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14. ABSTRACT

The Cooperative International Neuromuscular Research Group (CINRG) is a consortium of medical and scientific investigators and centers focused on improving quality of life of neuromuscular disease (NMD) patients by cooperatively conducting clinical research studies in NMD. The CINRG Coordinating Center (CC) is an infrastructure to support the network in conducting study protocols, standardizing clinical trial methodology, data collection and quality assurance, and performing data analyses. In this award period, we have continued to make progress on the revamping of the CINRG quantitative measurement system (CQMS); we have completed sixteen CINRG site visits for hands-on training of site physical therapists as well as monitoring of study procedures and data collection, four new grant applications were submitted, two new protocols were developed, and one manuscript was published. Two additional manuscripts were submitted and several others are in draft form. This infrastructure support yields better overall results in research for improving care in DMD in the largest network of institutions for this disease worldwide.

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Duchenne Muscular Dystrophy, CINRG, CQMS, Coordinating Center, Electronic Data Capture

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1. Introduction

Duchenne muscular dystrophy (DMD) is a rare disease occurring in 1 of 3,500 live born males worldwide. The Cooperative International Neuromuscular Research Group (CINRG) is a consortium of medical and scientific investigators from academic and research centers sharing a common goal of improving the quality of life of neuromuscular disease patients by cooperative planning, implementation, analysis and reporting of controlled clinical studies and of other research for neuromuscular disease. In order to support CINRG in its efforts to perform the highest quality of research, a Coordinating Center (CC) is required to coordinate efforts and protocols, standardize methods of clinical trial treatment administration and assessments, as well as data collection and quality assurance, and analyses of data. The goal of this project is to provide the CINRG clinical research network with an infrastructure for operational support to conduct its studies, database and data management support for collection of data from CINRG studies, specific support in training clinical evaluators (CEs) for muscle strength and biostatistical support for study design, assessment of feasibility and analysis of study results, as well as supporting new grant submissions. The CINRG CC will provide a centralized administrative and technical infrastructure to meet the complex needs of the program that is supportive of CINRG's scientific agenda.

2. Body

2.1 Revamp of the CINRG Quantitative Measurement System (CQMS)

CINRG continued to work with Near Infinity Corporation (NIC) to finalize the CQMS3 software to incorporate improved communication between CQMS3 and OpenClinica. Milestones 6 –7 were completed allowing the ability to manage and design clinical assessments for new study designs and new assessments, and create import/export of data between OpenClinica and CQMS3 so that all study data resides in a single database. Additionally, developments of software coding for skip patterns (branching processes) were created and successfully implemented in both OpenClinica and CQMS3 interfaces. The CINRG CC worked closely with Children's National Medical Center IT and NIC to develop a secure FTP site for storage of raw data on a secure server.

Enhancements were made in the audiovisual aspect of the software for compatibility with all Windows operating systems as well as improving the user experience with a more up to date visual motivation graphics design. NIC also developed an easy to use practice module within the CQMS3 that allows users to customize muscle groups for testing.

To ease the burden of the CINRG Clinical Evaluations Manager (CEM) performing manual installation of the CQMS3 software to all CINRG sites all software updates and upgrades are now accessed via the website. This download is similar to an installation wizard. Sites are currently working with their institutions' IT departments to ensure safe download of this software as some sites may have minor permissions issues with firewalls for installation of this type of software. Additionally, the CQMS3 manual for both user and administrator has been finalized and posted on the CQMS3 website. The CINRG CEM has currently trained 15 CINRG CEs on how to use the CQMS3 software. To ensure CEs receive trainings in parallel with study activation, future trainings are scheduled as sites get ethics approval for studies that will use the CQMS3 for data obtainment. Trainings for future studies are possible to do on the web essentially as webinars.

The CQMS3 generic software has been successfully installed at 90% of the CINRG sites. Currently, it is not only installed but functional and working with OpenClinica to import and export study data for half of the CINRG sites. At these sites, the DMD Natural history study

protocol has been launched and actively used as the software to obtain muscle strength data. The CINRG CC has been able to confirm successfully transfer of data from CQMS3 testing into OpenClinica.

Since the successful delivery of the CMQS3 software, NIC, which is a private company, has changed ownership. The CINRG CC is working with NIC to develop a short consulting contract to address difficulties with uploading some new CINRG studies onto CQMS3. CINRG has successfully uploaded two new studies onto CQMS3, but are experiencing errors with other studies that require technical troubleshooting. Additionally, not all sites have access to uploaded studies. We have found in-house expertise to provide technical assistance to troubleshoot the errors. The in-house software engineer will consult with NIC engineer to resolve these issues. The errors seem to be in the interface between CQMS3 and OpenClinica rather than in the CQMS software itself. The CINRG CC and the software engineer are in the process of troubleshooting with personnel from OpenClinica to resolve this issue in the near future.

Of the sites who have started using the CQMS3 and OpenClinica system for data obtainment, the CC has received positive comments on improved data quality, integration and user interface with the new software. Study participants have expressed enthusiasm with the new features of the "game" that encourages them to perform their best in the evaluations.

2.2 Training of new clinical evaluators

Training of new CEs in Year 4 focused on hands on instruction for standardized test assessments in muscle strength, anthropometric measurements, functional and timed tests that are part of the CINRG clinical outcomes toolbox. Reliability testing was performed with all newly trained clinical evaluators to ensure reproducibility of testing.

The CEM visited 5 CINRG sites. In addition, an experienced veteran CE from Melbourne also travelled to certify a new CE in Sydney. A total of 8 new CEs were certified as CINRG CEs and an additional 4 existing CEs were recertified in these total 6 on-site visits performed by the CEM and the senior CE from Melbourne.

- University of Tennessee in Memphis, TN: From Feb 26th-27th, 2013, the CEM certified 1 new CE and demonstrated proficiency in testing for CINRG outcome assessments. One CE was recertified for assessments with the DMD Natural History Study and the Clinical Trial of Coenzyme Q10 and Lisinopril in Muscular Dystrophies. All requirements for reliability were met and both CEs demonstrated proficiency in testing. Equipment and supplies were verified and new software programs for respiratory and muscle testing were successfully installed.
- The Children's Hospital at Westmead in Sydney, AUS: From April 18th-19th, 2013, a certified senior CE from Melbourne performed CINRG certification training for a new CE in Sydney, in order to increase efficiency and save travel costs. The senior CE from Melbourne is a veteran in CINRG and a member of CINRG's Outcomes Subcommittee. The CE used training materials provided by the CEM and performed reliability testing with the new CE. The new CE met reliability requirements and was proficient in performing tests for CINRG protocols. The CEM performed remote training and information regarding CINRG operations, software downloads and review of equipment checklist.
- Hadassah University Hospital in Israel: From June 11th-12th, 2013, the CEM trained 1 new CE and re-certified 1 CE. All requirements for reliability were met and both CEs demonstrated proficiency in testing for CINRG outcome assessments. Equipment and supplies were verified and new software programs for respiratory and muscle testing were successfully installed.

- University of California-Davis in Sacramento, CA: From July 16th-19th, 2013, the CEM certified 1 new CE as a back-up evaluator for assessments only in the DMD Natural History Study and recertified 1 CE to perform all assessments in the other CINRG protocols. The new CE for the site will only be able to perform some of the CINRG assessments due to not meeting CINRG minimal reliability standards. The new CE does not have a physical therapy degree and is therefore unfamiliar with manual muscle tests and joint goniometry. The site is currently recruiting an additional back up physical therapist to be the permanent back up for the site.
- Lurie's Children's Hospital in Chicago, IL: From Aug 1st- Aug 3rd, 2013, the CEM certified 2 new CEs and performed training on all CINRG protocols. All requirements for reliability were met and both CEs demonstrated proficiency in testing. Equipment and supplies were verified and new software programs for respiratory and muscle testing were successfully installed.
- Fundacion Favoloro in Buenos Aires, Argentina: From Aug 9th-12th, 2013, the CEM certified 2 new CEs and recertified 1 CE for assessments in the DMD Natural History Study and BMD Natural History Study. All requirements for reliability were met and both CEs demonstrated proficiency in testing. Equipment and supplies were verified and new software programs for respiratory and muscle testing were successfully installed. The CEM also met with the CEs to work on a project to develop CINRG training videos to be available online.

2.3 Updates on Protocols Related to Duchenne Muscular Dystrophy Research Supported by the CINRG Coordinating Center

In this section we have outlined the progress of each CINRG project that relates to DMD research made in Year 4 (August 2012-2013). The first three projects (see Sections **2.3.1, 2.3.2, and 2.3.3**) represent updates on closed studies. The last four projects (see Sections **2.3.4, 2.3.5, 2.3.6, and 2.3.7**) represent active and new studies.

2.3.1 National Initiative for Families with Duchenne (NIFD)

A. Overview

The purpose of this survey was to collect information about families of people with DMD all over the USA. The survey asked for information about the impact of DMD on the family, the needs of the family for health services, the use of those health and school support services, the overall wellness of people with DMD and attitudes toward newborn screening for DMD. A total of 237 families participated in this study. Participants were enrolled either through the CINRG DMD Natural History Study (discussed in section **2.3.5**) or directly through the NIFD study completed via a web-based survey. The data management team has merged the collected study data into one dataset.

B. Project Updates

The data management team has been applying a systematic approach to correcting data errors within the survey, section by section. In Year 4, the analysis of: Your Child's Health and Medical Care sections of the survey were completed. The researcher working with the data management and operations manager successfully defended their master's thesis that used this CINRG data and submitted an abstract to the Annual National Society of Genetic Counselors (NSGC) which was accepted for a platform presentation for the upcoming October 2013 meeting.

2.3.2 Comparative Study of Clinical Endpoints in DMD: HHM vs. CQMS protocol

A. Overview

The purpose of this study was to compare the commonly used pediatric strength testing measures: handheld myometry (HHM) and CQMS, with the goal of assessing which of these two methods had a higher intra-rater and inter-rater reliability in measuring muscle strength in children with DMD. The database was locked in May 2011.

B. Manuscript Preparation

The manuscript has been drafted and currently in review by the co-authors. We will submit the manuscript to the Muscle and Nerve Journal. Results found high reliability among the instruments. A mixed effects model confirmed that fatigue was not a factor in strength assessments ($p>.16$ for fatigue in all muscle groups models), thus supporting the reliability estimates without need for further adjustments. Inter-rater reliability was high in both devices ($\geq .88$). Intra-rater reliability showed more variation with the following ranges across all CEs: knee extensor CQMS (.81-99), HHM (.85-.97); knee flexor CQMS (.72-94), HHM (.67-.93); elbow extensor CQMS (.83-1.0), HHM (.92-.99); elbow flexor CQMS (.92-.99), HHM (.82-99). The study shows comparable inter-rater reliability and age-associated intra-rater reliability. Knee flexion had the least inter and intra-rater reliability. These results may impact the experimental design and sample size calculations in future clinical trials in DMD. The results are not generalizable beyond DMD as this population is weaker than most populations assessed with handheld myometry or other muscle strength measurement devices.

2.3.3 Cardiac Outcome Measures in Children with Muscular Dystrophy protocol

A. Overview

This project aimed at developing cardiac outcome measures that could be reliably implemented across a consortium of clinical sites devoted to the study of pharmaceutical treatments for muscular dystrophy. This study was funded as a CTSA supplement through the University of Pittsburgh. Funding for this project ended on June 30, 2011 and the two associated studies (one for echocardiographic measures and one for cardiac magnetic resonance measures) were closed.

B. Manuscript Preparation

In Year 4, further data analyses occurred. Statistical analysis of the completed study was conducted, yielding a manuscript in preparation. Echocardiogram (echo) and electrocardiogram (ECG) reading were compared between two readers to assess their agreement. Additionally, measures were compared to Speckle tracking echocardiography (STE) in a subset of subjects to observe if evidence of cardiac disease is detectable at an earlier point with STE than with traditional measures. Analysis methods included summary statistics of cardiac measures and demographic characteristics in the form of means, SD and graphical representation. Comparisons between categorical demographic and cardiac measures by medication use, genetic diagnosis and steroid use used chi-squared analyses. Comparisons with continuous measures used t-tests. Echo and ECG measures were summarized separately for each reader and reported as mean ± SD. Agreement between readers was assessed using an ICC calculated for each measure and relationships between measures were assessed using Pearson or Spearman correlations where appropriate. Lastly, additional evaluations of select cardiac measures (SF and MPI) were done to assess the stability and reliability of these measurements over a range of characteristics, including age and magnitude. Graphical representations of values over 1 year age intervals and over the range of magnitude were done to assess the variability of these measurements.

2.3.4 Clinical Trial of Coenzyme Q10 and Lisinopril in muscular dystrophies

A. Overview

The objective of this study is to test an angiotensin converting enzyme (ACE) inhibitor, lisinopril, and an anti-oxidant, coenzyme Q10 (CoQ10), to ameliorate the decline in cardiac muscle function that occurs in muscular dystrophies. The study treatment period is 24 months per patient. This project is primarily funded by the Department of Defense (grant W81XWH-04-1-0851). The activities that are related to Year 4 for this award cover work performed on regulatory and data management support.

B. Project Updates

The study team continues to work on enrollment challenges and has modified the protocol to include an additional cardiac inclusion criteria as well as identifying additional sites.

C. CINRG Site Updates and Site Monitoring

The table below provides a status update for all CINRG centers involved in this protocol.

CINRG Sites	Local Ethics Preparation	Local Ethics Approved	DoD HRPO Approved	Participant recruitment
University of Pittsburgh, Pittsburgh, PA		X	X	X
Children's National Medical Center, Washington, DC		X	X	X
University of Tennessee, Memphis, TN		X	X	X
Alberta Children's Hospital, Calgary, Canada		X	X	X
Carolinas Medical Center, Charlotte, NC		X	X	X
Lurie's Children's Hospital, Chicago, IL		X	X	X
National Center of Neurology and Psychiatry, Tokyo, Japan		X	X	X
Hadassah Medical Center, Jerusalem, Israel		X	Pending	
Apollo Hospitals, Chennai, India		X	In review	
University of California, Sacramento, CA		X	X	X
Centro Clinico NEMO, Milan, Italy	X			
Children's Hospital of Westmead, Sydney, Australia	X			
Duke Medical Center, Durham, NC	X			
Kobe University, Kobe, Japan	X			

In Year 4 the project management team visited the following 4 CINRG sites to monitor this study:

- University of Tennessee in Memphis, TN for a site monitoring visit.
- University of Pittsburgh in Pittsburgh, PA for an interim monitoring visit.
- Carolinas Medical Center in Charlotte, NC for an interim monitoring visit.
- Lurie's Children's Hospital in Chicago, IL for an interim monitoring visit.

D. Data Management

In Year 4, the electronic data capture (EDC) system OpenClinica has been continually maintained. The data management team has issued all active and enrolling sites monthly delinquency reports (for missing forms or missing data) as well as monthly data check reports.

E. Statistical Analysis

Since this is an ongoing randomized clinical trial, it is not appropriate to perform analyses that are not the formal interim analysis. Therefore, no statistical analyses were performed on this study within this past year.

2.3.5 A longitudinal study of the relationship between impairment, activity limitation, participation and quality of life in persons with confirmed Duchenne muscular dystrophy protocol

A. Overview

There are two purposes to this study. The first purpose of this research study is to establish a large long-term assessment of people with DMD to better understand the current natural history of this disease, to be better able to design clinical trials based on ongoing natural history parameters. In this study, we are collecting data on participants' physical abilities across all ages, medical problems, and how they use healthcare services. We are also collecting data on how families of people with DMD interact with their communities and how they rate their quality of life. The second purpose of this study is to see how long-term steroid therapy affects these aspects of lives of participants with DMD.

This project is funded by the following agencies:

- Department of Education: All patient related costs up to 5 annual visits for participants that have been enrolled since the start of the study.

- Department of Defense: An additional 2 visits (beyond the 5 annual) for participants that have been enrolled since the start of the study and the one-year follow-up visit for the newly enrolled control participants (new cohort funded by the NIH, see below).

- National Institutes of Health: Any new assessments (according to protocol amendment 4.1 onwards) up to 5 annual visits for participants that have been enrolled since the start of the study. In addition, the collection of study wide blood samples for biomarker analysis and the baseline visit for the newly enrolled control participants.

- Parent Project Muscular Dystrophy: All patient related costs up to year 2 for newly enrolled DMD participants (ages 4-7 years).

