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Meeting Report

Draft Guidance for Industry Duchenne Muscular Dystrophy, Becker Muscular Dystrophy, and Related Dystrophinopathies – Developing Potential Treatments for the Entire Spectrum of Disease

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Abstract.
Background: Duchenne muscular dystrophy (DMD) and related dystrophinopathies are neuromuscular conditions with great unmet medical needs that require the development of effective medical treatments.
Objective: To aid sponsors in clinical development of drugs and therapeutic biological products for treating DMD across the disease spectrum by integrating advancements, patient registries, natural history studies, and more into a comprehensive guidance.
Methods: This guidance emerged from collaboration between the FDA, the Duchenne community, and industry stakeholders. It entailed a structured approach, involving multiple committees and boards. From its inception in 2014, the guidance underwent revisions incorporating insights from gene therapy studies, cardiac function research, and innovative clinical trial designs.

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Results: The guidance provides a deeper understanding of DMD and its variants, focusing on patient engagement, diagnostic criteria, natural history, biomarkers, and clinical trials. It underscores patient-focused drug development, the significance of dystrophin as a biomarker, and the pivotal role of magnetic resonance imaging in assessing disease progression. Additionally, the guidance addresses cardiomyopathy's prominence in DMD and the burgeoning field of gene therapy.
Conclusions: The updated guidance offers a comprehensive understanding of DMD, emphasizing patient-centric approaches, innovative trial designs, and the importance of biomarkers. The focus on cardiomyopathy and gene therapy signifies the evolving realm of DMD research. It acts as a crucial roadmap for sponsors, potentially leading to improved treatments for DMD.

Keywords: Patient-Focused Drug Development (PFDD), Duchenne Muscular Dystrophy (DMD), Dystrophinopathies, Natural History of DMD, Genetic Testing and Diagnosis, Outcome Measures, Cardiomyopathy In DMD, Gene Therapy for DMD, Patient Experience and Engagement, Regulatory Guidance and Considerations

EXECUTIVE SUMMARY

This draft guidance represents an update of the first draft FDA guidance initially composed by a disease community, with input from industry, sponsors, academia, and the Duchenne muscular dystrophy patient community. When finalized, it should represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

INTRODUCTION

The purpose of this guidance is to assist sponsors in the clinical development of medical products (i.e., human drugs and therapeutic biological products) for the treatment of individuals with Duchenne muscular dystrophy (DMD) and related dystrophinopathies over the entire spectrum of the disease.

This updated guidance is the result of the first collaboration between the FDA and a disease-specific community in their respective disease area. The FDA invited the Duchenne community (including patients, parents and caregivers, clinicians, academic experts, and industry) to develop the earlier version of the guidance as provided under FDA's interpretation of Good Guidance Practice provisions.

The Duchenne muscular dystrophy community then embarked on an unprecedented journey to develop a draft guidance for industry to propose to the U.S. Food and Drug Administration (FDA) [1]. The push stemmed from a perceived inadequacy of existing draft guidelines. To remedy this, patient advocates mobilized over 200 community members, clinicians, academics, researchers, and other experts for the process of drafting the guidance. The strategy involved a structured Core Support Team, Steering Committee, expert working groups, and a Community Advisory Board. These entities ensured comprehensive desk reviews, transparent deliberations, and community representation. The guidance touched on pivotal issues, such as the willingness of the Duchenne community to accept potential treatment risks, diagnostic challenges, and innovative clinical trial designs. After meticulous development and revisions, the guidance was submitted to the FDA, emphasizing the community's urgency.

Upon receipt of the first iteration of the guidance on June 25, 2014, the FDA opened a docket and held further meetings with the DMD community and other experts, leading to revisions based upon regulatory and statutory requirements and additional published data, released in June 2015 (see https://www.parentprojectmd.org/wp-content/uploads/2021/07/2014_Community_Guidance.pdf).

These activities provided the impetus and laid the groundwork for the FDA to develop its own streamlined guidance for industry on DMD and related dystrophinopathies—the first for a specific rare disease—focused specifically on the clinical trial process. This guidance was finalized in February 2018 (refer to https://www.fda.gov/media/92233/download) [2].

