biopsy with CIC protein determination), and molecular (muscle biopsy with CIC RNA splicing assay). With regard to functional assessments, composite myometry measures that assess maximal voluntary isometric contraction from a composite of both midlimb and distal muscles may provide a better assessment of impaired muscle function in DM as compared to grip strength measures. Another test, timed hand opening, also has been shown to be sensitive to changes in myotonia.

Biogen Molecular Biomarkers Study

John Carulli, PhD, Biogen, noted that both DM1 and DM2 are caused by untranslated expansions of 3 (CTG for DM1) or 4 (CCTG for DM2) nucleotide repeats. In both cases, the repeat expansions give rise to a molecular hallmark of DM, abnormal regulation of alternative splicing. Importantly for clinical trials, assessment of splicing variants in tissue obtained from muscle biopsies has demonstrated that splicing defects correlate with muscle weakness, although not with CTG expansion size. Thus, splicing changes may reflect both disease severity and response to therapy. However, more data are needed to better understand longitudinal variation in splicing in untreated subjects, design and validate robust assays, and define meaningful change. Additionally, more data addressing correlation between molecular biomarkers and measures such as strength and myotonia will enhance functional interpretation of biomarker data.

FDA Perspective on Patient-Centered Drug Development

FDA’s history of implementing concerted efforts to expedite drug development for rare diseases (a disease prevalence of less than 200,000 in the United States), beginning with the Orphan Drug Act of 1983, was reviewed by Richard Moscicki, MD, CDER, FDA. The Act provides 7 years of market exclusivity, effective on the date of FDA approval, for a sponsor of a designated orphan drug. No approval will be given to a subsequent sponsor of the same drug for the same use or indication for 7 years. The Act also provides for tax credits for qualified clinical testing.

In 2014, FDA published the Guidance for Industry on Expedited Programs for Serious Conditions. The Guidance described 4 programs designed to address unmet medical needs for serious diseases when a new treatment could provide meaningful clinical benefit, including those in rare diseases: fast track designation, breakthrough therapy designation, accelerated approval, and priority review designation. Rare diseases account for most accelerated approvals through these mechanisms. The breakthrough therapy designation, which was established as part of the FDA Safety and Innovation Act (2012), expedites the development and review of drugs that treat serious or life-threatening diseases. Rare disease drug development also benefits from accelerated approval that may speed availability of drugs for serious, unmet medical needs [Section VI, A]. As of March 2015, CBER and CDER have designated 82 new therapies as breakthrough therapies, and 23 have received marketing approval. Through 2014, 11% of breakthrough therapy designations had been granted to rare disease therapies.

In parallel with the expedited drug approval programs, a Patient-Focused Drug Development (PFDD) initiative emphasizing patient involvement in all phases of the drug development pipeline has emerged at FDA. FDA has held, or plans to hold, at least 20 patient-focused meetings devoted to systematically gathering patients’ input on the severity of their disease and its impact on daily life, and patient views on current and future treatments. More information on the PFDD initiative and other FDA tools and resources for patient organizations and industry can be found on the FDA website.

Among the challenges that regulators, drug developers, clinicians, and patients face is whether and how the standards for demonstrating drug efficacy for rare diseases should differ from those for nonrare diseases. Although there is not a unique pathway for rare disease drug approval, FDA regulations provide for flexibility and judgment in applying the standards. For example, traditionally FDA has required at least two clinical
trials for adequate demonstration of drug efficacy. In 2014, however, a single trial was used to approve 75% of rare disease drugs (versus 26% of common disease drugs) demonstrating FDA flexibility with regard to endpoints, controls, and labelling. A review by the National Organization for Rare Disorders, updated in June 2014, suggests that the FDA has exercised “extraordinary flexibility” in its review of rare disease therapeutics.21

Pujiita Vaidya, MPH, CDER, FDA, provided an overview of FDA’s patient-centered research efforts. The Prescription Drug User Fee Act, enacted in 1992 and renewed 4 times since, allows the FDA to collect fees from companies that develop drugs and biologics in order to provide a stable source of funding that FDA uses to implement efficiencies in the drug review process. By statute, drugs can only be approved for marketing once safety and effectiveness have been demonstrated. Though the definition of “safe” is not clearly defined in the statute, the FDA recognizes that treating serious illnesses often requires balancing risks and benefits. Thus, FDA has developed the Benefit-Risk Assessment Framework, a structured approach to benefit-risk assessment in regulatory decision-making for human drug and biologic products.22