B. Project Updates

Protocol amendment 4.2 was generated to cover the one year follow-up for control participants, following the approval of protocol amendments 4.0 for the majority of changes resulting from the additional new assessments and adding the control group, and amendment 4.1 for further refinements and updates. Protocol amendment 4.2 has been approved by the CINRG CC and its IRB as well as the ethics committee overseeing the study at the site of the study chair, University of California, Davis. The CINRG CC personnel have been working with the sites to obtain ethics approval for protocol amendments 4.0, 4.1, and 4.2. In addition, continued data management and statistical support has been provided to ensure the integrity of the study data and to allow publications to move forward. The project management team has also continued to conduct monitoring visits to ensure accuracy and credibility of the study data.

C. CINRG Site Updates and Site Monitoring

In Year 4, the project management team performed 7 site monitoring visits. The following tasks are performed during each monitoring visit:

- Review of protocol conduct and adherence to regulatory guidelines

- Source document verification, including the review of informed consent documents and adverse event/serious adverse events
- Review of outstanding queries
- Review of strength and functional testing equipment and space
- Protocol training for any new staff
- Re-training of any identified areas of inconsistency or concern

Below is a summary of the findings from each completed on-site monitoring visit conducted since in Year 4:

- Mayo Clinic, Rochester, MN: From October 09th-11th, 2012, a CINRG project manager completed a site monitoring visit. Some minor discrepancies were noted surrounding the consent process and data records. Overall the site was found to be functioning well.
- Children's Hospital of Richmond, VA: From December 03rd- 05th, 2012, two CINRG project managers completed a site monitoring visit. Some discrepancies were noted surrounding the consent process and data records. It was requested that select consent discrepancies were reported to the site's ethics committee. Overall the site was found to be functioning well.
- Children's Hospital of Pittsburgh, PA: From February 26th – March 01st, 2013, the CINRG operations manager and a CINRG project manager completed a combined monitoring visit to monitor this study, the PITT0908 clinical trial, a study on facioscapulohumeral muscular dystrophy (FSHD), and PITT0112 Becker natural history study. The site was found to be functioning very well. The site was found to have very few data queries and their overall study compliance and documentation was in very good order.
- University of Tennessee-Memphis, TN: From March 11th-13th, 2013, a CINRG project manager completed a combined monitoring visit to monitor this study, the PITT0908 clinical trial, the FSHD study and PITT0112 Becker natural history study. Some discrepancies were noted surrounding the regulatory binder, consent process and data records. The site personnel have a scheduled plan with the CINRG CC personnel to bring their study documents/records back up to CINRG's standards, and have been following this schedule.
- Texas Children's Hospital, TX: From April 22nd -23rd, 2013, a CINRG project Manager completed a combined monitoring visit to monitor this study, the FSHD study, and PITT0112 Becker natural history study. Some very minor discrepancies were noted surrounding the consent process and data records. Overall the site was found to be functioning well.
- University of Puerto Rico, PR: From May 20th-22nd May, 2013, a CINRG project manager completed a site monitoring visit to follow up on the issues that were identified at the previous monitoring visit (difficulties with keeping their participants engaged in the study and missing long term follow-up visits). The project manager also reviewed the study records to date while onsite. A high priority plan was developed with the site personnel to get them back on track with the study.
- University of Minnesota, Minneapolis, MN: From May 30-31st, a CINRG project manager completed a combined monitoring visit to monitor this study, the FSHD study, and PITT0112 Becker natural history study. Some minor discrepancies were noted surrounding the consent process and data records. At completion of the visit the site binders were in good order.

D. Data Management

The data management team has continued to issue data checks to each site to ensure collected data are accurate and reliable. A data closure plan was developed for all data collected in the original database as the entire database is now in OpenClinica. The CINRG data management anticipates having all data from this database locked by the end of 2013.

In Year 4, the data management team continued to prepare reports for each monitoring visit described above.

Statistical Analysis

In Year 4 analyses were performed for several manuscripts:

- Updated analyses to complete the acceptance of two manuscripts, one describing the study methods and the second describing baseline and some first study year results manuscripts (see **Key Accomplishments**) were performed.
- Updated analyses were performed for a draft manuscript on height findings in DMD. Using growth charts from Center for Disease Control (CDC), we categorized whether the participants met the criteria for short stature. We explored the relationship between height, ambulatory status, steroid status, and years on steroid. Both observed and calculated (based on ulnar bone length) height were used in the analyses. Statistical techniques used included Fisher's Exact test, and logistic regression and linear regression modeling.
- To assist the strength and function manuscript working group in their conference presentations and several drafted manuscripts analyses were performed using both baseline data and longitudinal data. Scatter plot was used to explore the correlation between various components of muscle strength and function test. Box-and-whisker plots were generated for each age group and by steroid status. Timed function test was summarized at each time point from baseline to year 1 by age group and their change since baseline as well. Regression analysis was used to explore the correlation between lower muscle strength with the timed function test. Survival analyses were performed to predict the probability of reaching some clinically meaningful milestones after study entry within groupings based on timed function tests at study entry, hip/knee manual muscle test score and shoulder MMT score for upper extremity.
- To assist the pulmonary function working group in their conference presentations and development of manuscript, descriptive analyses were performed to summarize the baseline demographics and PFTs as well as their 12 months change. Spaghetti plots were generated by each age group to explore the trend change of PFTs in 12 months.
- Evaluations between genotype groups were done by comparing averages within age groups and with moving overlapping age groups. Longitudinal analyses used random coefficient mixed effects linear models to assess changes in outcomes over time between the genotype groups. Outcomes modelled longitudinally include QMT grip strength values and velocity derived from the time to run or walk 10 meters test. Velocity was defined as 10/value to yield a velocity with units of m/sec, where those unable to perform the test were given a value of zero velocity. In order to limit the bias associated with repeated zeros for non-ambulatory subjects, only the initial zero for each subject was included in the model. Similar analyses with other single

nucleotide polymorphisms in the TGFβ signalling pathway (i.e. ISBP (rs2616262) and LTBP4 (rs10880) are currently underway.

E. Manuscript Preparation

The main methodology/baseline results manuscript was separated into two manuscripts as part of a revision process from the initial submission and revision. Those are "The CINRG Duchenne Natural History Study – A longitudinal natural history study in the era of glucocorticoid therapy: Design of the protocol and methods" and "The CINRG Duchenne Natural History Study: Glucocorticoid treatment preserves clinically-meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures". These two manuscripts were published in 2013 Muscle and Nerve.

A manuscript from the cardiac working group was submitted to Muscle and Nerve and the authors are working to respond to reviewer comments.

Two draft manuscripts from the strength and function working group and height findings manuscript are currently in working stage and circulating among co-authors for editing.

2.3.6 Becker Muscular Dystrophy – A Natural History Study to Predict Efficacy of Exon Skipping

A. Overview

The objective of this study is to phenotype participants with in-frame mutations of the dystrophin gene, corresponding to target deletions generated by skipping exons 45, 51 and 53. This information will then be used to integrate phenotype information by severity associated with each deletion. This study will also evaluate potential clinical trial outcome measures for participants with Becker muscular dystrophy. The study period is 36 months per patient. This project is primarily funded by the National Institutes of Health (NIH).

B. Project Updates

In Year 4 we have obtained IRB approval at eight participating CINRG sites and four participants were enrolled.

2.3.7 Duchenne Muscular Dystrophy Tissue Bank for Exon Skipping

A. Overview

This project will create the first DMD Tissue Bank that will collect tissue and blood from DMD participants with specific genetic mutations within the dystrophin gene that could be treated by anti-oligonucleotide drugs. The DMD Tissue Bank will validate dystrophin mutations and provide a single, comprehensive, organized collection of properly prepared and retrievable de-identified fibroblast cell cultures and blood samples to be used for current and future research studies in muscular dystrophy for exon skipping research strategies. This project is primarily funded by the National Institutes of Health (NIH).

B. Project Updates

In Year 4 we have obtained IRB approval at four participating CINRG sites and recruited four non CINRG sites to join this study.

2.3.8 A Trial of Chronotherapy of Corticosteroid in Duchenne Muscular Dystrophy

A. Overview

This new protocol was initiated in May 2013 through funding received from the Foundation to Eradicate Duchenne (FED). This clinical trial will be conducted in the youngest age group

able to receive glucocorticoids orally and on whom study outcomes are measurable, ages 3 to 7. This will be a randomized, double blinded, double masked, placebo-controlled clinical trial that will explore whether better synchronization of glucocorticoid administration with the circadian rhythm, using a newly-available FDA-approved delayed release prednisone, will provide improved tolerability and at least comparable efficacy to current standards in which glucocorticoids are always given in the morning. Furthermore, the trial provides a unique opportunity to rigorously evaluate glucocorticoid effects in the young DMD patient, both for efficacy as compared to placebo and as a study of the impact of glucocorticoid chronotherapy, or delayed release, on increased tolerability over standard therapy. Although glucocorticoid therapy is accepted standard of therapy and recommended to be used at age 5 and older, there are currently no data to support its effect and tolerability in the young. This study will provide evidence-based data whether it is safe and effective to use glucocorticoid therapy and, in particular, the delayed formulation, in this age group.

B. Project Updates

A new protocol working group was developed and consultation with the CINRG outcome submitted was obtained.

2.4 CINRG Administrative Efforts

2.4.1 CINRG CC Team Meeting

The CINRG CC continued to hold regularly scheduled team meetings. The CINRG CC team discusses protocol progresses on the second and fourth Wednesdays of the month and infrastructure related updates on the third Wednesday of the month. Additionally the study team for the DMD Natural History Study discusses protocol progress on the first Monday of the month. Protocol related meetings are attended by all members of the CINRG CC along with the CINRG study chairs.

2.4.2 CINRG 2012 Membership and Scientific Meeting

The CINRG CC organized and conducted an Investigator meeting in November, 2012 at the Crystal City Marriott in Arlington, Virginia. This year the meeting was four days and called the 2012 Joint Meetings in Neuromuscular Disorders as it combined three different meetings: the CINRG Meeting, 5th Programs in Clinical and Translational Research: Muscular Dystrophy and Rehabilitation Medicine and the State of the Science on Outcome Measurements. The CINRG meeting included a review of the scientific and business function of CINRG. This meeting is intended to be attended by at least one of each of the CINRG site staff roles of investigator, coordinator, or CE. We had a very positive turn-out with 109 attendees. During this meeting, the following was presented and/or conducted (see Appendix for the meeting agendas):

- One day session attended by CINRG CEs: This training was conducted to provide re-certification to all previously certified CINRG CEs. At least one CE from each CINRG site attended the annual re-training and certification training. This session included a review of the techniques and positioning for established and new quantitative test measures using the CQMS, annual equipment checks and upkeep; review of current and future protocol testing measures, including new CE assessments and positioning for quantitative muscle testing, 6 minute walk test, Egan Klassification scale and new timed tests description for the supine to stand timed test. Additionally, CQMS replacement equipment including 9 hole peg tests, blood pressure cuffs and some load cells were distributed to site CEs to save in shipping costs to all sites.

- One half day involving OpenClinica training to any attendees who needed training or wanted a refresher course as well as a New Member Orientation Q& A session. This morning also included closed sessions for the Outcomes Subcommittee, Therapeutics Subcommittee and Executive Committee.
- One half day membership meeting was attended by all CINRG site investyigators and staff: This included an introduction from all new participating CINRG network sites, a summary of CINRG accomplishments since the last meeting in March of 2011, CQMS3 update, a Good Clinical Practice review as well as a review on the new By-Laws. The session also included panel discussion for analyses and glucocorticoid use.
- One full day scientific session: This included an overview of programs in translational and clinical research, CINRG study updates, translation research, exon skipping updates, and basic science updates.
- One full day to present research findings regarding the development of novel outcome measures and the conduct of recent clinical trials in neuromuscular disorders.
- One half day meeting of the Scientific Advisory Committee (SAC): This was a closed session, only attended by SAC members, CINRG Medical, Scientific, and Coordinating Center Directors.

The meeting planning and implementation was a team effort by all CC personnel, and consisted of addressing issues at the meeting location, site personnel travel arrangements, agenda and materials dissemination, as well as all training and presentation materials necessary to ensure success. This meeting in particular was considered a huge success by both CINRG participants and many outside CINRG people who came for the scientific sessions. The meeting bolstered CINRG's status as a major participant in the development of clinical research in DMD.

CINRG Executive Committee Meetings

The CINRG EC is responsible for, among other things, the review/approval of all protocols to be conducted by the network/utilize CINRG equipment; oversee programmatic activities of CINRG, and assess or implement recommendations from CINRG's Scientific Advisory Committee (SAC).

The CINRG Operation Manager coordinates the dissemination of necessary documentation and review/voting conduct of this committee. The committee has conducted 4 meetings, including the review/approval of a new version of the CINRG By-Laws (version 2.0), which was a major effort, review/approval of procedures and a report for site performance, review of 2 new CINRG network sites, review/approval of 3 new standard operating procedures (SOP), and continued oversight of CINRG activities and conduct.

2.4.3 CINRG Network Communication

The CINRG CC maintains formal communication and provides network updates to participating sites through periodic teleconferences. These teleconferences are sub-divided into two formats; one to accommodate site principal investigators and another to accommodate clinical coordinators and evaluators. In Year 4 one teleconference meeting was held as the other meetings were held during the in-person November 2012 meeting.

The CINRG website also provided CINRG members with a means of communication. The CC continues to upload necessary documents on the private section to communicate with

the CINRG sites. The CC also continues to work with the vendor to improve the look and features of the private site.

2.4.4 Collaborating with Other DMD Research Entities

In Year 4 several members of the CINRG CC have attended meetings with other DMD research entities and the CC continues their active collaborations with the DMD community.

- The Medical Director participated in the 2012 Muscle Study Group Scientific Annual Meeting from September 27-29, 2012 in Java Center, NY.
- The operations manager participated in the TREAT-NMD 2012 Global Database Oversight Committee meeting from September 29th-30th, 2012 in Istanbul, Turkey for which she is a committee member.
- The Medical Director participated in the Muscular Dystrophy Association (MDA) Medical Advisory Committee on October 19, 2012 in Tucson, AZ.
- The Medical Director participated and was a speaker in the Western Pennsylvania MDA Muscle Summit on November 17, 2012 in Pittsburgh, PA.
- The CINRG CC Director and Medical Director participated in the MDA Scientific Conference from April 21-24, 2013 in Washington, DC.
- The CINRG CC Director and Medical Director participated in the Symposium on Best Practices in Clinical Study Design for Rare Disease from April 29-30, 2013 in Washington, DC. Both were speakers at this conference.
- The CINRG CC Director participated in the TREAT-NMD Advisory Committee for Therapeutics (TACT) review meeting from April 27-28th, 2013 in Baltimore, MD. (http://www.treat-nmd.eu/resources/tact/reviews/past).
- The operations manager participated in the PPMD-sponsored conference '2013 PPMD Transition' on June 26th, 2013 in Baltimore, MD. The CC Director and operations manager then attended the PPMD CONNECT 2013 Annual Conference from June 27-30th, 2013 in Baltimore, MD.

2.4.5 Infrastructure Subcontracts

The CINRG CC did not renew their subcontracts with the seven sites, or the one consultant agreement for this reporting period. The contracts with OpenClinica and Evolve (see section 2.4.6) were continued.

2.4.6 CINRG Regulatory Compliance Assurance

The project management team continues to work with each CINRG site to assure ethical and regulatory compliance for each related protocols.

A. Ethics Submission Assistance

The CC continues to provide assistance with ethics application packets to all participating sites for each related protocols. The project management team has maintained regular contact with the sites to assist with the preparation of the submission documents. All informed consents and assents were reviewed by the study project manager before they were submitted to their respective ethics committees. All sites received assistance until protocol and consent/assent documents received local approval.

B. Assurance of Regulatory Compliance

The project management team continues to be responsible for ensuring that every site has their regulatory documents up to date in the Clinical Trial Management System (CTMS) called Evolve (https://se44sl2.studymanager.com).

2.4.7 CQMS Equipment and Supplies Summary

In year 4, CINRG continued to use the equipment and supplies pamphlet. The pamphlets have been used for CINRG new site set up and determination of site needs as well as successful ordering of equipment/supplies. Using the equipment pamphlet, CINRG has successfully worked with potential CINRG site applicants to estimate cost of equipment/supplies determine areas of shared cost for better utilization of funds.

The CEM has also successfully utilized the CTMS (see above section) to track supplies and equipment orders. A newly improved annual CQMS equipment/supplies checklist was developed and is uploaded into CTMS.

Laptops were ordered for the following CINRG sites: Pittsburgh, Minneapolis, Houston, , Puerto Rico, and Argentina. Updated laptops were required for full functionality with the new pulmonary function software and CQMS3. All sites were supplied with an updated version of the KOKO pulmonary function software v4.5 and Koko pneumotach.

Three sites (Sacramento, St Louis, and Pittsburgh) were provided new hi-lo tables used for CE assessments. These specialized tables allow for the CEs to appropriately position patients for assessments.