This process fortified relationships between the Duchenne community, FDA, and sponsors, fostering trust and enhancing credibility. The initiative not only spotlighted the patient's perspective but set a precedent, demonstrating how rare disease communities can actively shape the direction of potential treatments and research.

A. Revision of the guidance

Since that time, there have been numerous advances in DMD, including an increase in gene therapy studies and a growing recognition of the need to focus on the deterioration of cardiac function as a separate process from loss of skeletal muscle function. There are updated care considerations guidelines that include the care of adult patients, progress in the FDA's approach to patient engagement and preference studies, genotype / phenotype correlations and disease progression models, as well as new more sensitive outcome measures. In addition, there was also a need to expand the guidance to include considerations specific to development of treatments for Becker muscular dystrophy (BMD) and other dystrophinopathies.

After dialogues with the CDER and CBER divisions of the FDA, a consensus emerged that it was critical that all of the new knowledge be captured in an update to a patient-led guidance document focused on supporting the developing of treatments for DMD, BMD and related dystrophinopathies. In response, the community marshaled its resources, enlisting a technical management team to ensure project management, strategy formulation, editorial support, and to facilitate the steering committee's oversight of the guidance development activities.

The revision of the guidance was a meticulous process, leveraging the expertise of leading specialists from academia, industry, government research, regulatory organizations, and the patient community. The working groups were composed of topic experts, community advocates, patients, and caregivers, engaged in regular Zoom calls to dissect and enhance the existing framework. They embarked on a thorough examination of the initial guidance, discerning elements that remained pertinent and identifying areas requiring updates.

A rigorous desk review was conducted, compiling and scrutinizing relevant epidemiological, basic research, and clinical data, with references to evidence substantiated in peer-reviewed articles and regulatory documents. This exercise was pivotal in unearthing key findings, addressing challenges faced by industry engaged in dystrophinopathy research, and forging consensus while shedding light on topics that demanded further exploration.

Central to these discussions was the integration of patient and caregiver perspectives, ensuring that the Duchenne community's voice echoed throughout the document. The working groups were instrumental in steering the technical writer, meticulously reviewing draft iterations, and harnessing Google Docs for real-time, collaborative editing. Moreover, the process entailed a thorough consideration of feedback from both community and the pharmaceutical advisory boards, which was necessary for transparency and collective input.

Recognizing the distinct voices within the guidance reflects the multifaceted nature of the endeavor. Each working group lent its unique tone to the narrative: some sections adopted a more regulatory cadence, resonating with the precision required for policy and compliance, while others embraced an academic tone, allowing for a deeper exploration of the nuances inherent in natural history data, and the development of exploratory outcome measures and novel trial designs. This diversity in expression enriches the guidance, providing a spectrum of perspectives that mirror the complexity and depth of the field itself.

Like the previous community guidance, this updated guidance addresses and expands upon the FDA's current thinking regarding the consideration that should be given to the patient engagement of the DMD and BMD community. It also reflects the FDA's appreciation that recent evidence from patient registries, natural history studies, and clinical trial cohorts have updated both the understanding of DMD and BMD natural history and the causes for variability in outcomes. It addresses the selection of endpoints for clinical trials in populations with DMD as well as the manner in which disease modification might be demonstrated. Given the use of dystrophin as a surrogate endpoint marker for the approval of several drugs [3], this document provides up-to-date guidance on the state-of-the-art measurement of the biomarker. This updated guidance also provides similar guidance on the use of magnetic resonance (MR) imaging measures of both skeletal and cardiac muscle and function and encourages sponsors and regulators to consider their use as surrogate endpoints. Finally, the guidance expands beyond the development of pharmacological treatments (drugs) to consider the development of gene therapy products.