FDA has also committed to convening at least 20 disease-specific PFDD workshops between 2013 and 2017 to elicit perspectives from patients, caregivers, and advocates.23 An important message emerging from the first 14 workshops is that patients are experts on their own conditions—they are often in the best position to identify and articulate specific disease impacts and what is important to them regarding treatment benefits. Patients want to be closely involved in efforts to develop and evaluate new treatments. Patients and their caregivers are willing to engage via the Internet, social media, and other means, and they want help from regulatory bodies to identify the most effective pathways that play a major contributing role. These learnings have resulted in efforts by FDA to advance the science of patient input. By engaging the wider community, these efforts are designed to determine how to transition from the initial PFDD workshops to a more systematic collection of patient input to inform drug development and benefit-risk assessments.

Regulatory Perspective on Endpoint Selection and Biomarkers

The FDA requires substantial evidence of safety and efficacy from adequate and well-controlled clinical trials using methods of assessment that are well-defined and reliable for drug approval.24 Nikunj B. Patel, PharmD, CDER, FDA, provided an overview of FDA’s perspective on the development and use of clinical outcome assessments (COAs) such as PROs to demonstrate clinical benefit in DM clinical trials. He explained that a drug developer is required to demonstrate evidence that a drug provides a clinically meaningful change in how a patient feels, functions, or survives using outcome assessments that can accurately and reliably measure effects that can be interpreted as a clear treatment benefit.

There are 4 types of COA measures: (1) patient-reported outcomes; (2) clinician-reported outcomes; (3) observer-reported outcomes; and (4) performance outcomes. Prior to selection or development of a COA measure, FDA encourages drug developers to give adequate attention to understanding the disease or condition and conceptualizing clinical benefit. The selection of a COA type should be based on characteristics of the target patient population and concept of interest (ie, the thing measured by an assessment). Proximal concepts such as core signs and symptoms are closely linked to impact of the disease, and are thought to be sensitive to change in a clinical trial, whereas distal concepts (eg, work productivity) may be less interpretable and sensitive to change, and more likely to be influenced by factors beyond the treatment. While both proximal and distal concepts are important to patients, FDA recommends that drug developers focus on measuring concepts that are well defined and closely related to the disease.

FDA will allow the use of biomarkers to guide decisions in different phases of drug development, including safety evaluations in nonclinical studies and clinical trials, in dose-finding studies, and in phase 3 trials, where they can serve as surrogate endpoints when validated for the specific indications. A higher level of evidence is required to justify the use of biomarkers as surrogate endpoints compared to that needed for other categories of biomarkers, such as those used for enrichment of patient populations in clinical trials.

Shashi Amur, PhD, Biomarker Qualification Program, CDER, FDA, described two pathways by which biomarkers may be integrated into drug development at FDA.25,26 The first, for use in a single drug development program, allows sponsors to seek acceptance of the biomarkers as part of their Investigational New Drug (IND) application, New Drug Application (NDA), or Biologics License Application (BLA).

The second pathway, biomarker qualification, results in the qualification of a biomarker for use across multiple drug development programs, relieving sponsors of the need to provide validation data for each project. This pathway enables multiple sponsors to share both the risk and resources associated with biomarker qualification. This may be accomplished preemptively through collaborations of industry partners and, often, nonprofit organizations or public-private partnerships. The process encompasses several stages, and submitters are advised to engage in early communication with the FDA.

Biomarker qualification is defined as the conclusion that, within a carefully and specifically stated context of use, the biomarker can reliably support a specified manner of interpretation and application in drug development. The FDA has qualified 13 biomarkers, with 22 submissions to the Biomarker Qualification Program in process. These qualifications apply to the biomarker itself, not to the specific assay measuring the biomarker.