2.4.8 CINRG Subcommittee Updates

CINRG Scientific Advisory Committee (SAC): The SAC is a committee whose aim is to set research priorities and offer operational recommendations to the CINRG CC and routinely convenes during the CINRG Investigator meeting. The SAC held their meeting during the November 2012 meeting.

CINRG Publication Subcommittee (CPS): In Year 4, the CPS has received 21 review requests:

- Nineteen abstract review requests
- Two poster presentations

CINRG Therapeutic Subcommittee (CTS): The broad role of the CTS is to undertake an active role of bringing potential agents for evaluation towards clinical trials utilizing the CINRG network. In Year 4, the CTS held an in-person meeting during the November 2012 meeting as well as 4 follow-up meetings. The CTS reviewed a new potential CINRG protocol and provided feedback to the CINRG PI for modifying their protocol regarding treatment and administration of the therapeutic.

CINRG Outcomes Subcommittee (COS): The broad role of the COS is to undertake an active role of review outcomes for studies in the CINRG network. In Year 4, the COS held an in-person meeting during the November 2012 meeting as well as 3 follow-up meetings. They provided recommendations for the outcomes for a new potential CINRG protocol.

CINRG Data Safety Monitoring Board (DSMB): The DSMB is responsible for safety monitoring and monitoring of data integrity for all CINRG studies. The DSMB includes neurologists, patient advocates, and a statistician. The DSMB held one meeting during this grant period on February 19, 2013 and only discussed the PITT0908 – Clinical Trial of Coenzyme Q10 and Lisinopril in Muscular Dystrophies.

The DSMB approved the proposed modification to the protocol to include an additional cardiac inclusion criterion which effectively relaxed the entry criteria somewhat and hopefully will therefore increase enrollment.

3. Key Accomplishments

The following are a summary of the key accomplishments for the Year 4 funding period:

- Two manuscripts were published (see attached **Appendix**)
- Fifteen CINRG site visits were completed: six for CE training and seven for project management monitoring
- Eight new clinical evaluators were trained
- Four existing clinical evaluators were re-certified
- One new protocol was developed

4. Reportable Outcomes

The following are a summary of the reportable outcomes for the Year 4 funding period:

- Manuscript citation:
    - Henricson E, Abresch R, Cnaan A, Hu F, Duong T, Arrieta A, Han J, Escolar DM, Florence JM, Clemens PR, Hoffman EP, McDonald CM and CINRG Investigators. The CINRG Duchenne Natural History Study: Glucocorticoid treatment preserves clinically-meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle nerve 2013 48:55-67
    - McDonald C, Henricson E, Abresch R, Han J, Escolar D, Florence J, Duong T, Arrieta A, Clemens P, Hoffman E, Cnaan A, and CINRG Investigators. The CINRG Duchenne Natural History Study – A longitudinal natural history study in the era of glucocorticoid therapy: Design of the protocol and methods. Muscle nerve 2013 48:32-54

- Informatics:
    - NIC Software CQMS3 beta testing and launch to CINRG sites

- Funding applied for based on work supported by this award:
    - Submission of a Wellstone Center Grant (U54) entitled “Targeting onset and progression of myofiber damage in DMD” in November 2012
    - Submission of an MDA Grant proposal “A Trial of Chronotherapy of Corticosteroids in Duchenne Muscular Dystrophy” in December 2012
    - Start-up seed money was provided by the Foundation to Eradicate Duchenne (FED) for the chronotherapy study described above, and for a reliability study of novel measurement outcomes. This seed money will allow the CC to apply for additional funds to support the full clinical trial and other future studies.

5. Conclusion

2.4.2 The infrastructure support for CINRG’s CC has continued in Year 4 to be an invaluable resource to the network and to the neuromuscular community. This support allowed for the publication of results from the DMD natural history study, which is the largest to date, and the development of several new manuscripts that are in process of submission, review, or further write-ups. A new clinical trial has been developed and funding for it is being sought. The annual meeting was a tremendous success, increasing the visibility and contribution of CINRG to clinical

research in DMD. Collaborations with TREAT-NMD, MDA, and PPMD were all strengthened in this past year. Because of CINRG's strong infrastructure, several small pharmaceutical companies with promising therapeutic targets, but no infrastructure to conduct studies, contacted CINRG for further information and potential collaborations. The complex protocol amendment to the ongoing DMD Natural History is being implemented throughout the network and will define current natural history with the most up-to-date novel outcomes, and will include a new young cohort which has already enrolled one-third of the target accrual, all within 2013. The new CINRG Quantitative Muscle System (CQMS) version 3.0 was completed and implemented at most of the CINRG sites. This is a major accomplishment that has a new state-of-the-art interface to encourage DMD participants to provide the best muscle outcome results and a smooth interface to allow implementing new study designs efficiently and quickly. The CQMS 3.0 connects with the main database in OpenClinica, allowing CINRG to have all data from the studies in one place, increasing reliability and reproducibility of the data. The CINRG CC continued to support all participating clinical sites by completing fifteen on-site visits. These visits provided sites with hands-on training of new site personnel as well as on-going monitoring of studies. There are essentially only two remaining tasks for this award. One task is to finalize some minor interface issues between CQMS 3.0 and OpenClinica and complete implementation of CQMS 3.0 in the remaining CINRG sites. The second is to support the ongoing CINRG clinical trial of Coenzyme Q10 and Lisinopril in muscular dystrophies (W81XWH-04-1-0851, PI: P. Clemens). This study is still recruiting new patients and performing evaluations. It has funding for the study visits, but no longer for the Coordinating Center infrastructure efforts of project and data management and statistical analysis. As part of completing this infrastructure support, the remaining task for following years is to provide this support for this DMD clinical trial.

References

1. McDonald C, H.E., Abresch R, Han J, Escolar D, Florence J, Duong T, Arrieta A, Clemens P, Hoffman E, Cnaan A, and CINRG Investigators, *The CINRG Duchenne Natural History Study – A longitudinal natural history study in the era of glucocorticoid therapy: Design of the protocol and methods.* Muscle Nerve, 2013.

2. Henricson E, A.R., Cnaan A, Hu F, Duong T, Arrieta A, Han J, Escolar DM, Florence JM, Clemens PR, Hoffman EP, McDonald CM and CINRG Investigators, *The CINRG Duchenne Natural History Study: Glucocorticoid treatment preserves clinically-meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures.* Muscle Nerve, 2013.

Appendix

- Annual Meeting Agenda
- Published manuscripts

JOINT MEETINGS IN NEUROMUSCULAR DISORDERS PROGRAM OVERVIEW

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT

1999 Jefferson Davis Highway
Arlington, Virginia 22202

Thursday November 8th, 2012			
7:00	8:00		**Breakfast**
8:00	17:00		**CINRG Clinical Evaluator 2012 Meeting**
18:00	21:00		**Dinner Reception for CINRG Clinical Evaluators**

Friday November 9th, 2012				
8:00	9:00		**OpenClinica Training**	
9:00	10:20		**CINRG Outcomes Subcommittee – Closed Session**	**CINRG Therapeutics Subcommittee – Closed Session**
10:35	11:55		**CINRG Executive Committee – Closed Session**	**CINRG New Member Orientation and Open Q&A**
12:00	13:00		**Lunch**	
13:00	16:50		**CINRG Membership 2012 Meeting**	
18:00	21:00		**Dinner Reception for all CINRG Members and Invited Guests**	

Saturday November 10th, 2012			
7:30	8:30		**Breakfast**
8:30	17:00		**Scientific Symposium** **Fifth Program in Clinical and Translational Research: Muscular Dystrophy and Rehabilitation Medicine**

Sunday November 11th, 2012			
9:30	17:00		**State of the Science on Outcome Measures**

CINRG 2012 Meeting

DETAILED PROGRAM FOR CINRG CLINICAL EVALUATORS ONLY

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT

1999 Jefferson Davis Highway
Arlington, Virginia 22202

Thursday November 8th, 2012			
8:00	9:00		**Breakfast** *(Chesapeake Salon A)*
9:00	09:15		**Welcome: Review aims of meeting** *(Potomac Salon F)*
09:15	10:15		**Status of Current CINRG Studies, Annual CINRG Site Requirements, and Equipment/Supplies Process** *(Potomac Salon F)*
10:15	10:45		**BREAK** *(Chesapeake Salon A)*
10:45	11:45		**CINRG Toolbox: Overview of new tests, OpenClinica and CQMS3 Demonstrations** *(Potomac Salon F)*
11:45	12:45		**Lunch and Equipment Sign-out** *(Chesapeake Salon A)*
12:45	14:30		**Small Working Groups (Hands on Lab)*** *(Chesapeake Salon B-C and Potomac Salon F)*
14:30	15:00		**BREAK** *(Chesapeake Salon A)*
15:00	17:20		**Small Working Groups (Hands on Lab)*** *(Chesapeake Salon B-C and Potomac Salon F)*
17:20	17:30		**Open Discussion: Q and A** *(Potomac Salon F)*
19:00	20:00	**Dinner Reception for CINRG Clinical Evaluators**	

***Small Working Groups (Hands on Lab)**

1. OpenClinica
2. CQMS3
3. NSAA and Timed tests with grading
4. 6MWT and Functional Tests, 9 HPT
5. EK, AROM, PROM
6. MMT and QMT
7. PFT

CINRG 2012 Meeting

DETAILED PROGRAM FOR ALL CINRG MEMBERS

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT

1999 Jefferson Davis Highway
Arlington, Virginia 22202

Friday November 9th, 2012			
8:00	9:00		**OpenClinica Training** (Optional for anyone who would like new or additional training) *(Chesapeake Salon A)*
9:00	10:20		**CINRG Outcomes Subcommittee – Closed Session** *(Roosevelt Room)* **CINRG Therapeutic Subcommittee – Closed Session** *(Chesapeake Salon A)*
10:35	11:55		**Executive Committee – Closed Session** *(Roosevelt Room)* **CINRG New Member Orientation and Open Q&A for PIs, CCs, and CEs** *(Chesapeake Salon A)*
12:00	13:00		**Lunch** *(Chesapeake Salon B-C)*
13:00	13:10		**Welcome and Introduction of New CINRG Staff, New CINRG Sites, and New CINRG Members** *Paula Clemens* *(Potomac Salon D-E)*
13:10	13:35		**CINRG: What have we accomplished in the last 18 months?** *Avital Cnaan*
13:35	14:00		**Updates from the Subcommittees** *COS, CTS, and CPS Chairs*
14:00	14:15		**Good Clinical Practice Game Show** *Lauren Hache*
14:15	14:30		**Progress and Evolution of our Network: Proposed By Laws Changes** *Avital Cnaan*
14:30	14:45		**CQMS 3 Software Demonstration** *Tina Duong*
14:45	15:00		**Coloring Muscle Weakness** *Jose Corderi*
15:00	15:20		**Break**
15:20	16:10		**Challenges and Techniques for Managing Large Datasets into Meaningful Manuscripts** *Moderator: Craig McDonald* *Panelists: Tina Duong, Hanna Kolski, and Jean Mah*
16:10	17:00		**Clinical Care Panel – How are steroids used in the clinical setting?** *Moderator: Paula Clemens* *Panelists: Alberto Dubrovsky, Nancy Kuntz, Laura McAdams, and Monique Ryan*
18:00	21:00		**Dinner Reception** *(Chesapeake Ballroom)*

2012 JOINT MEETINGS IN NEUROMUSCULAR DISORDERS

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT
1999 Jefferson Davis Highway
Arlington, Virginia 22202

Saturday November 10th, 2012 ***Potomac Ballroom, unless other room specified***			
5TH PROGRAMS IN CLINICAL AND TRANSLATIONAL RESEARCH: MUSCULAR DYSTROPHY AND REHABILITATION MEDICINE			
7:30	**8:30**		**Welcome, Registration, and Breakfast** *(Potomac Foyer)*
8:30	**8:35**		**Welcome and Overview of Program** Eric Hoffman, Paula Clemens, and Craig McDonald
8:35	**8:55**		**PROGRESS REPORT: Preclinical and Translational Programs** *Eric Hoffman, Children's National Medical Center*
8:55	**9:25**		**PROGRESS REPORT: Cooperative International Neuromuscular Research Group (CINRG) and State of the Science Outcome Measurements Meeting** *Paula Clemens, University of Pittsburgh* *Craig McDonald, University of California, Davis*
9:25	**10:05**		**EXON SKIPPING PROGRAMS: Specialized Centers in Research in Pediatric Developmental Pharmacology Program (NIH/NIAMS)**
9:25	9:45		**1. Program Overview** *Eric Hoffman, Children's National Medical Center*
9:45	10:05		**2. Enhancers of Antisense Oligonucleotide Drugs** *Carrie Miceli, University of California, Los Angeles*
10:05	**10:25**		**Break**
10:25	**11:30**		**EXON SKIPPING PROGRAMS: Center for Research Translation of Systemic Exon-skipping in Muscular Dystrophy (NIH/NIAMS)**
10:25	10:35		**1. Program Overview** *Paula Clemens, University of Pittsburgh*
10:35	10:55		**2. RNA Fidelity and Protein Function** *Alyson Fiorillo, Children's National Medical Center*
10:55	11:15		**3. Optimization of Antisense Oligonucleotides Drugs** *Qi Lu, Carolinas Medical Center*
11:15	11:30		**4. International Duchenne Exon Skipping Collaboration** *Abby Bronson, Children's National Medical Center*
11:30	**11:50**		***Optimizing the Predictive Value of Preclinical Animal Research*** *John Porter, NIH NINDS*
11:50	**12:10**		***NIAMS Research Programs and Funding Opportunities*** *Glen Nuckolls, NIH NIAMS*
12:15	**13:15**		**Lunch** *(Chesapeake Ballroom)*
13:15	**13:55**		**VBP15 dissociative steroid development**
13:15	13:35		**1. Preclinical Results** *Chris Heier, Children's National Medical Center*
13:35	13:55		**2. Drug Development Plan** *Ed Connor, CEO ReveraGen*

2012 JOINT MEETINGS IN NEUROMUSCULAR DISORDERS

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT
1999 Jefferson Davis Highway
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13:55 13:55 14:15 14:35	**14:55** 14:15 14:35 14:55		**CINRG STUDY RESULTS:** **1. Evaluation of Limb-Girdle Muscular Dystrophy Study** *Susan Sparks, Carolinas Medical Center* **2. Cardiac Outcome Study and Exploratory Cardiac Measures** *Chris Spurney, Children's National Medical Center* *Paula Clemens, University of Pittsburgh* **3. *OPN* Genetic modifier effect on progression** *Avital Cnaan, Children's National Medical Center*
14:55	15:15		**Break**
STATE OF THE SCIENCE ON OUTCOME MEASUREMENTS (DAY 1)			
15:15	**15:50**		**DMD Natural History Study Overview and Future Plans** **Ambulatory Clinical Endpoints in DMD** *Craig McDonald, University of California, Davis*
15:50	**16:10**		**Clinical and Strength Testing in DMD** *Tina Duong, Children's National Medical Center*
16:10	**16:30**		**NeuroQOL and Patient Reported Outcome Measures** *Erik Henricson, University of California, Davis*
16:30	**16:50**		**Challenges in the Translation of Clinical Outcome Measures For Pharmaceutical Development in Neuromuscular Disorders** *Lawrence Charnas, Shire Human Genetics Therapies*

Sunday November 11th, 2012 ***Potomac Ballroom, unless other room specified***			
7:30	9:30		**Closed Session for Scientific Advisory Board Executive Meeting** *(King Room)*
STATE OF THE SCIENCE ON OUTCOME MEASUREMENTS (DAY 2)			
9:30 9:30 9:50 10:10	**10:30** 9:50 10:10 10:30		**MUSCULAR DYSTROPHY BIOMARKERS UPDATES** **1. Genotype-Phenotype Relationships and Polymorphisms** *Kevin Flanigan, Nationwide Children's Hospital* **2. Surrogate Biomarkers in DMD** *Kanneboyina Nagaraju, Children's National Medical Center* *Yetrib Hathout, Children's National Medical Center* **3. Skeletal Muscle MRI Endpoints in DMD** *Krista Vandenborne, University of Florida*
10:30	10:45		**Break**