In the pursuit of advancing the development of therapies for DMD and related dystrophinopathies, this comprehensive draft guidance presents a level of detail that surpasses the practical constraints of this journal publication's format. With the objective to disseminate key insights and foundational elements of this guidance, we have distilled its essence into

an executive summary tailored for broad accessibility. This overview publication serves to elucidate the most consequential aspects of the guidance, focusing on regulatory matters, the evolving understanding of natural history, innovations in outcome measures and biomarkers, and considerations in clinical trial design. Furthermore, it highlights the community's concerns, the evolving opportunities in gene therapy, and the need to consider cardiomyopathy in clinical trials. Crucially, it underscores the application of patient engagement in drug development as a necessary scientific and ethical component in our collective effort to meet the therapeutic needs of individuals with a dystrophinopathy. Thus, while the full guidance (provided as an online supplement), remains a comprehensive resource for pharmaceutical sponsors, this executive summary aims to share the elements that inform and drive the development of effective treatments within the wider scientific and medical communities.

GUIDANCE STRUCTURE OVERVIEW

The guidance is structured to provide comprehensive insights into the broad range of topics that sponsors should consider when developing treatments for dystrophinopathies. It is composed of an executive summary, eight detailed sections or chapters, some inclusive of figures and appendices, reflecting the collaborative efforts of various stakeholders.

Executive Summary: It serves as an introduction, detailing the impetus and methodology behind the guidance, FDA's initial response, and the necessity for a revised update. It encapsulates a brief technical background on dystrophinopathies, summarizes the key considerations identified by the working groups for each section, and concludes with community imperatives and formal directives on the use of FDA guidance.

Main Guidance Sections:

A. **The Science of Patient Engagement and Patient Experience Assessment:** This section delves into the background of patient-focused drug development, existing FDA guidance, and how Duchenne patient experience data related to patient preferences can advance drug development programs.
B. **Criteria for Diagnosis in the Clinical and Research Settings:** Offers a detailed background on classic Duchenne Muscular Dystrophy, including clinical features, genetic confirmation, genotype-phenotype associations, and the role of muscle biopsy.
C. **The Current Understanding of the Natural History of Duchenne Muscular Dystrophy:** Discusses the stages of DMD disease progression, the heterogeneity and predictability of the disease, and natural history across the spectrum of dystrophinopathy.
D. **Considerations for Outcome Measurement Selection:** This segment addresses general comments on outcome measures, specific ones in DMD, including developmental scales, motor measures, pulmonary outcome measures, and considerations for cardiomyopathy.
E. **Biomarkers in Duchenne Muscular Dystrophy:** Provides a general commentary, delves into dystrophin quantification as biomarkers, considerations related to muscle biopsies, and a comprehensive look at non-biopsy-based biomarkers.
F. **Specific Trial Design and Analysis Issues for Clinical Trials in DMD:** Discusses the learnings from past DMD trials, key features of DMD trial design and analysis, the use of models and natural history data, innovations in trial designs, and specific trial considerations in BMD and other dystrophinopathies.
G. **Cardiomyopathy:** This crucial section introduces the topic, provides a background on the natural history of cardiomyopathy in dystrophinopathies, and discusses cardiac assessment, trial designs, potential outcome measures, and concludes with thoughts on the future direction.
H. **Gene Therapy for DMD and Other Dystrophinopathies:** Covers an introduction to gene therapy, background, considerations for chemistry, manufacturing, controls, preclinical and clinical trial considerations, patient engagement, and expedited programs, culminating in an appendix on informed consent in gene therapy trials.

Each of these sections could serve as a standalone FDA guidance in their respective areas, addressing the various facets of dystrophinopathy-related topics. The culmination of these sections presents a holistic and in-depth guide for the advancement of treatment and research in dystrophinopathies.

BACKGROUND ON DYSTROPHINOPATHIES

Dystrophinopathies result from genetic mutations in the *DMD* gene that decrease the amount of dystrophin protein and/or cause dysfunction of the protein [4]. In association with other proteins, dystrophin protects muscle fibers against the mechanical forces of contraction—in the absence of dystrophin, muscle is prone to damage, and progressive muscle degeneration [5]. Downstream pathologies including inflammation and fibrosis interfere with muscle regeneration and cause loss of ambulation, loss of upper limb function and other movement, orthopedic complications, and, ultimately, respiratory, and cardiac failure.