Regulatory Considerations for Trial Design in DM

Designing trials for a slowly progressive, multisystemic, highly variable, rare, heterogeneous disease such as DM presents
special challenges, and FDA has responded with a number of programs, outlined through a series of guidance documents including a recent draft guidance on rare diseases.\(^2\) Ronald Farkas, MD, PhD, Division of Neurology Products, CDER, FDA, gave an overview of the agency’s views on trial design. With regard to safety evidence, FDA believes it is ethically necessary to study a drug in animals before conducting studies in humans, but in rare, serious conditions FDA can be flexible about the type, size, and duration of nonclinical studies required at each phase of development. Moreover, FDA is open to community views about how much safety data are needed before a drug is approved. As mentioned earlier with regard to benefit-risk assessments, more work is needed to understand what constitutes a reasonable risk and whether patients understand the actual risk they are assuming.

To demonstrate efficacy, FDA has signaled that trials involving a small number of patients may be sufficient for approval. With small trials, the design, conduct, and analysis must be especially rigorous. Independent substantiation is critical and can be provided in several different ways, for example, through studies in related diseases or other disease phases, or where there is a particularly well-understood pharmacologic effect.

Aspects of trial design relevant to studies of rare, heterogeneous, and slow progressive diseases like DM include issues related to trial type, the use of enrichment to increase power, the selection of appropriate controls (eg, placebo or historical controls), duration of studies, selection of endpoints, and statistical considerations. For example,

- **Enrichment**, which can be based on clinical or biomarker evidence. Enrichment based on a patient’s molecular response to a drug is one of the most powerful clinical trial options available, but may raise concerns about generalizability.
- **Crossover, parallel-arm plus randomized withdrawal, and adaptive designs**, which may maximize the amount of data that are collected from a small number of patients.
- **Placebo-controlled trials**, which are strongly recommended by FDA and which are usually the most efficient and rapid way to demonstrate efficacy. External controls may be used in some situations but are unlikely to be interpretable unless the drug has a dramatic effect on objective endpoints. However, in such cases, one would likely need a large effect size to demonstrate that there is no bias.
- **Study duration**, which often depends on how quickly the symptoms change. Three months can be adequate for drugs that rapidly affect symptoms, but for drugs where the effect size is expected to increase over time, longer studies may be advantageous for statistical power. Twelve months is often selected by sponsors, but 18 months or longer may be particularly advantageous to increase statistical power in rare diseases in which studies may, because of feasibility issues, be smaller.

- **Evidence in support of FDA approval**. For studies to provide evidence to support FDA approval, the statistical analysis plans must be carefully prespecified.
- **Accelerated approval**, for which adequate and well-controlled trials are necessary that demonstrate that the drug has an effect on a surrogate endpoint that is reasonably likely to predict a clinical benefit, or an effect on an intermediate clinical endpoint other than, but predictive of, an effect on survival or irreversible morbidity. A postmarketing confirmatory trial is required.

**Moving Forward**

Several observations were proffered to expedite efforts focused on developing new treatments for DM, including

- the need for new animal models and biomarkers, including serum biomarkers that could eliminate the need for muscle biopsies;
- standardization of biomarkers, their measurement, and other outcome assessments to enable comparison of data from multiple sites and studies;
- more natural history, because the natural history data currently available are not sufficient for robust trial planning and needs to be expanded;
- earlier predictors of treatment efficacy; and
- clearer definition of go/no go decision-making points to reduce the time and effort required to conduct studies and limit risks that companies assume when committing to a DM drug development program.

**Conclusion**

Effective drug development for rare diseases like DM requires an understanding of disease natural history, reliable and clinically meaningful endpoints, biomarkers, and appropriate clinical trial designs. The Myotonic Dystrophy Patient-Centered Therapy Development Workshop brought together patients, clinicians, basic and applied scientists, drug developers, industry, and regulators. Together with FDA scientists, they explored issues facing DM therapy development at the clinical trial stage with an emphasis on translational science, development of improved animal- and cell-based model systems, novel biomarkers, and more sensitive patient-centric clinical endpoints and trial design. The Workshop emphasized that successful therapeutic drug development and clinical trial design for rare diseases requires patient and family engagement to help establish infrastructure and partnerships, define meaningful clinical outcomes, accurately describe disease burden, and encourage participation in clinical studies via patient-centric outcome measures.
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