2012 JOINT MEETINGS IN NEUROMUSCULAR DISORDERS

CRYSTAL CITY MARRIOTT AT REGAN NATIONAL AIRPORT
1999 Jefferson Davis Highway
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13:50	**14:45**		**NEW DIRECTIONS IN NON-AMBULATORY PATIENTS**
10:45	11:05		**1. Natural History Study of Non-ambulatory Measures in DMD** *Julaine Florence, Washington University St. Louis*
11:05	11:25		**2. Novel Upper Arm Measures** *Eugenio Mercuri, Catholic University*
11:25	11:45		**3. Novel Quantitative Upper Limb Measures** *Laurent Servais, Institute of Myology*
11:45	12:05		**4. Quantitative Measures of Reachable Workspace** *Jay Han, University of California, Davis* *Gregorij Kurillo, University of California, Berkeley*
12:05	13:05		**Lunch**
13:05	**14:05**		**CARDIAC OUTCOME MEASURES UPDATES**
13:05	13:20		**1. Cardiac Outcomes – A CINRG Perspective** *Paula Clemens, University of Pittsburgh*
13:20	13:35		**2. Cardiac Outcomes – An MDA Consortium Perspective** *Kevin Flanigan, Nationwide Children's Hospital*
13:35	13:50		**3. Emerging Techniques in Cardiac MRI** *Glenn Walter, University of Florida*
13:50	14:05		**4. Cardiac Panel Q & A**
14:05	**14:45**		**NEW DEVELOPMENTS IN AMBULATORY OUTCOMES**
14:05	14:25		**1. Infant / Toddler Endpoints** *Anne Connolly and Julaine Florence, Washington University St. Louis*
14:25	14:45		**2. Rasch Analysis of Ambulatory Outcomes (North Star, MFM, MMT)** *Anna Mayhew, Newcastle Hospitals*
14:45	15:00		**Break**
15:00	**15:40**		**COMBINING INFORMATION AND ITS IMPACT**
15:00	15:20		**1. Efforts at Data Harmonization** *Kate Bushby, Newcastle Hospitals*
15:20	15:40		**2. Burden of Care / Economic Costs** *Chris Bell, GlaxoSmithKline*
15:40	16:30		**OPEN DISCUSSION**

THE COOPERATIVE INTERNATIONAL NEUROMUSCULAR RESEARCH GROUP DUCHENNE NATURAL HISTORY STUDY—A LONGITUDINAL INVESTIGATION IN THE ERA OF GLUCOCORTICOID THERAPY: DESIGN OF PROTOCOL AND THE METHODS USED

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Abbreviations: CDC, U.S. Centers for Disease Control and Prevention; CIDD, Clinical Investigations of Duchenne Dystrophy; CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; NHS, natural history study; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICF, International Classification of Functioning, Disability and Health; LSI, Life Satisfaction Index; LVEF, left ventricular ejection fraction; MDCC, Muscular Dystrophy Coordinating Committee; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MMT, manual muscle test; MRC, Medical Research Council; NG, no prior glucocorticoids; PedsQL, Pediatric Quality of Life Inventory; PEFR, peak expiratory flow rate; POSNA, Pediatric Orthopedic Society of North America Pediatric Musculoskeletal Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QMT, quantitative isometric muscle strength test; SF, shortening fraction; TFT, timed function test (timed motor performance); WHO, World Health Organization

Key words: adolescent; adult; child/preschool; follow-up study; health status; human; locomotion; male; muscle strength/physiology; muscular dystrophies/classification; muscular dystrophies/Duchenne/physiopathology; muscular dystrophies/therapy; phenotype; quality of life/psychology; respiratory function test

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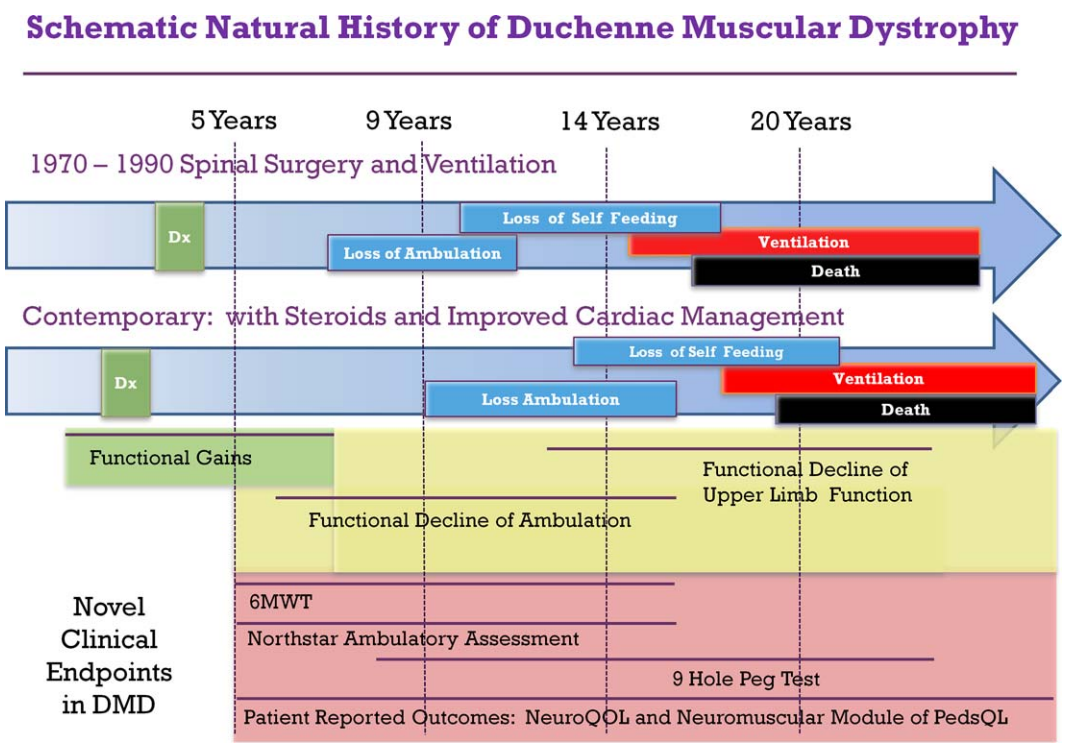

FIGURE 1. Changing the natural history of DMD and the application of novel clinical endpoints in 2012. Dx, age at diagnosis; 6MWT, 6-minute walk test. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

ABSTRACT: Contemporary natural history data in Duchenne muscular dystrophy (DMD) is needed to assess care recommendations and aid in planning future trials. *Methods:* The Cooperative International Neuromuscular Research Group (CINRG) DMD Natural History Study (DMD-NHS) enrolled 340 individuals, aged 2–28 years, with DMD in a longitudinal, observational study at 20 centers. Assessments obtained every 3 months for 1 year, at 18 months, and annually thereafter included: clinical history; anthropometrics; goniometry; manual muscle testing; quantitative muscle strength; timed function tests; pulmonary function; and patient-reported outcomes/health-related quality-of-life instruments. *Results:* Glucocorticoid (GC) use at baseline was 62% present, 14% past, and 24% GC-naive. In those ≥6 years of age, 16% lost ambulation over the first 12 months (mean age 10.8 years). *Conclusions:* Detailed information on the study methodology of the CINRG DMD-NHS lays the groundwork for future analyses of prospective longitudinal natural history data. These data will assist investigators in designing clinical trials of novel therapeutics.

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Tremendous advances over the past 3 decades have improved knowledge of disease pathogenesis caused by dystrophin deficiency. Nonetheless, effective treatments for Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD) remain limited. Improvements in disease management in DMD, including treatment with glucocorticoid (GC) medications, surgical management of spine deformity, non-invasive ventilation, and more effective treatment of cardiomyopathy, have improved function and survival. This is reflected in a changed natural history of the disease (Fig. 1).[1–5] Despite these advances, patients with DMD continue to lose ambulation in adolescence, frequently require ventilatory support prior to adulthood, develop significant cardiomyopathy in the second to third decade, and have early death in their late teens and into the third and fourth decades of life.[2–6]

Pharmaceutical companies and academic groups have become increasingly interested and involved in DMD-directed therapeutics. These approaches include antisense oligonucleotide (AON)-mediated exon skipping, gene transfer therapy, stem cell delivery, and several small-molecule administration approaches (e.g., compounds that induce read-through of premature stop codon mutations, promotion of muscle growth by myostatin inhibition, upregulation of utrophin, and GC analogs with improved side-effect profiles).[7] Although not curative, these therapeutic approaches offer hope to significantly alter disease progression and improve quality of life.

The effectiveness of these novel agents will need to be assessed against a background of GC administration. Standards of care for DMD have evolved to incorporate GC use, which is supported by both basic and clinical research studies over the last 20 years.[3,4,8,9] Recent population-based studies in the USA have shown that >50% of patients with DMD are treated with GC therapy.[10] This change in clinical management has slowed the progression of DMD during the first 2 decades, prompting a reexamination its natural history.

Previous studies have provided a valuable foundation for our current understanding of the natural history, genetic variation, physiological impairments, functional decline, and associated secondary impairments in DMD.[1,11–16] However, these natural history studies were limited in their scope of domains, addressed a restricted spectrum of disease severity, and employed shorter durations of follow-up. One of the current fundamental barriers in both the evaluation of DMD-care standards and the optimal design of DMD clinical trials is the lack of contemporary natural history data with clinical trial endpoints obtained across a broad age range and disease-severity spectrum. The varied rate of progression of DMD also necessitates prospective, longitudinal study of a diverse cohort of patients.

To address this gap, the Cooperative International Neuromuscular Research Group (CINRG) has launched the Duchenne Muscular Dystrophy Natural History Study (DMD-NHS) at 20 centers around the world, collecting the most comprehensive and largest, prospective, longitudinal natural history data to date on a cohort of DMD patients. This CINRG DMD-NHS study was designed using the World Health Organization International Classification of Functioning, Disability, and Health (ICF)[17] framework, which includes consideration of body structure and function, individual activities and participation, and environmental factors that impact the overall physical and mental health of the individual in a societal context. We use retrospective–prospective case–cohort study designs in individuals with confirmed Duchenne muscular dystrophy to evaluate the effectiveness of both long-term administration of GC and preventive interventions. These were identified by the CDC DMD Care Considerations Group[3] as requiring further study. Specifically, we aimed to: (1) study the relationship between impairment, activity limitation, participation, and quality of life across a wide age range and spectrum of DMD disease severity using common clinical endpoints employed in clinical trials and novel outcome measures; (2) study the natural history of changes in measures of impairment, activity limitation, and quality of life over periods of 12 months to >5 years of follow-up; (3) examine the associations between both disease characteristics and the use of interventions and the onset of life-altering clinical milestones that are due to the progression of disease; and (4) assess the incidence of secondary conditions of DMD and the relative risks of developing these conditions based on exposure to standard treatment (e.g., glucocorticoids) and preventive interventions recommended by the CDC Care Considerations.[3,4]

The DMD-NHS protocol follows an assessment schedule that models frequent early time-points and long-term follow-up common to clinical trials, and therefore the data will help inform the design of future clinical trials in DMD. These data will also help identify clinically meaningful endpoints, define changes in endpoints that predict occurrence of clinically meaningful milestones, and help determine minimally clinically important differences.

Here we provide detailed information on our study methodology and lay the groundwork for future analyses of its prospective, longitudinal, natural history data.

METHODS

Participants. ***Inclusion Criteria.*** We sought initially to enroll between 10 and 15 participants per year who were between 2 and 28 years years of age. All participants were required to have a clinical picture consistent with typical DMD. Participating caregivers were parents or legal guardians of DMD-NHS participants. Participants between the ages of 2 and <5 years were required to have a diagnosis of DMD confirmed by at least 1 of the following *or* have an older male sibling who met at least 1 of the following criteria: (1) dystrophin immunofluorescence and/or immunoblot showing complete dystrophin deficiency; (2) positive gene deletion test (missing 1 or more exons) in the central rod domain (exons 25–60) of dystrophin, where the open reading frame (ORF) could be predicted as "out-of-frame"; or (3) complete dystrophin gene sequencing showing an alteration (nonsense point mutation, insertion, deletion, duplication, etc.) that was expected to shift the ORF and preclude production of the dystrophin protein. Affected subjects aged ≥5 years and <29 years were required to meet the aforementioned criteria or have documented clinical symptoms referable to DMD (progressive proximal weakness evident by 5 years of age, characteristic gait, positive Gower sign, calf pseudohypertrophy), and direct support of the diagnosis by either (1a) a positive DNA analysis for dystrophin mutation, (2a) a muscle biopsy demonstrating abnormal dystrophin, or (3a) an elevated creatine kinase (CK) level (>5-fold the upper limit of normal), and X-linked pedigree and an affected family member who met either criteria (1a) or (2a) as just described.

Exclusion Criteria. Individuals with DMD were excluded from the study if they were: (1) GC-naive and could ambulate without assistance beyond the 13th birthday; or (2) on GC therapy and could ambulate without assistance beyond the 16th birthday. However, once patients were considered eligible and were enrolled (e.g., 12 years and younger, GC-naive and ambulating) they remained enrolled, regardless of later ambulation status. Our decision to initially exclude patients who continued to

ambulate independently beyond the age of 16 years while on GC therapy and beyond 13 years if GC-naive was based on 3 published observations. First, our previous DMD natural history study of GC-naive patients showed the average age at full-time wheelchair transition to be 10 years, with a range of 7–13 years.[13] Second, GC therapy prolonged ambulation by 2–3 years in longer term studies.[8,9] Third, prior to the application of modern diagnostic testing, clinical criteria held that ambulation past the age of 16 years was consistent with a BMD diagnosis.[18]

History of Enrollment. The initial study cohort of 340 patients was recruited from 2009 to 2012. To increase the pool of young DMD participants and to study the impact of GC therapy initiation, beginning in 2012 we began enrolling 100 additional DMD patients between the ages 4 and 8 years of age, using the same criteria as for the initial cohort.

Study Logistics and Support. The study was designed by the study's principal investigator (C.M.M.) and the study chairs at the UC Davis Medical Center (E.K.H. and R.T.A.) and the Children's National Medical Center (A.C.), with early assistance from D.M.E. at Kennedy Krieger Institute. The organizational structure for CINRG is provided in Appendix 1. The CINRG Coordinating Center, located at the Children's National Medical Center, provides operational, data management, and statistical support for the study, as described previously.[19,20] Clinical evaluators (CEs) participate in annual central training and reliability testing.[19–21] Two full-time expert CE trainers are available to train new CEs. Standardized equipment is used at all study sites. The excellent reliability for clinical assessments among the CINRG clinical evaluators has been reported previously and continues to be maintained in the annual testing and when training new CEs who join the network.[21] The CE trainers also receive training on new methods. When they are certified, they train other CINRG CEs, and the new method is added to the network portfolio. Quality control of the data is achieved by the data management team. A comprehensive series of edit-check programs are run against the data sets on an ongoing basis. Sites are queried for any unclear, missing, or inconsistent results of any measure. Sites then respond to queries and correct the data as appropriate. In addition, the Coordinating Center conducts monitoring visits at all sites to ensure data integrity.

Participant-completed assessment tools were translated into languages spoken at the study sites by certified translators and were back-translated into English for verification prior to use.

Protocol Approvals. The institutional or ethics review boards at each participating institution approved the study protocol and the consent/assent documents. Informed consent/assent was obtained from each participant or caregiver as appropriate prior to conducting the study procedures.

Schedule of Assessments. After central review of diagnostic testing results, participants had assessments at baseline and months 3, 6, 9, and 12 (ambulatory), or months 6 and 12 (non-ambulatory), which were timed to approximate the visit frequency commonly employed in DMD clinical trials. One site employed an alternate-visit schedule consistent with local care standards. Long-term follow-up visits were at months 18, 24, and annually thereafter, and are ongoing. Study teams collected age-appropriate measures of functional ability, health status, anthropometrics, timed motor performance, range of motion, skeletal muscle strength, pulmonary function, cardiac function, and health-related quality of life. DNA samples from peripheral blood, buccal swabs, or saliva samples were centrally banked for genotype/phenotype analysis.

Adaptive Nature of Study Design and Protocol Revisions. We utilized an adaptive study design to permit evolution of the protocol in response to ongoing determination of the feasibility, usefulness, and applicability of promising novel clinical endpoints in DMD. Some patient-reported outcomes (PROs) were discontinued during the course of the study, because it was considered that sufficient prospective natural history data had been obtained. A major modification to the study protocol occurred in 2012, 6 years after initiation of data collection. Original and added measures categorized by the ICF framework are shown in Table 1, along with time of administration. Details concerning descriptions of the outcome measures and chronology of application of the measures are presented in Appendix 2.

Health Status Assessment. We performed a detailed physical examination and health status history interview at each visit based on DMD-care guidelines[3,4,76–78] and expert opinions from clinicians and researchers with expertise in the care of patients with DMD. Data collected include participant demographics, molecular diagnostics history, family history of DMD, and a complete medical history.

Patients or their parent or primary caregiver completed a survey derived from the National Initiative for Families with Duchenne (NIFD)[79] questionnaire to provide information regarding medical histories beginning with the diagnostic process and including neurological, neuromuscular, neurodevelopmental, respiratory, cardiac, dermatological, nutritional, gastrointestinal, and

Table 1. Clinical Endpoints used in CINRG Duchenne Natural History Study.