The most common and generally most severe dystrophinopathy is DMD, with a birth prevalence of about 1 in 3,500 to 6,000 males [6]. DMD causes delay and/or failure to reach developmental milestones, functional losses in the first decade of life, and a loss of independent ambulation before the age of 13 years in the absence of disease-modifying treatment. In nonambulatory boys and young men, there is gradual loss of upper limb and neck functions, so that grooming, toileting, bathing, dressing, and eating become impaired or impossible to perform by oneself—affecting the quality of life of patients, their caregivers, and families [7]. This is accompanied by weakness affecting respiratory muscles and the heart that contributes to decreased respiratory function and cardiomyopathy—and greatly decreased life expectancy. Heart disease is now the most common cause of death in boys and young men with DMD [8, 9].

BMD has later onset of symptoms and slower progression [10]. BMD is characterized by wide interpatient variability in severity, with some patients having a clinical course similar to that observed for DMD, while other patients remain nearly, or in some cases, completely asymptomatic, and cardiac dysfunction may progress more rapidly than for skeletal muscle [11]. The cumulative birth incidence of BMD was once estimated be at least 1 : 18,500 males (pregenetic confirmation) [12], and more recently, at least 7.2 : 100,000 in a study with genetic confirmation [13] — but incidence and prevalence may vary by population. A small percentage of female carriers may also exhibit a range of muscle symptoms from the full Duchenne phenotype to milder skeletal muscle weakness (see more on related dystrophinopathies in the Diagnosis section) [14].

Over the past decade, patient organizations, academia, and industry have worked together to develop several patient registries, disseminate improved standards of care, and explore clinical outcome measures and biomarkers. This experience and data collection has resulted in a greatly improved understanding of the pathogenesis and the natural history of DMD and BMD, including factors that may lead to variability in the course of the disease.

Natural history studies as well as clinical trials have shown that the use of glucocorticoids and the management of spine deformity, and pulmonary and cardiac dysfunctions have altered the timing of some of the clinical milestones of the disease [7, 15, 16]. But with improved medical management have come new complications, and quality of life often suffers [17]. For instance, adverse events known to be associated with glucocorticoid usage include excessive weight gain, growth inhibition, bone fragility with a high risk of fractures, risk of diabetes, behavioral abnormalities, Cushingoid features, change in pubertal progression, and cataracts [18]. Of particular concern is the issue of weight gain since this can compound the physical limitations of a dystrophic myopathy.

At the time of this update, it should be acknowledged, with gratitude, that there have been some advances in treatment since the previous guidance with an FDA-approved corticosteroid drug, and also several FDA-approved DMD-specific exon-skipping drugs that provide some benefit for individuals with specific DMD mutations. These latter agents were approved based on surrogate marker-evidence [19], and there is increasing evidence of clinical benefit based on longer term observation on treatment [20]. We urge the sponsors, however, to complete the FDA-recommended post-marketing placebo-controlled trials in an expeditious manner, thus, better characterizing the extent of this clinical benefit.

However, these advances in no way reverse the underlying condition. Duchenne is characterized by a progressive, irreversible loss of one function after the other, from the loss of standing from the floor to the loss of ambulation, to the loss of the ability to self-feed, and the inability to breath without assisted ventilation. Once a functional capacity is lost in an individual with DMD, it is gone forever. Death can happen without warning, at any moment, even in younger boys [21]. Complications such as cardiomyopathy commonly cause early death in patients with BMD [22].

There is an urgent unmet need to develop new treatments, especially those that address the under-

lying cause of dystrophinopathy. With a number of potential therapeutic agents in or entering clinical development, sponsors need formal guidance on how best to demonstrate a treatment's effectiveness and safety in this rare disease and what sort of effect would be clinically meaningful to patients and their caregivers.

GUIDANCE UPDATE OVERVIEW

This iteration of the draft guidance contains updates to the sections of the first draft guidance. As with the initial draft guidance, the community chose to place the topic of patient engagement at the start of the document, because it was recognized that sponsors should be guided by patient engagement and patient and caregiver preferences from the very start of a product's clinical development. The diagnosis section follows, to help guide sponsors in the selection of patients, and to prepare for the introduction of newborn screening. This is followed with sections on natural history, outcome measure selection, and a section on biomarkers that has been moved before the updated clinical trials section as biomarkers are increasingly incorporated into these studies and often used as surrogate endpoints.

