March 10, 2015

Alan Guttmacher, MD
Chair, Muscular Dystrophy Coordinating Committee
Director, Eunice Kennedy Shriver National Institute of Child Health and Human Development, National Institutes of Health, Department of Health and Human Services

Dear Chairman Guttmacher:

The Myotonic Dystrophy Foundation is grateful for the opportunity to comment on the Draft 2015 Action Plan for the Muscular Dystrophies. The Myotonic Dystrophy Foundation (MDF) is the world's largest patient organization focused solely on myotonic dystrophy. Our mission, "Care and a Cure," is to enhance the quality of life of people living with myotonic dystrophy (DM) and advance research focused on treatments and a cure. Myotonic dystrophy is one of the nine major categories of muscular dystrophy and is the most common form of the disease, with a diagnosed prevalence of 30,000 – 40,000 people in the US.

The 2015 Action Plan represents a significant amount of work with input from numerous experts in basic, translational, and clinical science of the muscular dystrophies, and articulating comprehensive Report Objectives in five key domains. We commend the working group participants and the leadership roles of both Glen Nuckolls and John Porter for their contributions.and the listed report objectives.

In general we agree with the emphasis on the development of natural history data, endpoints and biomarkers for all of the muscular dystrophies and on the need for better incidence, prevalence and burden of disease data. We appreciate the recognition that there is a need to evaluate the safety and efficacy of gene silencing as a therapeutic avenue, and the recognition that "emerging treatments that address the molecular defects in DM have the potential to change manifestations of this multi-system disease at multiple levels and will have to be understood and subsequently accounted for in the care guidelines." In addition, we endorse recommendations on the need for practice parameters or care guidelines, and we strongly support all of the recommendations under "Lifestyle, education and employment issues" including the identification of strategies to include patient integration into educational and employment systems and addressing mental health needs and opportunities for improving social connectedness throughout the life-span of individuals and their family members.

Specifically we propose the following changes/additions to the draft plan:

1. [p.5] The description of myotonic dystrophy provided in the introduction does not accurately describe the disease. We recommend the following change: "It can affect body systems in addition to skeletal muscles…" should be changed to "It affects body systems in addition to skeletal muscles, which commonly include symptoms such as day-time sleepiness, gaps in executive function and follow through, central fatigue , myotonia and gastrointestinal symptoms …"

2. [p. 32] Section 8, under "Diagnosis, Screening and Biomarkers for Muscular Dystrophy" makes recommendations around establishing the incidence and prevalence of muscular dystrophy, and particularly of "confirmed, diagnosed" cases.

The section goes on to make the statement that "This effort is relatively straightforward for diseases with one or two genetic causes and a distinct phenotype (e.g., DM)." While we agree that it is very important to establish the incidence and prevalence of these diseases, the focus on *diagnosed* based upon both phenotype and genotype may underestimate the mutation load in the population. For example, we know that diagnosis often takes as long as 10 years in myotonic dystrophy type 1, and even longer in DM2. We also know that undiagnosed individuals are capable of passing along a severe form of the disease to their children. For these reasons werecommend that a population-based screen be developed and implemented to better understand the prevalence of the expanded repeat in the general population, whether clinically diagnosed or not.

3. [p.34] In Section 11, under "Diagnosis, Screening and Biomarkers for Muscular Dystrophy," examples of candidate biomarkers for Duchenne and FSHD are highlighted. We propose that the following sentence be added "And for myotonic dystrophy a wide range of mis-splicing events have been shown to be correlated with clinical symptoms" [Berglund and Wang, Report on "Measuring Drug Effects in Clinical Trials: Endpoints & Biomarkers," the Myotonic Dystrophy Foundation Science Workshop, September 2014]

4. [p. 44] In the section on "Clinical Therapy Development for the Muscular Dystrophies," under "optimizing available therapies," two subsections focus on corticosteroids and a third focuses on existing immune-modulating and anti-fibrotic drugs. We recommend the inclusion of a fourth section titled "Evaluating the efficacy of existing therapies for the management of day-time sleepiness, executive function and follow through, muscle and central fatigue, myotonia and gastrointestinal symptoms," which are significant problems in myotonic dystrophy. This section would need to be developed with input from relevant clinical specialists in the field.

5. [p. 53] The section on "Clinical Therapy Development for the Muscular Dystrophies," contains a subsection labeled "Identify, develop, and encourage the use of standardized instruments to measure disease burden, quality of life, cognitive and central nervous system function…." Although we agree that the ability to measure burden of disease in the muscular dystrophies is be important, the question of disease burden in myotonic dystrophy has not been answered definitively as the MDA study had several significant drawbacks, as highlighted in the discussion section of the study publication, particularly the use of a prevalence number from Orphanet of 4.5/100,000 in Europe. The diagnosed prevalence in Europe is more likely to be 10/100,000 (median estimate from European studies—none have findings as low as 4.5/100,000). Using this prevalence data would change the estimate of disease burden from $448M/year to almost $1B/year. Given that the diagnosed prevalence is likely to be lower than the actual prevalence which includes undiagnosed phenotypical expression of DM and DM genotype with mild symptoms or as yet asymptomatic we suggest that language such as "preliminary findings" be used as many cases of DM likely are unrecognized.

6. We note that throughout the Action Plan the recommendation is made repeatedly to standardize data collection using the NIH-developed Common Data Elements (CDEs) for each disease. Since the FDA will soon require all data submissions to use CDISC standard (http://www.cdisc.org/fda-announces-intent-to-require-cdisc-standards) and data collected for clinical trials by sponsors will likely take this format, we recommend this issue be reconciled between FDA and NIH and that the term "or CDISC standard" be used every time a reference to the CDEs appears.

7. Finally, while we recognize that each of the listed objectives are resource dependent, we recommend that the Report include a discussion of prioritization of the 73 Objectives listed along with a timeline for implementation.

Again, thank you for this opportunity to comment on the Action Plan. We look forward to seeing the final draft. Please do not hesitate to contact the Myotonic Dystrophy Foundation if you have any questions about the comments submitted here.

Sincerely,

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Senator Kane
Senator Boxer
Senator Feinstein
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