Body Structure / Function	**Standard Protocol? Amb / NonAmb**	**Time Required**
Molecular Diagnostics	+ All	Chart Review
Dystrophin Analysis by Muscle Biopsy (Immunohistochemistry)	±	Chart Review
Health Status / Review of Systems, Medications, Clinical Complications	+	15 min
Glucocorticoid History	+	5 min
Anthropometric measures (standing height, weight, ulnar lenth, tibial length)	+ All	5 min
Vital Signs	+ All	2 min
Body Composition (DEXA)[23]	± All	Chart Review
Body Composition (Bioelectrical impedance)[24]	± All	Chart Review
Bone Health (DEXA)[25]	± All	Chart Review
Passive Range of motion (Goniommetry) [11,26]	+ All	5 min
Spine Deformity Evaluation	+ All	Clinical Exam & Chart Review
Strength: Quantitative Grip Strength[19,21]	+ All	2 min (unilateral)
Strength: Quantitative Tip Pinch and Key Pinch strength	+ All	2 min (unilateral)
Strength: Isometric Strength with Fixed Devices[19,21]	+ Amb	10 min (unilateral)
Strength: Manual Muscle Testing (or MRC%)[1,11,26]	+ All	10 min
Pulmonary fuction tests: FVC, FEV1, PEFR, Peak Cough Flow, MIP, MEP[27–31]	+ All	15 min
Cardiac: ECG	± All	Chart Review
Cardiac: Echocardiography	± All	Chart Review
Cardiac: Holter Monitoring	± All	Chart Review
Activities (Clinical Evaluator Determined Scales)	**Standard Protocol? Amb**	**Time Required**
Vignos Lower Extremity Functional Grade[32]	+ All	2 min
Brooke Upper Extremity Functional Grade[11]	+ All	2 min
North Star Ambulatory Assesssment (NSAA)[33–37]	+ Amb	15 min
Egen Klassification Scale v. 2 (EK Scale)[38,39]	+ Non-Amb	10 min
Activities (Functional Tests with Timed Dimension)	**Standard Protocol? Amb / Non-Amb**	**Time Required**
Time to rise from the floor (supine to stand)[1,11,26]	+ Amb	2 min
Time to climb four steps[1,11,26]	+ Amb	2 min
Time to walk/run 10 meters or 30 feet[1,11,26]	+ Amb	2 min
6-Minute Walk Test [40–42]	+ Amb	15 min
9-Hole Peg Test [43–46]	+ All	10 min
Patient-Reported Outcome Measures (PROs) / • Health-related Quality of Life • Participation • Satisfaction	**Standard Protocol? Amb / Non-Amb**	**Time Required**
Pediatric Quality of Life Questionnaire (PedsQL™) Generic Core Scale[47–54]	+ All	5 min
POSNA pediatric musculoskeletal functional health questionnaire / Pediatric Outcomes Data Collection Instrument (PODCI).[55–59]	+ All	15 min
PedsQL Neuromuscular Module [60,61]	+ All	10 min
NeuroQoL Patient-reported Quality of Life [62–69]	+ All	15 min (short forms)
Life Satisfaction Scale (Life Satisfaction Scale for Adolescents) [70]	+ NonAmb	10 min
WHO Quality of Life – Bref [71–73]	+ NonAmb All Adults	10 min
Medical Outcomes Study (MOS) 36-Item Short Form (SF-36) [74]	+ NonAmb	10 min
Pittsburgh Sleep Quality Index [75]	+ All	5 min
Total Time (complete assessment)		216 min

+ Standard Protocol; +: administered to all; ±: Physician's Descretion; Amb: ambulatory; Non-Amb: non-ambulatory.

For compete details see Appendix 2.

genitourinary issues. Patients and their caregivers provided information about health-care providers they consulted, use of assistive devices, and school support. English-speaking patients and caregivers in the USA also completed the full NIFD health economics and service utilization questionnaire.

Echocardiograms were not required study evaluations, but measures of left ventricular ejection fraction (LVEF) and shortening fraction (SF) were abstracted from the participant's medical chart for any echocardiogram performed within 1 year prior to the baseline visit and within 1 year of the annual study visits.

Glucocorticoid History. Historical and current use of GC therapy was documented at the time of each visit in addition to all medications and supplements used. As the steroid regimen was not specified in this study (thus leading to considerable variation), it was necessary to create 3 exposure groups to allow summary of grouped data of sufficient size. Participants were grouped as either: (1) GC-naive (not treated with GC ever, or treated for <1 month total and not currently receiving GC); (2) current GC treatment; or (3) past GC treatment for ≥1 month, but not currently receiving GC therapy).

Anthropometrics Assessment. We measured weight and ulnar length (in centimeters) in all patients. For patients who could stand without major truncal deviations we also measured standing height. For all patients (ambulatory and non-ambulatory) we also estimated height using a prediction equation based on ulnar length.[22]

Functional Assessments Using Standardized Scales. ***Vignos Lower Extremity Functional Grade and Brooke Upper Extremity Grade.*** Subjects were classified by clinical evaluators according to the Vignos Lower Extremity Functional Grade[32] and the Brooke Upper Extremity Functional Grade.[11] Beginning in 2012, we added the use of lifting weights (200 g, 500 g, and 1000 g), for subjects who score a 1 or 2 on the Brooke Upper Extremity Grade to decrease ceiling effects seen in the more ambulatory subjects.

North Star Ambulatory Assessment. The North Star Ambulatory Assessment (NSAA) is a clinician-rated 17-item functional scale designed for ambulant boys with DMD who are able to stand.[33–37] Although the NSAA was not available when the CINRG DMD-NHS was initiated, it was since validated in other studies and is in use in international clinical trials.[33–37,80–82] The NSAA was added to the study protocol in 2012.

Egen Klassifikation Scale. The Egen Klassifikation Version 2 (EK2) scale was administered to non-ambulatory subjects beginning in 2012. The EK2 scale was developed and validated as a reliable clinical tool to assess functional ability in non-ambulatory patients with DMD.[38,39]

Additional Functional Tests with Timed Dimension. ***Timed Function Tests.*** Clinical evaluators obtained timed function measures, including time to rise from the floor (supine to stand), time to climb 4 steps, and time to run/walk 10 meters, in ambulatory subjects who could perform the tests.[1,11,26] The primary variables from these tests are the velocities in which the tests were performed.

6-Minute Walk Test. We added the DMD-specific modification of the 6-minute walk test (6MWT) based on our experience in validating the measure[40,41] and the subsequent widespread utilization of the measure as a primary endpoint or primary efficacy endpoint in DMD multicenter clinical trials.[15,34,80–85] The primary variable derived from the 6MWT is the 6-minute walk distance (6MWD, in meters). To account for maturational influences we have described the use of age- and height-based percent predicted values for 6MWD.[42] The 6MWT has been chosen by the National Institute of Health (NIH) Toolbox project (www.nihtoolbox.org) as a global measure of ambulatory function and endurance.

9-Hole Peg Test. In 2012, we added the 9-Hole Peg Test (9-HPT). The 9-HPT is a reliable, valid, portable, and rapidly administered test used to measure upper limb function and dexterity.[43] The 9-HPT is sensitive to change in adults with neuromuscular and musculoskeletal disorders,[44,45] and adult and pediatric norms are available.[46] It has been chosen by the NIH Toolbox project as a measure of dexterity, because it is a viable tool for longitudinal epidemiological studies and intervention trials.

Passive Range of Motion Assessment. Passive range of motion (PROM) assesses the extensibility of muscles, tendons, and ligaments through an available ROM. We obtained PROM for knee extension, ankle dorsiflexion, elbow extension, and wrist extension measured to the nearest 5° using standardized goniometry techniques.[11,26,86]

Skeletal Muscle Strength Assessment. *Manual muscle testing.* We performed manual muscle testing (MMT)[1,11,19,26,87,88] to measure strength in all participants who could follow 1-step directions and who were strong enough to perform a 1-person assisted stand–pivot transfer to the examination table, as in the previous natural history studies. Attempts to conduct this assessment began at 4 years of age. If the subject was unable to cooperate, the test was skipped and reintroduced at the next visit. Initially, 34 muscle groups were assessed bilaterally.[1,11,26] Due to the symmetric nature of

Table 2. Participant Characteristics.

Age (Years)	< 4	4–6	7–9	10–12	13–15	16 - 18	> 18	Total
Total	17(5%)	53(16%)	78(23%)	62(18%)	51(15%)	29(9%)	50(15%)	340 (100%)
Glucocorticoid Therapy Status								
GC-Naïve or treated <1 month	13	26	8	6	9	4	16	82 (24%)
Prior GC treatment ≥1 month	0	0	2	9	12	10	15	48 (14%)
Current GC treatment at baseline	4	27	68	47	30	15	19	210 (62%)
Race (NIH Categories)								
White / Caucasian	12	44	51	38	34	25	43	247 (73%)
Black or African American	0	0	1	1	1	1	2	6(2%)
Pacific Islander	0	0	2	1	0	0	0	3 (1%)
Asian	3	6	19	13	9	2	3	55 (16%)
Other	2	3	5	9	7	1	2	29 (8%)
Country of Origin								
Argentina	0	2	1	2	2	3	5	15 (4%)
Australia	3	11	10	1	1	0	3	29 (9%)
Canada	4	7	12	14	14	4	12	67 (20%)
India	3	5	16	11	4	2	0	41 (12%)
Israel	0	3	6	3	2	1	0	15 (4%)
Italy	0	1	1	2	1	1	0	6 (2%)
Sweden	0	8	0	2	3	5	2	20 (6%)
United States / Puerto Rico	7	16	32	27	24	13	28	147 (43%)

the disease and data that showed a high degree of correlation of bilateral measures, the protocol was modified in 2012 so that MMT assessments in ambulant participants were performed unilaterally on the subject's dominant-hand side for 18 muscles (including neck flexors). For non-ambulant participants, we will continue to perform bilateral assessments.

Quantitative muscle testing (QMT). We measured isometric strength of elbow flexors and extensors and knee flexors and extensors using the CINRG Quantitative Measurement System (CQMS).[19–21] Hand-grip measurements were also obtained using the CINRG CQMS system in all participants, regardless of mobility status.

Quantitative tip pinch and key pinch strength. Tip pinch and key pinch strength were added as quantitative measures of distal strength in 2012. Tip pinch grip, which measures thenar strength, is an important functional test to evaluate progression of strength loss and function in older non-ambulatory boys and men with DMD. Thenar strength is required to pick up objects, perform fine motor tasks required for operating a power chair joystick, writing, or holding eating utensils. Key pinch (precision grip) is also frequently used in activities of daily living to manipulate and pick up objects.

Pulmonary Function Assessment. We measured forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow rate (PEFR), peak cough flow, maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP). Pulmonary function tests were not performed in children <6 years of age who were developmentally appropriate and in some participants <7 years of age who were not developmentally able to cooperate with the testing.

Patient-Reported Outcomes (Health-Related Quality of Life Assessment). We measured a battery of PROs (Table 1) assessing health-related quality of life (HRQOL) for study participants and their parents or primary caregiver. Study participants completed age-appropriate measures, including the Pediatric Quality of Life Questionnaire (PedsQL),[47–53] the Pediatric Orthopedic Society of North America Pediatric Musculoskeletal Functional Health Questionnaire (POSNA),[55–59] the Life Satisfaction Index (LSI),[70] the World Health Organization (WHO) QoL-Bref,[71–73] the Medical Outcome Study 36-item Short-Form Health Survey (SF-36),[74] and the modified Pittsburgh Sleep Quality Index (PSQI).[75] Caregivers completed age-appropriate proxy measures for the perceived HRQOL of their child using the PedsQL, POSNA, and PSQI measures. Caregivers completed a self-report concerning their own well-being using the PSQI, the SF-36, and the WHO QoL-Bref. In 2012, the PedsQL Neuromuscular Module (NMM)[60,61] and adult and pediatric NeuroQOL[62–69] were added to the protocol. Four measures (LSI, PSQI, SF-36, and WHO QOL-Bref) were discontinued after a minimum of 3 years of serial data collection, because sufficient longitudinal data had been collected.

RESULTS

Population Characteristics. Between May 2006 and July 2009, we enrolled 340 individuals with DMD, aged 2–28 years, and their primary caregiver(s) at 20 participating study centers (Table 2). Median

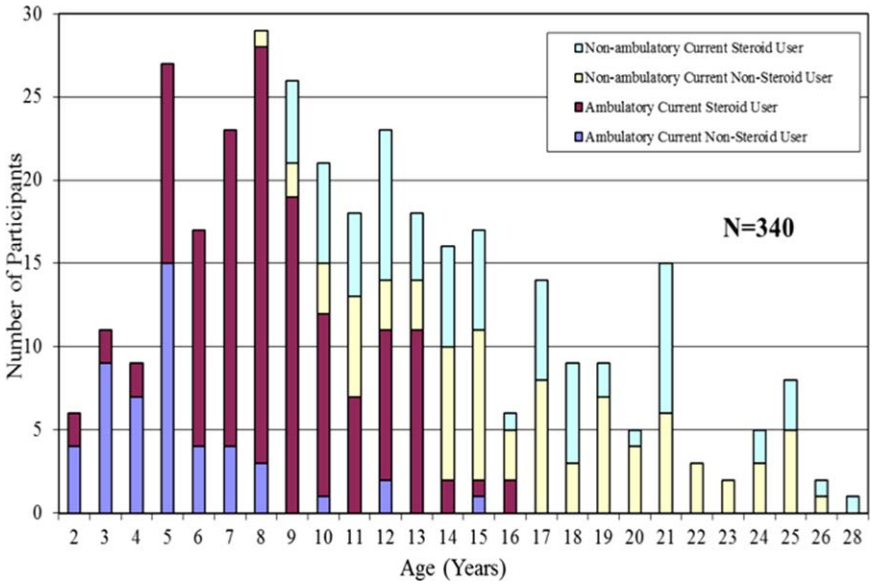

FIGURE 2. Distribution of glucocorticoid treatment by age groups and ambulatory status at study entry. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

site enrollment included 14 participants (3–49 participants per site). At baseline, 210 of 340 (62%) participants were receiving GC therapy, 48 of 340 (14%) were past GC users, and 82 of 340 (24%) were GC-naive. At baseline, 194 of 340 (57%) participants were ambulatory. The number of participants enrolled by age and their GC use is shown in Figure 2.

There were a total of 141 participants with DMD who were $\geq$6 years of age and ambulatory at baseline (an age criterion typically utilized in clinical trials). Among these 141 subjects, there were 23 (16%) who lost ambulation over the first 12 months of the study. For these 23 patients, the age at which ambulation was lost ranged from 7.25 to 17.17 years (mean 10.8 years). From 2006 to 2011, 18 of the 340 DMD patients enrolled in the natural history study died (5%) with the age range of death being 9.9–29.5 years. The oldest patient currently in the study is 32.95 years of age.

DISCUSSION

DMD-NHS Aims Will Address Priorities for DMD Longitudinal Research and More Detailed Characterization of Clinical Trial Outcome Measures across all Stages of DMD. The CINRG DMD-NHS is one of the largest and most comprehensive DMD natural history studies to date and will provide a revised natural history in the era of glucocorticoid therapy. Our first aim is to study the relationship between measures of impairment, activity limitation, participation, and quality of life across a wide age range and spectrum of DMD disease severity using common clinical endpoints employed in clinical trials as well as novel outcome measures. This will provide evidence for the clinical meaningfulness of endpoints by associating changes in endpoints with patient-reported outcomes. The second aim (study the natural history of changes in measures of impairment, activity limitation, and quality of life over periods of 12 months to >5 years of follow-up) will provide prospective data collected in a similar manner to therapeutic trials to inform clinical trial design, inclusion criteria, and sample size calculations. The third aim (examine the associations between both disease characteristics and the use of interventions and the onset of life-altering clinical milestones that are due to the progression of disease) will help define clinically meaningful, functional milestones associated with progression of disease. The fourth aim (assess the incidence of secondary conditions of DMD and the relative risks of developing those conditions based on exposure to standard treatments, such as glucocorticoids, and preventive interventions recommended by the CDC Care Considerations[3,4]) will provide data that can be used to develop, evaluate, and improve clinical practice guidelines.