The following are key considerations in these updated sections.

A. The Science of Patient Engagement and Patient Experience Assessment

(Formerly the Benefit/Risk Assessment section)

Key considerations in this section:

- *Patient-focused drug development (PFDD) has evolved considerably since the 2014 community-led Duchenne Guidance was released, with FDA providing clearer direction via guidance documents on the collection of data related to patient experiences [23, 24].*
- *Patient experience data comes in many forms [25, 26] and are intended to provide information about patients' experiences with DMD and BMD. More data related to BMD patient experiences are needed to inform drug development [27].*
- *Patient and caregiver preferences for treatments have been measured and are well documented in the Duchenne community and can inform all stages of drug development [27–35].*
- *Preference data has shown that patients and caregivers have similar preferences and that they are willing to accept risk and uncertainty in exchange for therapies aimed at slowing disease progression [30, 33].*
- *Sponsors should engage patient groups and FDA on the collection of new patient experience data related to their development programs.*

B. Criteria for Diagnosis in the Clinical and Research Settings

This section provides sponsors with an overview on the diagnosis of dystrophinopathies and differs from the section in the earlier guidance in some key areas.

- *The updated section approaches dystrophinopathies as a spectrum of disorders rather than focusing solely on DMD, adding a list of clinical features for typical DMD and those with later-onset of clinical progression.*
- *While it is emphasized that genetic testing remains the gold standard for diagnosis, it needs to be considered within the clinical context [7]. Muscle biopsy is usually not required in a clinical setting [36], but often still necessary in the research setting.*
- *The discussion on the multiple testing options for genetic confirmation of a dystrophinopathy has been expanded and an algorithm that charts a diagnostic pathway has been added. It also reviews variants of uncertain significance in the DMD gene which have become more common with the advent of next generation sequencing and population screening (expanded carrier screening).*
- *Forward-looking statements have been added regarding newborn screening for Duchenne. A nomination for the Recommended Uniform Screening Panel (RUSP) was submitted in 2022. The formal evidence review started in 2023, with a final vote anticipated in 2024. Implementation would enable diagnosis and management during the presymptomatic stage for infants.*

Another change in the drafting of this guidance, was to combine the working groups drafting the Natural History, Outcome Measures and Clinical Trials sections into one larger group, as in the previous guidance, the work of each working group often informed the other. In addition, there has

been increasing use and acceptance of DMD natural history data both in the development of disease progression models and as real-world evidence of disease progression and natural history, which, in the absence of novel therapies that can augment or potentially replace data from placebo arms by serving as an external comparator group [37, 38].

C. The Current Understanding of the Natural History of Duchenne Muscular Dystrophy

Key considerations in this section:

- *This section provides an updated overview of DMD natural history concepts, including a new schematic illustrating the typical progression of DMD using violin plots to depict the median and range of timing when milestones occur, (e.g., loss of ambulation, loss of standing ability from the floor, etc.), derived from extensive natural history cohorts. It also highlights key outcome measures employed to monitor disease progression across the different stages of disease.*
- *Progression models such as the HERCULES Model [39] and the UC Davis Model [17] link events and outcome measures to add granularity to the characterization of disease stage and trajectory. One important feature of these models is the recognition of a brief transitional stage starting during late ambulation where individuals are able to either stand independently or with assistance and can transfer their own weight.*
- *There now exists a more comprehensive body of DMD natural history data [16], allowing for a refined characterization an individual's disease course [17] and the sources of heterogeneity that sponsors can take into account when designing clinical trials [40].*

D. Outcome Measurement Selection

Key considerations in this section:

- *This section describes outcome measure selection for staging disease, stratifying cohorts, and for monitoring disease progression.*
- *Certain outcome measures, including the North Star Ambulatory Assessment, time function tests, 6-minute walk tests, 10-meter walk run tests, and upper limb functional measures can serve as intermediate clinical endpoints or can be used to identify populations of participants at risk of progression and functional losses during the course of a DMD trial [17, 41–45]. By using these outcome measures during participant screening and for stratification, the risk of underpowering a study and failing to reach a conclusive answer regarding a potential therapy's effectiveness can be mitigated. While a study might have broad inclusion criteria, stratification can enrich a group that the study's primary prespecified analysis is based on.*
- *Recent data highlight specific changes in outcome measures that are clinically meaningful to patients and families at different disease stages [44, 46–49]. The performance measured by certain tools is predictive of progression to disease milestones, potentially serving as intermediate clinical endpoints.*
- *In addition to developmental and motor measures, this section reviews the use of pulmonary outcome measures [50], upper limb function measures [45], and activities monitored by digital technologies and wearable devices [51–54]. These tools can track the course of progression during the transitional phase, through loss of ambulation, and through the nonambulatory stages of DMD.*

E. Biomarkers in Duchenne Muscular Dystrophy

Key considerations within this section:

- *Dystrophin quantification has been used been used as an informative biomarker to support accelerated approval of several genetic therapies in DMD [3]. A variety of quantification methods have been used for assessing dystrophin; underscoring the potential need for multiple methodologies to accurately represent the expression and biodistribution of protein [55].*
- *Sponsors are advised to minimize patient trauma associated with muscle biopsies [56]. It is imperative to have well-defined protocols for the handling and preparing samples to prevent the loss of invaluable tissue [57].*
- *There is a robust body of evidence that MR measures are related to patient function [58–62]. These measures are not only predictive of future functional changes but are also suitable for use in both ambulatory [59, 62, 63] and nonambulatory patients [60, 61]. To further substantiate MR measures as potential surrogate endpoints,*

sponsors are encouraged to incorporate them in their trials.

- *While circulating biomarkers can offer insights into disease progression and response to treatment, there remains a need for further research to connect circulating biomarkers to specific mechanisms of action [64, 65].*

F. Specific Trial Design and Analysis Issues for Clinical Trials In DMD

Key considerations within this section:

- *This section contains key learnings from past trials,[66, 67] including the chief finding that baseline disease severity characteristics are better than age as criteria for enrichment of patient trajectories [46, 68, 69].*
- *The section describes key considerations in DMD trial design and analysis, including recommendations on concurrent therapy, particularly corticosteroid therapy [17, 70], trial duration, and cohort selection required to measure clinical benefit at different disease stages.*
- *The section considers advances in the collection and analysis of natural history data and real-world data and their use in informing the design of clinical trials [37, 40, 71]. Innovative trial designs can also include delayed placebo (or run-in trials, in which natural history data are used in the run-in to the trial) and rollover trials in order to make trials more efficient and reduce participants' exposure to placebo [38]. For instance, the DMD community has been working on a master protocol for a platform trial that can share placebo patients and reduce the proportion of individuals randomized to placebo.*
- *Finally, a brief discussion of clinical trial considerations in BMD and other dystrophinopathies is included. For instance, there is a significant body of natural history data to support the design of clinical trials in BMD and other dystrophinopathies, although decreased disease severity and slower rate of clinical progression may affect endpoint selection and trial duration [72–74].*

This updated version of the guidance also contains two new sections, one on cardiomyopathy and the other on gene therapy. Cardiomyopathy is now the leading cause of death among young men with DMD [8], and some sponsors are looking specifically at heart function in patients with dystrophinopathies, and the use of imaging methodologies to monitor pathogenic changes to the heart. The guidance calls on sponsors to gather evidence linking these pathogenic changes to clinical progression to support regulatory acceptance of these imaging biomarkers as surrogate markers.

Finally, at the time of the original guidance drafting, most of gene therapy research was preclinical. Now, with a few years' worth of data in clinic, the community saw a need to engage with the Center for Biologics Evaluation and Research to develop a section that consolidates the existing FDA guidance on gene therapy and provides specific recommendations on patient considerations unique to DMD and related dystrophinopathies.

