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Clinical Outcome Measures in DMD  
July 10 and 11, 2011  
Meeting Summary

On July 10 and 11, 26 participants from Europe and the US met in Baltimore, MD to continue discussions on Clinical Outcome Measures in Duchenne Muscular Dystrophy and build upon the work that was done at the first meeting (<http://www.future-science.com/doi/full/10.4155/cli.11.113>). The meeting was organized by TREAT-NMD and Children's National Medical Center and supported by CureDuchenne, the Foundation to Eradicate Duchenne, Ryan's Quest, Parent Project Muscular Dystrophy and MDA. This meeting was the second in what is planned to be an annual meeting, continuing to follow up on regulatory directives specifying that an international consensus needed to be developed to provide guidance on age appropriate clinical outcome measures for use in clinical trials for DMD, especially as these relate to clinically meaningful events.

This year's meeting started with an industry forum, building on the success of PTC's participation in last year's meeting and the growing number of companies with interest in DMD trials. Key themes that emerged related to the need for consistency of measures, better biomarkers, outcomes that can be used for the non-ambulant populations such as cardiac outcomes and relating regulatory approved outcome measures to clinically meaningful events to facilitate reimbursement as therapies move into the clinical trial stage. Additionally there was much discussion over the role that the group could play in terms of providing uniform clinical evaluator training, to ensure quality of training and uniform assessments in DMD clinical trials.

The meeting continued with a discussion of the issues surrounding patient selection for clinical trials, specifically in a younger group, ages 5 – 7. This age group is particularly hard to study as the disease course is variable during this time, making it difficult to produce reliable results. Dr. Craig McDonald outlined some of the critical issues in patient selection and outcome measures in very young DMD patients as they relate to function and clinical meaningfulness. The discussion pointed to the need for normative data to understand the role of growth and development in DMD boys and how growth and development impact reliability of test measures. Overall, there is a need for a more developmentally based approach to measure the very young. Additionally, Dr. McDonald presented timed test data converted to velocity to predict when the loss of a skill would occur. He also addressed the need for z scores and percent predicted values in timed tests and muscle testing from control data to better understand the role maturation has in outcome measures. Dr. McDonald ended his talk with describing plans to continue the current CINRG

natural history study past the initial 5 year plan, increase the younger cohort and add outcome measures (Northstar, 6MWT, pinch strength, EK scale and 9 hole peg) measures to provide a greater breath of knowledge in the very young and non-ambulatory cohort. In addition, he outlined 2 ancillary studies one to assess timed tests and quantitative muscle strength in a normal controlled population between 4-18 years and the second to obtain over 400 serum samples of boys with DMD to conduct a serum biomarkers discovery study..

Laurent Servais, Julaine Florence and Elena Mazzone presented data on some of the challenges in developing outcome measures for the non-ambulant group. Dr. Servais began by summarizing his work developing and validating new tools for upper limb assessment in non-ambulant DMD patients. He examined 6 different tools (myogrip, myopinch, moviplate, tapping, myowrist and actimyo) in terms of their ability to meet expectations, whether they were available and if they were validated. These tools were tested and retested on 100 wheelchair bound patients from ages 8 – 30 at time 0, and then again at 6 months and 1 year. Results showed that there was excellent reliability of the handgrip, pinch and moviplate even in extremely weak patients (i.e. 28 year old DMD patients), these tools had no floor or ceiling effects, they were validated in DMD, and they correlated with important outcome measures such as vital capacity, Brooke score, and time since loss of ambulation. These methods did not correlate well with contractures or poor ejection fraction. A follow up study is being planned to define sensitivity to change and provide further information on measures in the non-ambulant population.

Dr. Mazzone gave an interim summary on a study designed to establish optimal and reliable clinical assessment in non-ambulatory DMD population. The study currently has 95 subjects enrolled, who will be assessed twice per year for two years. Assessments include: strength, pulmonary function, range-of-motion, INQoL and care-giver burden, medications and events, vitals and height, and genetic information if available. The study will inform a protocol for assessment of non-ambulatory patients in terms of reliability, feasibility, sensitivity and validity. The study is fully enrolled and should be completed in two years. Crucial from this work will be the development of measures that will have consistency across the ambulant and non-ambulant groups.

The meeting next focused on another smaller population of DMD patients - the very young. Julaine Florence reviewed a study being conducted at St. Louis University on DMD boys ages 1 month through 5 years, designed to establish optimal and reliable clinical outcomes, establish gross motor development as an effective outcome measure, assess language and cognitive development using the Bayley, Stanford Binet and ABAS scales, and assess ultrasound as a marker of disease progression. The study expects to be fully enrolled (n=22) by August 1, 2011 and will be completed in 2 years. Results of the study will be important in terms of defining outcome measures that can be used for clinical trials in this population, and also how these infants compare to age-matched normal infants. Additionally, the study could provide suggestions for early intervention and education methods. Dr. Valeria Ricotti discussed the issues surrounding how to best manage pre-symptomatic DMD patients, i.e. those diagnosed early in life or upon genetic screening at birth, and early symptomatic patients, i.e. those diagnosed around three year of age. She presented a framework of assessment based on evaluation of gross motor, language and cognitive skills that will be tested in early diagnosed and pre-symptomatic patients.