Longitudinal DMD research and more detailed characterization of clinical trial outcome measures across all stages of DMD were identified as a high priority by the NIH and U.S. Centers for Disease Control and Prevention and by the European Union TREAT–NMD collaboration. The NIH-led Muscular Dystrophy Coordinating Committee (MDCC) called for additional research to assess the prevalence and natural history of secondary conditions in muscular dystrophy using existing longitudinal study efforts, and to assess the effectiveness of clinical management approaches to prevent and treat secondary conditions using clinically meaningful outcomes.[89]

Conceptual Framework and Comparison of DMD-NHS with other Natural History Studies. The first aim of the DMD-NHS is to study the relationship between measures of impairment, activity limitation, participation, and quality of life across a wide age range and spectrum of DMD disease severity. This aim utilizes a conceptual framework grounded in the biopsychosocial conceptual model of health, function, and quality of life using the World Health Organization International Classification of Functioning, Disability, and Health (ICF).[17] The ICF model includes 4 major domains consisting of body structures, body functions, activities and participation, and environmental factors. It acknowledges reciprocal interactions between domains from the individual genetic and cell function level on up through and including interaction of the individual with his or her environment over time. Body structure items assessed in our study include musculoskeletal, cardiovascular, respiratory, and skin and integumentary systems. Body function items include musculoskeletal movement–related and cardiovascular functions, such as strength, pulmonary function testing, timed motor performance, upper and lower extremity function, and functional activities of daily living, pain, fatigue, and sleep. Activity and participation items include basic topics such as mobility and transfers, ambulatory ability, sports and exercise participation, emotional health, social health, communication, life satisfaction, depression, anxiety, and stigma. Environmental factors assessed in our study are somewhat limited but include items such as family demographics and resources, education and health services utilization, life events, and home and community-built environment. Appendix 3 summarizes the diverse outcome measures that have been used in other natural history studies of persons with DMD organized according this modified ICF framework. Our choice of clinical endpoints and a broad array of PRO measures allow a unique opportunity to develop evidence as to the clinical meaningfulness of endpoints by associating changes in endpoints with PROs.

Significance for Biotechnology and Drug Development: Natural History Data for Novel, Responsive, and Clinically Meaningful Endpoints. Tremendous advances have occurred since the discovery of the dystrophin gene and characterization of the dystrophin protein.[90–93] Although promising therapeutic targets have emerged for muscular dystrophies, significant barriers to the development of clinical trials remain.[94,95] Federally mandated NIH scientific advisory committees and expert panels assembled by consumer organizations have identified crucial deficiencies in the design and conduct of translational clinical trials. These include lack of a detailed understanding of the characteristics and natural history of specific neuromuscular diseases, lack of objective clinical outcome measures that are sensitive to changes in disease course, and lack of data that link changes in clinical outcome measures to patient-perceived well-being.[94–96] In August 2005, the NIH-led MDCC identified research priorities for muscular dystrophies that included: (1) natural history studies; (2) determination of the sensitivity of clinical endpoints to changes in disease severity; (3) determination of the magnitude of changes in endpoints that are clinically meaningful to patients; (4) study of the interrelationship of clinical endpoints for specific muscular dystrophies; (5) development of standardized data collection tools and minimum study data sets; and (6) identification and development of standardized instruments to measure quality of life.[89] Our first 3 study aims address these important needs for therapeutic trials.

Consumers, clinical researchers, the FDA, and industry have increasingly recognized the importance of PRO measures in the determination of clinically meaningful outcomes and validation of endpoints that can be used in therapeutic trials.[97,98] Regulatory requirements mandate that registration studies incorporate primary endpoints for the measurement of objective, clinically meaningful, "life-changing" events with significant impact on health and well-being. In addition, the FDA has recommended inclusion of PRO measures as an endpoint in clinical trials.[97] The CINRG DMD-NHS includes a broad array of PROs across the lifespan that encompass both patient self-perceived and caregiver/proxy-perceived health and well-being. The sensitivity of these measures to treatment effects in patients with DMD remains to be determined.

Prior Natural History Studies in DMD Were Conducted Prior to Widespread Use of Glucocorticoids, and There Is a Need for Greater Focus across the Spectrum of Disease. The first large, multicenter study of DMD natural history by the Clinical Investigation in Duchenne Dystrophy (CIDD) group in the 1980s was undertaken prior to the discovery of the dystrophin gene. This DMD cohort comprised 283 boys from early childhood to the early twenties (average age 3.5 years at enrollment). Strength and function were measured longitudinally for up to 10 years. From this data, MMT sample size calculations could be performed and natural history control methods were developed for clinical trials.[1,11,12,87,88] With that foundation, the group conducted the first comprehensive series of multicenter clinical trials in DMD, establishing the modified MRC MMT as the standard method of strength evaluation for DMD clinical

trials and influencing the design of nearly every DMD clinical trial conducted since that time.

Simultaneously, between 1982 and 1992, investigators from the University of California Davis [including the principal investigator (PI) of this study] prospectively followed a cohort of 162 boys and young adults with DMD in a comprehensive single-center observational study.[13,26] The study PI and colleagues produced a profile of DMD[13] that provided data on anthropometrics, goniometry, strength, cardiac, and respiratory function consistent with the CIDD reports and further added comparisons with healthy age-matched controls using quantitative isometric and isokinetic strength testing, measures of intelligence, school achievement, psychosocial adjustment, and neuropsychological performance. The study also provided data on young adults into their mid-twenties and showed that overall MMT score and individual muscle component scores declined at differing slopes that depended on muscle group tested and participant age.[13] This highlighted the concept that some measures in DMD might be more or less appropriate for short-term clinical trials at specific ages or stages of disease.

The CIDD group demonstrated efficacy of prednisone with a series of clinical trials beginning in 1987.[99–105] Over the next 15 years, GC therapy gradually became the standard of care for boys with DMD, with a profound effect on disease course. Despite those findings, and American Academy of Neurology Practice Parameters,[8] Cochrane Reviews,[9] and CDC-sponsored care considerations,[3,4] which provide strong recommendations concerning the early administration of GC, the utilization of GC therapy has not been universal due to concerns regarding side effects.[10]

Need to Focus on Natural History of Individuals with DMD Who Are Non-Ambulatory. Few studies of GC use in DMD have focused on non-ambulatory or older patients or clinical endpoints, such as pulmonary function,[105–108] upper limb function,[107,108] and spine deformity.[107–110] Our study presents a unique opportunity to evaluate the long-term impact of years or even decades of GC use and to evaluate clinical effectiveness of GC *vis à vis* varying durations of exposure and the impact of discontinuing GC therapy in a non-ambulatory population. In addition, many of the broad multidisciplinary CDC care considerations, such as pulmonary or cardiac care, focus on management strategies important to the population of individuals with DMD who have transitioned to the wheelchair or who are approaching and entering adulthood. The DMD-NHS will provide data that can be used to plan trials for these individuals and develop, evaluate, and improve clinical practice guidelines across the spectrum of disease.

Limitations of the Study. ***Inherent Imprecision in Diagnosis and Prediction of Phenotype.*** The focus of the CINRG DMD-NHS is on patients with dystrophin deficiency clinically diagnosed as DMD. Therefore, the study does not include the entire spectrum of dystrophinopathy. We attempted to include patients who would typically be included in clinical trials of DMD. There is an inherent limitation that patients destined to have milder disease progression might be included in the study, but this is a common limitation of any clinical trial in ambulatory DMD. Despite our best efforts to include a relatively homogeneous population with regard to disease severity, it is possible that we enrolled younger patients who will show milder progression regardless of their GC therapy status. This limitation is inherent in the current imprecision of the prediction of clinical course in dystrophinopathy patients.

The DMD-NHS study is similar in many regards to challenges inherent in all DMD clinical trials that enroll younger ambulatory patients. Most clinical trials in dystrophinopathy have historically targeted patients on the more severe end of the spectrum and labeled by clinicians as "DMD." However, enrollment of young dystrophinopathy patients results in inclusion of patients with milder severity who may improve due to growth and maturational changes or who continue for long periods in a stable "plateau" phase. This presents a challenge when powering a trial to demonstrate a treatment effect. Our study cohort represents a wide spectrum of disease severity and will inform future studies to include design aspects such as stratification by disease severity (even within anbulatory patients) to have different progression expectations for different strata. For example, a study group may expect a novel therapeutic to decrease the rate of decline in older patients, and to increase strength in younger patients. We also have continued to retain patients even if they continue to ambulate past accepted clinical ranges for DMD. *Post hoc* exclusion of such patients would not be acceptable to the FDA in the context of a prospective, randomized, double-blind clinical trial.

Biases Created by Clinical Evaluation Protocols. Some of our decisions regarding safe, appropriate, and feasible use of outcome measures truncated our data ranges to specific age- or function-related groups despite the fact that some individuals may have been able to produce measurable results. For instance, our initial decision to limit manual and quantitative strength testing (except for hand grip) to boys who were able to safely complete a 1-person assisted stand–pivot transfer creates a floor effect for those measures beyond which we could have possibly gathered more data. To address this issue we changed the protocol to define that all testing follows standardized positioning in sitting,

supine, and prone positions based on muscle strength. Thus, for participants who are unable to perform MMT in the standardized supine positions due to muscle weakness and transfer safety, MMT is now assessed in an alternative sitting position.

Our decision to not enroll patients who were ambulating past age 16 years while on glucococorticoids could conceivably eliminate a small percentage of outlier or intermediate DMD patients who at study initiation ambulate beyond 16 years of age. However, in reality, most ambulatory DMD trials actually enroll very small numbers of such patients in an effort to avoid enrolling Becker muscular dystrophy patients who do not decline much over 12 months. As a case in point, only 2 of 174 patients enrolled in the PTC Therapeutics Ataluren Trial, which focused on severe dystrophinopathy (including both Duchenne and Becker muscular dystrophy), were ambulatory at study entry at beyond 16 years of age.[83] Thus, our inclusion criteria, although perhaps not inclusive of every outlier patient on GC who may have stable function near adulthood, is nonetheless consistent with the typical criteria employed in most ambulatory DMD trials.

Racial/Ethnic and Geographic Composition of Study Cohort. It is common, even in the case of multinational observational studies, to accrue a study cohort whose racial and ethnic profile is not completely reflective of the overall affected population. Here we established a network with a high degree of geographic variability to enroll participants who closely mirror the populations surrounding participating centers. Despite inclusion of centers on nearly all continents, we still lack an appreciable population of individuals of African descent. Reasons for this remain unclear, but may include environmental factors, such as lack of access to clinics; social factors, such as lower willingness to participate in clinical research; or biological factors, such as true differences in disease prevalence rates.

This study represents the first large natural history study in DMD since GC treatment has become accepted as standard therapy by most clinicians. The study is prospective, geographically varied, and comprehensive, using data from both well-validated and newer measures of strength, function, and HRQOL. Careful documentation of all aspects of the disease process at different ages and stages of severity is essential to the design and interpretation of future therapeutic trials. Future descriptions of this cohort will provide data on the magnitude of change and variability of strength and function over time that will facilitate informed study design features and sample size calculations for trials in different ages and functional groups (including subgroups among ambulatory and non-ambulatory subjects). Our longitudinal data will also provide expanded information on risks and benefits associated with GC treatment and critical information about associations between body structure and body function impairments, activity limitations, medical outcomes, clinically meaningful events or milestones, and PROs such as HRQOL that will inform design of future intervention studies and evaluation of clinical practice guidelines.

APPENDIX: 1

ORGANIZATIONAL STRUCTURE FOR THE COOPERATIVE INTERNATIONAL NEUROMUSCULAR RESEARCH GROUP (CINRG)

The Cooperative International Neuromuscular Research Group (CINRG) is organized into an elected Executive Committee, a CINRG Coordinating Center, an external Scientific Advisory Committee, a Therapeutics Subcommittee, an Outcome Measures Subcommittee, and a Publication Subcommittee. There is also an elected Medical Director, a Scientific Director, and a Coordinating Center Director. The CINRG Coordinating Center, located at the Children's National Medical Center, provides operational management, data management, and statistical support for all studies.

APPENDIX: 2

Clinical endpoints used in the CINRG Duchenne Natural History Study.

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
Molecular diagnostics	Specific description and extent of deletions, duplications, point mutations, and stop codon mutations in the dystrophin gene; genetic polymorphisms associated with rate of disease progression.	+ All	Chart review	2006–present

APPENDIX 2. *Continued*

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
Dystrophin analysis by muscle biopsy (immuno-histochemistry)	Percentage of muscle fibers seen in cross-section in a high-powered view (obtained from an open muscle biopsy) that show positive dystrophin by immunohistochemistry.	+	Chart review	2006–present
Health status/review of systems medications, clinical complications	Available upon request (chart review items below are included in this assessent).	+	15 min	2006–present
Glucocorticoid history	Includes the specific GC being administered (e.g., prednisone, prednisolone, deflazacort, etc.), the target dose, actual current GC dose (in mg/kg and frequency), total duration of therapy, side effects experienced, and reason for discontinuation (if patient was previously on GC).	+	5 min	2006–present
Anthropometric measures (standing height, weight, ulnar lenth, tibial length, skinfolds)	Standing height is measured in centimeters (cm) using calibrated stadiometers for participants who could stand unassisted with heels touching the floor. Ulnar length is measured in millimeters in all participants from the distal tip of the styloid process to the tip of the olecranon using the Rosscraft segmometer (Rosscraft Innovations, Inc.), and that measurement is used to estimate standing height using the formula described by Gauld *et al*.[22] Weight is assessed in kilograms and grams (kg or g) or pounds and ounces (lbs or oz) using calibrated scales. Participants are weighed out of their wheelchair if they can stand unassisted. Non-ambulatory participants are weighed in their wheelchairs. Wheelchairs are weighed separately and subtracted from the total weight of wheelchair plus participant to arrive at the participant weight.	+ All	5 min	2006–present
Vital signs	Heart rate, respiratory rate, and blood pressure.	+ All	2 min	2006–present
Body composition (DEXA)	As described in Skalsky *et al*.[23]	+ All	Chart review	2006–present
Body composition (bioelectrical impedance)	As described in McDonald *et al*.[24]	+ All	Chart review	2006–present
Bone health (DEXA)	As described by Escolar *et al*.[25]	+ All	Chart review	2006–present
Passive range of motion (goniometry)[11,26]	Knee and elbow extension ranges are from 20 to −150 degrees. Ankle dorsiflexion range is from 20 to −80 degrees, with 0 degree considered full passive range of motion. Wrist extension range with fingers extended is from 100 to −90 degrees, with 90 degrees considered full range of motion.	+ All	5 min	2006–present

APPENDIX 2. *Continued*

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
Spine deformity evaluation	Includes clinical assessment of severity and radiographic assessment with Cobb angle.	+ All	Clinical exam and chart review	2006–present
Strength: quantitative grip strength	Hand-grip measurements are obtained using the CINRG CQMS system described by Escolar *et al*.[19] and Mayhew et al.[21] It has been chosen by the NIH Toolbox project (www.nihtoolbox.org).	+ All	2 min (unilateral)	2006–present
Strength: quantitative tip pinch and key pinch strength	Tip and key pinch are assessed using a hydraulic pinch gauge (Jamar Industries).	+ All	2 min (unilateral)	2012–present
Strength: isometric strength with fixed devices	Isometric strength of elbow flexors and extensors, and knee flexors and extensors are measured using the CINRG quantitative measurement system (CQMS) as described by Escolar *et al*.[19] and Mayhew *et al*.[21] Quantitative lower extremity strength measures have been chosen by the NIH Toolbox project (www.nihtoolbox.org) as measures of strength.	+ Amb	10 min (unilateral)	2006–present
Strength: manual muscle testing (or MRC%)	The manual muscle test (MMT) measurements are based on an 11-point ordinal scale modified from the Medical Research Council (MRC) scale with identical measurements employed employed by the CIDD natural history studies and clinical trials as described by Brooke *et al*.[1,11] and Fowler *et al*.[26] All testing follows standardized positioning in sitting, supine, and prone based on muscle strength. For participants who are unable to perform MMT in the standardized positions due to muscle weakness, MMT is assessed in gravity-eliminated alternative positions. Levels are: 5—Normal strength. 5^{-}—Barely detectable weakness. 4^{+}—Muscle is weak, but moves the joint against a combination of gravity and moderate–maximum resistance. 4—Muscle is weak, but moves the joint against a combination of gravity and moderate resistance. 4^{-}—Muscle is weak, but moves the joint against a combination of gravity and minimal resistance. 3^{+}—Joint is moved against gravity and a small amount of resistance. Muscle is capable of transient resistance, but collapses abruptly. Not to be used for muscle capable of sustained resistance throughout the whole range of motion. 3—Joint is moved through the full available range of motion against gravity but cannot accept resistance.	+ All	10 min	2006–2012 (Amb; bilateral) 2012–present (All; unilateral)