G. Cardiomyopathy

Key considerations within this section:

- *DMD-related cardiomyopathy is characterized by fibrofatty replacement of the myocardium, with an extended timeline of cardiac disease progression culminating in full thickness fatty replacement of the myocardium [75–77]. This suggests maximum therapeutic benefit will be garnered only by developing trials focused on BOTH early and later stage disease. A singular focus on trials powered to examine late-stage disease in order to incorporate mortality outcomes may miss an important therapeutic window prior to irreversible, fatty replacement of the myocardium [78].*
- *Harmonization of diagnostic evaluation and therapeutics between trial centers is integral to trial design but must be balanced with the need for inclusivity and access. Consensus recommendations regarding potential cardiac biomarkers and their consideration in trial design will not only facilitate effective trial design but would also provide a means to develop a more robust real-world data infrastructure [79]. This infrastructure is currently needed to assess ongoing clinical trials and for future trials, both cardiac and noncardiac.*
- *The understanding of cardiac disease progression has evolved as longitudinal, granular cardiac data has emerged over the last decade. These data and the creation of multicenter networks have made cardiac clinical trials in DMD more feasible [80]. Creation of a roadmap*

to assess effectiveness of cardiac therapies in DMD will further facilitate the timely development of therapies.

H. Gene Therapy for DMD and Other Dystrophinopathies: Approaches, Patient-Centered Considerations, and Development Pathway

Key considerations within this section:

- *This section draws upon existing FDA guidance on gene therapy (GT) and considers how sponsors can apply it to the development of GT products for DMD.*
- *Technical challenges for the development of GT products that are unique to dystrophinopathies include the target tissues—both skeletal muscle and cardiac muscle—as well as the size and complexity of DMD gene that a GT would be designed to restore or correct [81–85].*
- *Sponsors should consider the implications of the immune responses and safety issues that currently limit the administration, and preclude re-administration, of some of the GT products furthest along in development [86].*
- *Priorities for preclinical studies include dose selection so that clinical trials start with a dose expected to have a therapeutic effect, as well as early evaluation of the effects of GT on the heart [87, 88].*
- *While well-controlled placebo-controlled studies are recommended for GT products that are not expected to have large, self-evident effects, sponsors are encouraged to discuss novel trial designs with FDA that limit the time or necessity that a trial participant is on placebo.*
- *The section includes guidance on corticosteroid treatment prior to and during clinical trials, participant selection criteria and safety considerations including long-term monitoring of GT trial participants.*
- *Efficacy endpoints considerations are the same as in trials of non-GT product for DMD. Intermediate clinical endpoints and surrogate endpoints reasonably likely to lead to or predict clinical benefit could be the basis for a GT to be granted accelerated approval. Given the inability to repeat dosing at the present time, there should be some evidence suggestive of clinical benefit, whether through demonstration of high levels of expression of a functional transgene or demonstration of restored expression of the endogenous gene after gene editing, for the proteins produced by gene therapy to be considered a surrogate endpoint meeting the "reasonably likely" standard for accelerated approval. Evidence from other candidate surrogate endpoints (such as imaging) could support an application.*

IMPERATIVES AND IMPLICATIONS

Finally, the guidance document concluded with a section on the community's imperatives for regulators and sponsors in the development of treatments across the spectrum of dystrophinopathies, based upon consultation with our community guidance board consisting of patients, caregivers, and other representatives of the DMD and BMD community (this is not included in the online supplement but can be found at https://www.parentprojectmd.org/wp-content/uploads/2022/10/Dystrophinopathy-Guidance-Master_Sept30Final.pdf.

It should be noted that the FDA has acknowledged the concerns expressed by the DMD and BMD community that flexibility be exercised in the review of products for these diseases—recognizing that many patients and caregivers are willing to take greater risks for a treatment that may slow clinical deterioration or delay the loss of functional milestones, each of which is clinically meaningful [2]. The FDA shares the Duchenne and Becker community's goal to work with industry to get new therapeutic agents onto the market as rapidly and responsibly as possible. This updated community-drafted guidance for industry is but a step towards achieving that goal.

This guidance is intended to serve as a focus for continued discussions among the FDA, the medical industry, sponsors, academic community, the patient and caregiver community, and the public.

FDA's guidance documents, including this community guidance, do not establish legally enforceable responsibilities. Instead, guidance documents describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidance documents means that something is suggested or recommended, but not required.

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SUPPLEMENTARY MATERIAL

The Supplemental Material is available in the electronic version of this article: https://dx.doi.org/10.3233/JND-230219.

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