The second day began with a discussion led by Dr. McDonald on the use of Patient Reported Outcomes in clinical trials for DMD. There are a multitude of generic and disease specific instruments available but many are not validated for use in clinical trials, have limited sensitivity, have floor and ceiling effects, are burdensome for the patient and are cost intensive to complete. One instrument, the PEDsQoL was used in the Ataluren trial and using this instrument, it was found that PROs didn't change much over the course of the trial and weren't very sensitive to treatment effect. Given the problems with the current instruments available, the NIH funded a study to develop a more precise Neuro-QoL instrument that will be applicable

to specific neuromuscular diseases using Computerized Adaptive Tests. The study is now in the validation phase. Future work will focus on developing domains for non-ambulatory boys.

The meeting continued with an overview of two MDA sponsored Cardiac Outcomes Meeting that took place in January and March of 2011 in Columbus Ohio led by Dr. Kevin Flanigan. The first meeting was an overview of what is known about cardiac function and management in DMD. Sessions focused on the pathophysiology of cardiomyopathies in DMD, the use of imaging in cardiac management, therapeutics used in cardiac management, genotype/phenotype observations and an overview of therapeutic trials in cardiac management. The conclusions of the meeting were that there should be a central registry of cardiac data in DMD, MRI should be used more frequently as a clinical measure yet ECHO remains the standard, investigators with extensive clinical datasets should be encouraged to mine them, there is a need for analysis of various drug therapies to determine which may be superior in light of potential risk for cardiac muscle if the therapy is effective for skeletal muscle, and that a DMD cardiac study group should be organized. In the second follow on meeting, specific MDA sponsored existing protocols were reviewed and the details of the formation of the DMD cardiac study group were discussed. In summary, there are many ongoing efforts in DMD cardiac management and the group wishes to build upon these to facilitate better standards of care and create best practices in DMD cardiac management.

The next session discussed Rasch analysis and how it could be applied to DMD. Rasch analysis has been very successfully used in SMA to evaluate 9 scales typically used in clinical evaluations. A pilot analysis on the North Star Ambulatory Assessment (NSAA) and the MFM in DMD has provided preliminary results which show that a robust analysis of all scales could provide meaningful feedback and an opportunity to define and refine the conceptual frameworks that make up the scales. The group is continuing to use Rasch to evaluate other scales in DMD and refine current scales.

The meeting continued with a presentation from Joanne Odenkirchen of the NIH on the progress of the Common Data Elements project. Much progress has been made in several disease areas although DMD has not yet been formally added to the roster.

The last presentation was given by Annie Kennedy of the MDA who gave an overview of the clinical network that the MDA sponsors in all disease areas. There are over 200 MDA and MDA/ALS clinics throughout the US. Five of these (Boston Children's, Nationwide Children's, Washington University, University of Minnesota and UC - Davis) form the DMD Clinical Research Network. The current initiatives of the Network are to 1) further treatment of dystrophin-deficient cardiomyopathy by establishing echocardiography standards, conducting a clinical trial of losartan versus lisinopril and evaluate the genotype-phenotype correlation; 2) develop outcome measured for DMD patients <5 years old and non-ambulatory and 3) conduct regional outreach meetings annually.

The meeting concluded with a robust discussion of initiatives to take forward and demonstrated that there is strong commitment to continuing to collaborate and share information to develop clinical outcome measures in all DMD patient populations. The groups' specific initiatives, where they thought they could provide the most value, were two fold. The first initiative is to work to develop and an upper limb scale for use in DMD that will cover the change that occurs in motor performance of the upper limb over time from when a boy is still ambulant to the time he loses all arm function when non-ambulant. Motor performance in DMD is defined as a demonstrated ability to perform a skill under certain test conditions. This performance changes as the condition progresses and is based on the observed response on the test day. Motor performance will be impacted by muscle weakness, contractures and growth and the scale will aim to incorporate performance of shoulder, elbow, wrist and hand function and domains within the scale will reflect this. Domains could relate to specific joints or to a specific range of motor performance such as

performance above shoulder height or to table height. The group will develop a test scale, drawing from existing scales. A workshop is being planned with patients and clinicians to beta test the scale and collect results. Rasch analysis will be used to evaluate the scales' relevance and then the scale will be retested at individual sites and Rasch analysis will again be used. This iterative process will continue until the scale is developed and will take approximately one year. The second initiative is to hold a State of the Science Meeting alongside the CINRG Annual meeting and the National Institute on Disability and Rehabilitation Research Training Grant Meeting. This meeting would include participation from all stakeholder groups; academia, FDA/EMA, industry and patient groups. The meeting would focus on key topics related to clinical outcome development; general considerations for clinical trials in DMD and other muscular dystrophies, efforts at international data harmonization, endpoints for the ambulatory population, progress in developing endpoints for the non-ambulatory population, and cardiac measures and biomarker development. Each session would seek the perspective of each stakeholder group. Draft manuscripts would be available one month prior and abstracts would be available at the meeting. The manuscripts would be published in a leading neuromuscular journal post meeting.

While this meeting was weighted to explore the data and efforts in the non-ambulant and very young patients, it reinforced the progress that has been made in creating a framework for identifying the challenges in designing clinical trials in DMD, the benefits of coordinated planning and the power of collaboration among academics. By continuing to collaborate we are confident that we can accomplish the goals set out and make a lasting impact in clinical trial research in DMD.

**Co-Chairs**

Kate Bushby, MD  
Ed Connor, MD

**Presenters**

Kevin Flanigan, MD  
Julaine Florence, PhD  
Anna Mayhew, PhD  
Elena Mazzone,  
Craig McDonald, MD  
Joanne Odenkirchen, MPH  
Laurent Servais, MD

**Other Participants**

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JoAnne Auld, MBA  
Abby Bronson, MBA  
Avital Cnaan, PhD  
Paula Clemens, MD  
Pablo Cure, MD  
Tina Duong, MPT  
Michelle Eagle, PhD  
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