APPENDIX 2. *Continued*

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	3⁻—Joint is moved against gravity but not through the full available range of motion. 2—Joint is moved when the effects of gravity or minimized with a position change. 1—A flicker of activity is seen or palpated in the muscle. 0-No palpable muscle activity.			
Pulmonary fuction tests: FVC, FEV_1, PEFR, peak cough flow, MIP, MEP	We measured forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and peak expiratory flow rate (PEFR) using a KoKo spirometer and digidoser (nSpire Health, Inc.) and interpreted the pulmonary function data using the Crapo and Polgar normative reference set for 6–7-year-old participants or the Hankinson normative reference set for ≥8-year-old participants.[27–29] We measured maximal inspiratory pressure (MIP) and maximal expiratory pressure (MEP) using a Dwyer pressure gauge and ventilated T-tube assembly. Interpretations of MIP and MEP values were based on Wilson *et al*.[30] and Domenech-Clar *et al*.[31] normative pediatric reference sets. Participants were evaluated in a seated position with support for the back and feet. Participants wore nose clips or had their noses held closed by hand during testing. If necessary, cardboard mouthpiece adapters were used to enable participants to make a full lip seal.	+ All	15 min	2006–present
Cardiac: electrocardiography	Standard 12-lead electrocardiogram.	± All	Chart review	2006–present
Cardiac: echocardiography	Chart abstraction of fractional shortening (SF) and left ventricular ejection fraction (LVEF).	± All	Chart review	2006–present
Cardiac: Holter monitoring	Chart abstraction of 12–24-h Holter monitoring.	± All	Chart review	2006–present

Activities (clinical evaluator determined scales)	Description of measures	Standard protocol? Amb	Time required	Chronology
Vignos Lower Extremity Functional Grade[32]	1—Walks and climbs stairs without assistance. 2—Walks and climbs stairs with the aid of a railing. 3—Walks and climbs stairs slowly with the aid of a railing. (over 12 s for 4 standard stairs). 4—Walks unassisted and rises from chair but cannot climb stairs. 5—Walks unassisted but cannot rise from chair or climb stairs. 6—Walks only with the assistance or walks independently with long leg braces. 7—Walks in long leg braces but requires assistance for balance. 8—Stands in long leg braces but unable to walk even with assistance.	+ All	2 min	2006–present

APPENDIX 2. *Continued*

Activities (clinical evaluator determined scales)	Description of measures	Standard protocol? Amb	Time required	Chronology
	9—Is in a wheelchair. 10—Is confined to bed.			
Brooke Upper Extremity Functional Grade[11] (*note*: beginning in 2012, we added the use of lifting weights (200 g, 500 g, 1000 g), for subjects who score a 1 or 2 on the Brooke Upper Extremity Grade to decrease ceiling effects seen in the more ambulatory subjects	1—Starting with arms at the sides, the patient can abduct the arms in a full circle until they touch above the head. 2—Can raise arms above the head only by flexing the elbow (i.e., shortening the circumference of the movement) or using accessory muscles. 3—Cannot raise hands above head but can raise an 8-oz glass of water to mouth using both hands if necessary. 4—Can raise hands to mouth but cannot raise an 8-oz glass of water to mouth. 5—Cannot raise hands to mouth but can use hands to hold pen or pick up pennies from the table. 6—Cannot raise hands to mouth and has no useful function of hands. As an optional measure if the patient has a Brooke grade of 1 or 2 measured by the therapist, it is determined how many kilograms of weight can be placed on a shelf above eye level, using 1 hand.	+ All	2 min	2006–present
North Star Ambulatory Assessment (NSAA)[33–37]	NSAA assesses functional activities including standing, getting up from the floor, negotiating steps, hopping, and running. The assessment is based on a 3-point rating scale of 2 = ability to perform the test normally, 1 = modified method or assistance to perform test, and 0 = unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 (no impairment on these assessments).	+ Amb	15 min	2012–present
Egen Klassification Scale Version 2 (EK2 Scale)[38,39]	The EK scale includes assessments comprised of functional ability measuring upper extremity grade, muscle strength measured with the manual muscle test, and forced vital capacity defined as a percentage of normal values (FVC%). The construct is based on the interaction of physical components such as muscle strength, range of motion, respiratory status, wheelchair dependence, and age. The EK2 scale assesses ten functional categories (EK 1–10), each on a scale of 0 = normal to 3 = very impaired, contributing to an overall function score of 0 to 30.	+ Non-Amb	10 min	2012–present

Activities (functional tests with timed dimension)	Description of measures	Standard protocol? Amb/non-amb	Time required	Chronology
Time to rise from the floor (supine to stand)[1,11,26]	For standing from supine the velocity was calculated as 1 divided by the time to complete the task. Subjects are given 60 seconds to complete the task. A subject who is unable to complete the task is given a score of 99 and a velocity of zero.	+ Amb	2 min	2006–present
Time to climb 4 steps[1,11,26]	The time to climb 4 standard assessment is performed in children age 2 years and older. For the total task of climbing 4 standard stairs, velocity was calculated as 1 divided by the time to complete the task. Subjects are given 60 seconds to complete the task. A subject who is unable to complete the task is given a score of 99 and a velocity of zero.	+ Amb	2 min	2006–present

APPENDIX 2. *Continued*

Activities (functional tests with timed dimension)	Description of measures	Standard protocol? Amb/non-amb	Time required	Chronology
Time to walk/run 10 m or 30 ft[1,11,26]	Time to walk/run 10-m assessment is performed in children age 2 and older. Timed function test velocities were calculated as distance divided by completion time. Velocity for the 10-m walk/run test was determined by dividing distance (10 m) by the time to complete the task (in seconds). Subjects are given 60 seconds to complete the task. A subject who is unable to complete the task is given a score of 99 and a velocity of zero.	+ Amb	2 min	2006–present
6-minute walk test[40–42]	The 6MWT has been modified specifically for DMD[40,41] by utilizing standard video instructions, a safety chaser to assist the subject up in the event of a fall, and constant rather than intermittent encouragement. Subjects walk around 2 cones placed 25 m apart. The 6MWT is attempted in all participants who can be expected to walk at least 75 m. A subject who is unable to ambulate 10 m on a 10-m walk/run test is given a "0" value for the 6MWT and defined as "non-ambulatory." For the DMD subjects we also measure the number of steps taken in the first 50 m with a visual count. This allows the calculation of average stride length.	+ Amb	15 min	2012–present
9-Hole Peg Test[43–46]	The 9-HPT is a measure of upper limb function and dexterity, which records the time to pick up 9 pegs from a container, put them into the holes, and then return them to the container. The primary variable derived from the 9-HPT is completion time in seconds.	+All	10 min	2012–present
Patient-reported outcome measures (PROs): Health-related Quality of Life; Participation; Satisfaction	**Description of measures**	**Standard Protocol? Amb/Non-Amb**	**Time Required**	**Chronology**
Pediatric Quality of Life Questionnaire (PedsQL™) Generic Core Scale[47–53] (Distributor)	The Pediatric Quality of Life Inventory (PedsQL™) was designed by Varni and colleagues[47–53] to measure the core dimensions of health-related quality of life as delineated by the World Health Organization. Dimensions include physical function, social function, emotional function, and school functioning. The PedsQL Generic Core Scales include child self-report for ages 5–18, parent proxy report for ages 2–18, and young adults aged 18–25 years.[47–53] A strength of the PedsQL Generic Scales is that normative data exists on approximately 14,000 ethnically diverse children and adolescents who are typically developing and healthy and it has been used extensively for children with chronic health conditions. In DMD, the physical function domain of the PedsQL has been shown to be significantly associated with disease progression and traditional clinical outcome measures employed in ambulatory clinical trials.[54]	+ All	5 min	2006–present
POSNA Pediatric Musculoskeletal Functional Health Questionnaire/Pediatric Outcomes Data	This POSNA instrument was developed by Daltroy and colleagues with support by the Pediatric Orthopedic Society of North America (POSNA).[55] The POSNA is a 108-item questionnaire that evaluates global functioning in the pediatric orthopedic population utilizing 4 components:	+ All	15 min	2006–present

APPENDIX 2. *Continued*

Patient-reported outcome measures (PROs): Health-related Quality of Life; Participation; Satisfaction	Description of measures	Standard Protocol? Amb/Non-Amb	Time Required	Chronology
Collection Instrument (PODCI).[55–59]	upper extremity functioning; transfers and basic mobility; sports and physical functioning; and a comfort/pain score. Global functioning is assessed by the average of the 4 previous scores. All scales are scored from zero to 100, with 100 representing the highest level of functioning and least pain. The POSNA asks questions such as "During the last week, was it easy or hard for you to …lift heavy books." Both parent proxy and adolescent self-report forms have been validated. This is a self-administered questionnaire which takes about 15–20 minutes to complete. In DMD, the PODCI transfers/basic mobility and sports/physical function domain scores are significantly associated with age (and hence disease progression) and traditional clinical outcome measures employed in ambulatory clinical trials.[54]			
PedsQL Neuromuscular Module[60,61]	The 25-item PedsQL 3.0 Neuromuscular Disease Module (NMM) is a disease-specific HRQOL measure encompassing 3 scales: (1) "About My/My Child's Neuromuscular Disease" (17 items related to the disease process and associated symptomatology); (2) "Communication" (3 items related to the patient's ability to communicate with health-care providers and others about his/her illness); and (3) "About Our Family Resources" (5 items related to family financial and social support systems). The parent proxy report includes ages 2–4 (toddler), 5–7 (young child), 8–12 (child), and 13–18 (adolescent), and assesses parent's perceptions of the child's HRQOL. The instructions ask how much of a problem each item has been during the past 1 month. A 5-point response scale is utilized across child self-report for ages 8–18 and parent proxy-report (0 = never a problem; 1 = almost never a problem; 2 = sometimes a problem; 3 = often a problem; 4 = almost always a problem). Items are linearly transformed to a 0–100 scale (0 = 100, 1 = 75, 2 = 50, 3 = 25, and 4 = 0), so that high scores indicate better HRQOL. Scale scores are computed as the sum of the items divided by the number of items that were answered. The NMM total score has shown internal consistency reliability and test–retest reliability for children with DMD and caregivers, and concurrent validity of the NMM total score for children and caregivers in comparison to the PedsQLTM generic total score and forced vital capacity.[61]	+ All	10 min	2012–present
NeuroQoL Patient-Reported Quality of Life[62–69]	Neuro-QOL (www.neuroquol.org) is an NIH-funded instrument that assesses health-related quality of life (HRQOL) in adults and children with a variety of neurological disorders. The Neuro-QOL provides assessments of person-reported outcomes (PROs) of social, psychological, and mental well-being as they impact function. the	+ All	15 min (short forms)	2012–present

APPENDIX 2. *Continued*

Patient-reported outcome measures (PROs): Health-related Quality of Life; Participation; Satisfaction	Description of measures	Standard Protocol? Amb/Non-Amb	Time Required	Chronology
	areas of focus are pain, fatigue, emotional distress, physical function, and social function. The individual Likert-scale item responses are compared with population response frequencies using item response theory and yield a *z*-score for each response and a standard score with mean of 50 and standard deviation of 10. These evaluations are completed by parent proxies for all DMD participants aged 6 years and older and by DMD children aged 10 years and older.[69]			
Life Satisfaction Scale (Life Satisfaction Scale for Adolescents)[70]	The Life Satisfaction Index for Adolescents[70] consists of 5 domains: general well being; interpersonal relationships; personal development, personal fulfillment, and leisure and recreation. Each item is ranked on a 5-point rating scale. Domain scores and a total score are derived. The Life Satisfaction Index was collected in teens (ages 11–17) with DMD and in adults with DMD at every visit.	+ NonAmb	10 min	2006–2012
WHO Quality of Life-Bref[71–73]	The World Health Organization Quality of Life Assessment-Bref (WHO QOL Group, Geneva)[71–73] has been widely used to assess adult individuals perceptions of their quality of life with respect to culture, values, goals, standards, and concerns. The 26-item assessment covers major domains of physical health, psychological health, social relationships, and environment. This is a self-administered questionnaire administered both to adults with DMD (18 years and older) as well as to all adult primary caregivers.	+ NonAmb all adults	10 min	2006–2012
Medical Outcomes Study (MOS) 36-item Short Form (SF-36)[74]	The SF-36[74] was used as a measure of health-related quality of life (HRQOL) for adult DMD study participants and their parents or primary caregivers. This instrument has been widely used to assess HRQOL and to facilitate group comparisons involving age-, disease-, or treatment-specific generic health concepts in adults and youths 14 and older. Adult DMD subjects and their parents' quality of life is assessed with the SF-36 at every visit.	+ NonAmb	10 min	2006–2012
Pittsburgh Sleep Quality Index[75]	The DMD Sleep Quality Index is an adaptation of the Pittsburgh Sleep Quality Index (PSQI).[75] The PSQI is self rated and assesses sleep quality over the preceding 1 month. Major domains include subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of medication and daytime dysfunction. The DMD-related modification incorporates items associated with common DMD-related orthopedic and respiratory complications that are thought to impact sleep in affected individuals. The PSQI with DMD modifications was collected at every visit in DMD patients ages 11–17 years, adults with DMD, and in parents/guardians.	+ All	5 min	2006–2012
Total time (complete assessment)			216 min	

+ standard protocol; +, administered to all; ±, physician's discretion; Amb, ambulatory.

APPENDIX: 3

Clinical endpoints used in Duchenne muscular dystrophy prospective natural history studies. [Color table can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

Body structure/function	CINRG	CIDD	UC Davis	UDP	Shriners	MDA non-Amb	MDA infant	MDA cardiac	North Star UK	North Star Italy	MFM France	Danish	MRI U.S.
Molecular diagnostics	+			+	±	+	+	+	+	+		+	+
Dystrophin analysis by muscle biopsy (immunohistochemistry)	±			±	±	±	±	±	±	±		±	±
Health status/review of systems, medications, clinical complications	+		+	+	+			+	+		+	+	+
Anthropometric measures (standing height, weight, ulnar lenth, tibial length, skinfolds)	+	+	+	+	+	+	+	+	+				+
Vital signs	+	+	+	+	+	+	+	+	+				
Body composition (DEXA)	±			±									
Body composition (bioelectrical impedance)	±			±									
Magnetic resonance imaging, magnetic resonance spectroscopy (muscle)													+
Ultrasound imaging (muscle)						±	±						
Bone health (DEXA)	±			±					±				
Passive range of motion (goniometry)	+	+	+	+	+	+			+			+	+
Spine deformity evaluation	+	+	+	+								+	
Strength: quantitative grip strength	+	+	+	+	+	+							
Strength: quantitative tip pinch and key pinch strength	+					+							
Strength: isometric strength with hand-held devices				+		+							+
Strength: isometric strength with fixed devices	+		+		+								
Strength: isokinetic strength with fixed devices			+		+								
Strength: manual muscle testing (or MRC%)	+	+	+	+		+			+			+	+
Pulmonary function tests: FVC, FEV_1, PEFR, peak cough flow, MIP, MEP	+	+	+	+	+	+			+			+	
Cardiac: electrocardiography	+		+	±				+	±				
Cardiac: echocardiography	±			±				+	±				
Cardiac: Holter monitoring	±							+					
Cardiac: MR imaging													
Cognitive and neuropsychological testing			+	±									
Vignos Lower Extremity Functional Grade	+	+	+	+	+				+				
Brooke Upper Extremity Functional Grade	+	+	+	+	+	+			+				
North Star Ambulatory Assessment (NSAA)	+						+		+				
French Motor Function Measure (MFM)											+		
Bayley Scales of Infant Development							+						
Hammersmith Functional Motor Scale							+					+	
Modified Hammersmith Functional Motor Scale (extended)													
Gross Motor Function Measure (GMFM)					+								
Egen Klassification Scale Version 2 (EK2)	+					+						+	
Time to rise from the floor (supine to stand)	+	+	+	+	+				+	+		+	+
Time to climb 4 steps	+	+	+	+	+							+	+
Time to walk or run 10 m or 30 ft	+	+	+	+	+				+	+		+	+
Time to stand from a chair		+	+		+								
Tine to propel a manual wheelchair 10 m or 30 ft			+										
Time to put on a t-shirt		+	+										
Time to cut out a 4-inch square		+	+										
6-minute walk test	+									+			+
10-minute walk test with energy expenditure using COSMED $K4B^2$					+								

APPENDIX 3. *Continued*

Body structure/function	CINRG	CIDD	UC Davis	UDP	Shriners	MDA non-Amb	MDA infant	MDA cardiac	North Star UK	North Star Italy	MFM France	Danish	MRI U.S.
Gait kinematics, kinetics with time–distance parameters					+								+
Stepwatch step activity monitoring					+								
ActiCal													+
9-Hole Peg Test	+					+							
Jebsen Taylor Hand Function Test						+							
Patient-reported outcome measures (PROs)													
Pediatric Quality of Life Questionnaire (PedsQL) Generic Core Scale (distributor)	+				+								+
POSNA pediatric musculoskeletal functional health questionnaire/Pediatric Outcomes Data Collection Instrument (PODCI)	+				+								
PedsQL Neuromuscular Module	+												
NeuroQoL Patient-Reported Quality of Life	+												
Life Satisfaction Scale (Life Satisfaction Scale for Adolescents)	+												
Individualized Neuromuscular QoL (InQoL)						+							
Child Behavioral Checklist (ASEBA)					+								
Canadian Occupational Performance Measure (COPM)													
Caregiver Burden Scale						+	+						
WHO Quality of Life-Bref	+												
SF-36	+												
Pittsburgh Sleep Quality Index	+												

Key: +, assessment included on all patients evaluated; ±, assessment included if clinician obtained as a clinically indicated test. Non-entry indicates assessment not included as part of protocol. ICF framework adapted from the National Institutes of Health NINDS Common Data Elements for Pediatric Neuromuscular Diseases (www.commondataelements.ninds.nih.gov/). DEXA, dual-energy X-ray absorptiometry; WHO World Health Organization. ***CINRG****: Cooperative International Neuromuscular Research Group Duchenne Natural History Study [C. McDonald (PI); 22 CINRG centers; see Acknowledgments]. CIDD: Clinical Investigation in Duchenne Dystrophy.*[1,10,29,87,88] ***UC Davis:*** *UC Davis Duchenne Natural History Study (C. McDonald, R.T. Abresch, G.T. Carter. W.M. Fowler Jr., E.R. Johnson, D.D. Kilmer, B.J. Sigford, UC Davis, Sacramento, California).*[13] ***UDP****: United Dystrophinopathy Project [K.M. Flanigan (PI); K.J. Swoboda, University of Utah, Salt Lake City, Utah; K.M. Flanigan, J.R. Mendell, Nationwide Medical Center, Columbus, Ohio; A. Pestronk, J.M. Florence, Washington University, St. Louis, Missouri; K.D. Mathews, University of Iowa, Iowa City, Iowa; Richard S. Finkel, Children's Hospital/University of Pennsylvania, Philadelphia, Pennsylvania; B. Wong, Cincinnati Children's Hospital, Cincinnati, Ohio; J.W. Day, University of Minnesota, Minneapolis, Minnesota; C.M. McDonald, University of California Davis, Sacramento, California].*[14] ***Shriners:*** *M. Shriners Hospital for Children Biomechanical Analysis of Gait in Individuals with Duchenne Muscular Dystrophy [M. Sussman (PI); Shriners Hospital for Children, Portland, Oregon; C. McDonald, Shriners Hospital for Children of Northern California, Sacramento, California; E. Fowler, UCLA, Los Angeles, California].*[54] ***MDA non-Amb:*** *Muscular Dystrophy Association Duchenne Muscular Dystrophy Clinical Research Network: Clinical Outcome Validation in Non-ambulatory Boys/Men with Duchenne Muscular Dystrophy (DMD) [A. Connolly (PI), J.M. Forence, Washington University, St. Louis, Missouri; J.R. Mendell, K.M. Flanigan, Nationwide Medical Center, Columbus, Ohio; C.M. McDonald, University of California Davis, Sacramento, California; J.W. Day, University of Minnesota, Minneapolis, Minnesota; B. Darras, The Children's Hospital Boston, Massachusetts];* ***MDA Infant:*** *Muscular Dystrophy Association Duchenne Muscular Dystrophy Clinical Research Network: Natural History of Dystrophinopathy Patients: Clinical Outcomes for DMD Infants and Children Age 1 Month to 5 Years [A. Connolly (PI), J.M. Florence, Washington University, St. Louis, J.M. Forence, Missouri J.R. Mendell, K.M. Flanigan, Nationwide Medical Center, Columbus, Ohio; C.M. McDoanld, University of California Davis, Sacramento, California; J.W. Day, University of Minnesota, Minneapolis, Minnesota; B. Darras, The Children's Hospital Boston, Massachusetts, K. Bushby, Institute of Genetic Medicine, International Centre for Life, Newcastle University, Newcastle upon Tyne, UK];* ***MDA Cardiac:*** *Muscular Dystrophy Association Duchenne Muscular Dystrophy Clinical Research Network: Natural History of Dystrophinopathy Patients: Correlation of the Severity of the Dystrophin-Deficient Cardiomyopathy with Dystrophin Gene Mutations and Skeletal Muscle Function [J.R. Mendell (PI), K.M. Flanigan, H. Allen, Nationwide Medical Center, Columbus, Ohio; A. Connolly, Washington University, St. Louis, Missouri; C.M. McDonald, University of California Davis, Sacramento, California; J.W. Day, University of Minnesota, Minneapolis, Minnesota; B. Darras, The Children's Hospital Boston, Massachusetts].* ***North Star UK:*** *North Star Clinical Network for Pediatric Neuromuscular Disease [F. Muntoni, A. Manzur, Great Ormond Street Hospital for Children (GOSH), London, UK; E. Scott, Muscular Dystrophy Campaign, London, UK; M. Eagle, A. Mayhew, International Centre for Life, Newcastle Upon Tyne, UK].*[5] ***North Star Italy:*** *North Star Italian data set (E. Mercuri, Università Cattolica del SacroCuore, Rome, Italy).*[5] ***MFM France:*** *The Motor Function Measure data set (C. Payan, Hôpital Pitié-Salpêtrière, Paris, France; C. Berard; Hôpital Femme Mère Enfant, Bron, France).*[5] ***Danish:*** *The Danish dataset (B.F. Steffensen National Rehabilitation Centre of Excellence in Neuromuscular Disorders, Aarhus, Denmark).*[5] ***MRI U.S.:*** *Magnetic Resonance Imaging and Biomarkers for Duchenne Muscular Dystrophy [K. Vandenborne (PI), G. Walter, B. Byrne, University of Florida; L. Sweeney, U. Penn; R. Finkel, D.J. Wang, J. Meyer, Children's Hospital for Children Philadelphia; W. Rooney, B. Russman, Oregon Health Sciences University (www.imagingdmd.org)].*

APPENDIX: 4

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THE COOPERATIVE INTERNATIONAL NEUROMUSCULAR RESEARCH GROUP DUCHENNE NATURAL HISTORY STUDY: GLUCOCORTICOID TREATMENT PRESERVES CLINICALLY MEANINGFUL FUNCTIONAL MILESTONES AND REDUCES RATE OF DISEASE PROGRESSION AS MEASURED BY MANUAL MUSCLE TESTING AND OTHER COMMONLY USED CLINICAL TRIAL OUTCOME MEASURES

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ABSTRACT: *Introduction:* Glucocorticoid (GC) therapy in Duchenne muscular dystrophy (DMD) has altered disease progression, necessitating contemporary natural history studies. *Methods:* The Cooperative Neuromuscular Research Group (CINRG) DMD Natural History Study (DMD-NHS) enrolled 340 DMD males, ages 2–28 years. A comprehensive battery of

Abbreviations: ANOVA, analysis of variance; CDC, U.S. Centers for Disease Control and Prevention; CIDD, Clinical Investigation of Duchenne Dystrophy; CINRG, Cooperative International Neuromuscular Research Group; CK, creatine kinase; DMD, Duchenne muscular dystrophy; DMD-NHS, CINRG Duchenne Natural History Study; FEV_1, forced expiratory volume 1 second; FVC, forced vital capacity; KAFO, knee–ankle–foot orthosis; LSI, Life Satisfaction Index; LVEF, Left ventricular ejection fraction; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MMT, MRC modified manual muscle test; MRC, Medical Research Council; NG, no prior glucocorticoids; PedsQL, Pediatric Quality of Life Inventory; PEFR, peak expiratory flow rate; POSNA, Pediatric Orthopedic Society of North America Pediatric Musculoskeletal Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QMT, quantitative isometric muscle strength testing; SF, left ventricular shortening fraction; TFT, timed function testing; WHO, World Health Organization

Key words: adolescent; adult; child/preschool; follow-up studies; health status; humans; locomotion; male; muscular dystrophies/classification; muscular dystrophies/Duchenne/physiopathology; muscular dystrophies/therapy; muscle strength/physiology; phenotype; quality of life/psychology; respiratory function tests

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C.M.M. is the study's principal investigator; E.K.H., R.T.A., A.C., and C.M.M. are study chairs.

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measures was obtained. *Results:* A novel composite functional "milestone" scale scale showed clinically meaningful mobility and upper limb abilities were significantly preserved in GC-treated adolescents/young adults. Manual muscle test (MMT)-based calculations of global strength showed that those patients <10 years of age treated with steroids declined by 0.4±0.39 MMT unit/year, compared with −0.4±0.39 MMT unit/year in historical steroid-naive subjects. Pulmonary function tests (PFTs) were relatively preserved in steroid-treated adolescents. The linearity and magnitude of decline in measures were affected by maturational changes and functional status. *Conclusions:* In DMD, long-term use of GCs showed reduced strength loss and preserved functional capabilities and PFTs compared with previous natural history studies performed prior to the widespread use of GC therapy.

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Duchenne muscular dystrophy (DMD) is an X-linked degenerative disorder of the dystrophin protein that causes progressive muscle weakness, usually leading to death in early adulthood.[1] DMD is the most common neuromuscular disease of childhood and occurs with an incidence of about 30 per 100,000 live-born males across all ethnic groups.[2] Although it is accepted that a majority of cases of DMD are inherited, studies have demonstrated that between 20% and 50% of DMD cases in various populations are the result of spontaneous mutations.[3–6] The course of physical impairment is severe and inexorably progressive, and its description has varied little since Meryon's and Duchenne's early descriptions of the disease in the mid-19th century.[7,8] In early childhood, motor developmental milestones are delayed and, by 4–5 years of age, these children rise from the floor in the classic adaptive standing pattern first described by Gowers,[9] have increasing difficulty climbing stairs, and begin to have frequent falls. Muscles show a classic pattern of pseudohypertrophy, most notably in the calf muscles. With disease progression, boys begin to walk with a characteristic waddling gait with compensatory lumbar lordosis, shortened stride length, and widened base of support, which advances to a point where they require constant physical support and stabilization.[10,11] Mean age to loss of ambulation in steroid-naive children is between ages 9 and 10 years.[12–16] Over the ensuing years, patients typically develop worsening contractures, scoliosis, and progressive impairment of respiratory and cardiac function. From the earliest reports until the 1960s, death has typically occurred in the early to mid-teens due to respiratory complications or cardiac failure, but advances in preventive and supportive respiratory and cardiac therapies have led to a median survival in the middle to late twenties and growing chances of survival into the thirties for patients who receive aggressive care.[13]

Clinical trials have demonstrated that administering glucocorticoid (GC) therapy improves strength within weeks to a few months, and that these increases in strength can preserve ambulation for up to 2–3 years longer than for steroid-naive patients.[17–22] However, few studies have assessed the long-term impact of GC-mediated improvements on maintaining strength, preserving function, and developing or preventing secondary health conditions. The aims of this study were to: (1) assess baseline levels of impairment and prevalence of secondary conditions from age 2 years to adulthood; and (2) evaluate the effect of chronic GCs in DMD on: (a) preservation of functional capabilities using a novel composite functional "milestone" scale scale showing clinically meaningful mobility and upper limb abilities; (b) progression of strength loss based on manual muscle

Abbreviations: ANOVA, analysis of variance; CDC, U.S. Centers for Disease Control and Prevention; CIDD, Clinical Investigation of Duchenne Dystrophy; CINRG, Cooperative International Neuromuscular Research Group; CK, creatine kinase; DMD, Duchenne muscular dystrophy; DMD-NHS, CINRG Duchenne Natural History Study; FEV_1, forced expiratory volume 1 second; FVC, forced vital capacity; KAFO, knee–ankle–foot orthosis; LSI, Life Satisfaction Index; LVEF, Left ventricular ejection fraction; MEP, maximal expiratory pressure; MIP, maximal inspiratory pressure; MMT, MRC modified manual muscle test; MRC, Medical Research Council; NG, no prior glucocorticoids; PedsQL, Pediatric Quality of Life Inventory; PEFR, peak expiratory flow rate; POSNA, Pediatric Orthopedic Society of North America Pediatric Musculoskeletal Health Questionnaire; PSQI, Pittsburgh Sleep Quality Index; QMT, quantitative isometric muscle strength testing; SF, left ventricular shortening fraction; TFT, timed function testing; WHO, World Health Organization

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testing versus historical reports of strength loss in steroid-naive patients; and (c) preservation of respiratory function based on pulmonary function tests (PFTs) across the age span.

METHODS

Participants and Schedule of Assessments. This prospective, multicenter, international study enrolled between 10 and 15 participants per year, ranging in age from 2 to <29 years. All participants were required to have a clinical picture consistent with typical DMD and family history and molecular diagnostic characterization of DMD-associated dystrophinopathy, as detailed in our companion study.[23] Participants underwent assessments at baseline and months 3, 6, 9, and 12 (ambulatory) or months 6 and 12 (nonambulatory), which were timed to reproduce visit frequencies commonly employed in therapeutic clinical trials. One site conducted evaluations on an alternative schedule that was consistent with local care standards.

Protocol Approvals. The institutional review board or ethics review board at each participating institution approved the study protocol, consent, and assent documents. Informed consent/assent was obtained for each participant prior to conducting the study.

Assessment of Glucocorticoid Use. Historical and current use of GC therapy was documented, including medication used, age at onset of use, total duration of use, dose, and dose modification history. Patients were grouped as either: (1) GC-naive (not treated with GC ever, or treated <1 month total and not currently receiving GC); (2) current GC treatment recipients; or (3) past GC treatment recipients (treated in the past for ≥1 month with GC, but not currently receiving GC therapy).

Timed Function Testing, Functional Grades, and Functional Milestone Assessments. We measured timed function tests of standing from supine, climbing 4 standard stairs, and walking/running 10 meters. We did not test a small proportion of children <4 years of age due to their level of developmental ability. Standing from supine is defined as being able to stand without the use of furniture or assistance. We measured upper extremity function using the scale described by Brooke *et al.*[24] and lower extremity function and mobility using the scale developed by Vignos *et al.*[25] We created a 6-level composite of individual functional "milestone" tasks combining the results from the ability to perform the timed function tests and the Brooke and Vignos functional scales. The levels of this composite scale are: 0—able to complete all 3 timed tests; 1—unable to stand from supine, but performed the 4-step climb and the walk; 2—unable to climb 4 standard stairs, can walk 10 m, and with Vignos grade <5; 3—cannot rise from chair, but can walk 10 m, and with Vignos grade <7; 4—cannot walk 10 m, but can raise hand to mouth, and with Brooke grade <5; and 5—unable to raise a hand to the mouth, and with Brooke grade 5 or 6.

Health Status Assessment. Musculoskeletal and orthopedic history included spine or limb fractures, surgical tendon releases for contractures, spine stabilization surgery, and use of knee–ankle–foot orthoses (KAFOs) for ambulation and the dates of these events. Respiratory history included use of influenza and pneumococcal vaccinations, breathing exercises, cough assistance, and ventilatory assistance. History of gastrointestinal/nutritional issues included history of gastrostomy tube feeding for caloric supplementation.

Assessment of Anthropometrics. Anthropometric measures described by McDonald *et al.*[23] included standing height (in centimeters) for participants who could stand unassisted, ulnar length (in millimeters; used to estimate standing height[26]), and weight (in kilograms or pounds).

Outcome Measures Commonly Used in Clinical Trials. We measured timed function tests (TFTs, in seconds) for standing from supine, 10-m walk/run, and timed stair climbing (for 4 stairs), as described by McDonald *et al.*[23] We measured passive range of motion for knee extension, ankle dorsiflexion, elbow extension, and wrist extension to the nearest 5°.[24,27,28] We measured skeletal muscle strength[23] in all participants who were able to follow 1-step directions and who were strong enough to perform a 1-person assisted stand–pivot transfer to the examination table. Measurements included the modified Medical Research Council (MRC) manual muscle test (MMT)[29–31] and quantitative isometric strength of hand grip, elbow flexors and extensors, and knee flexors.[32,33] We measured forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak expiratory flow rate (PEFR), maximal inspiratory pressure (MIP), and maximal expiratory pressure (MEP).[23]

Statistical Methods. Analyses were conducted primarily using cross-sectional data from the baseline visits except for the 1-year longitudinal analysis of MMT scores, which used data from baseline and 3-, 6-, 9-, and 12-month visits. Frequencies of events or functional levels were shown as percentages and compared within age groups by GC status using exact chi-square tests due to the small numbers in some groups. Measurements of strength and range of motion were summarized using mean and standard deviation. Due to skewness (see below), TFTs

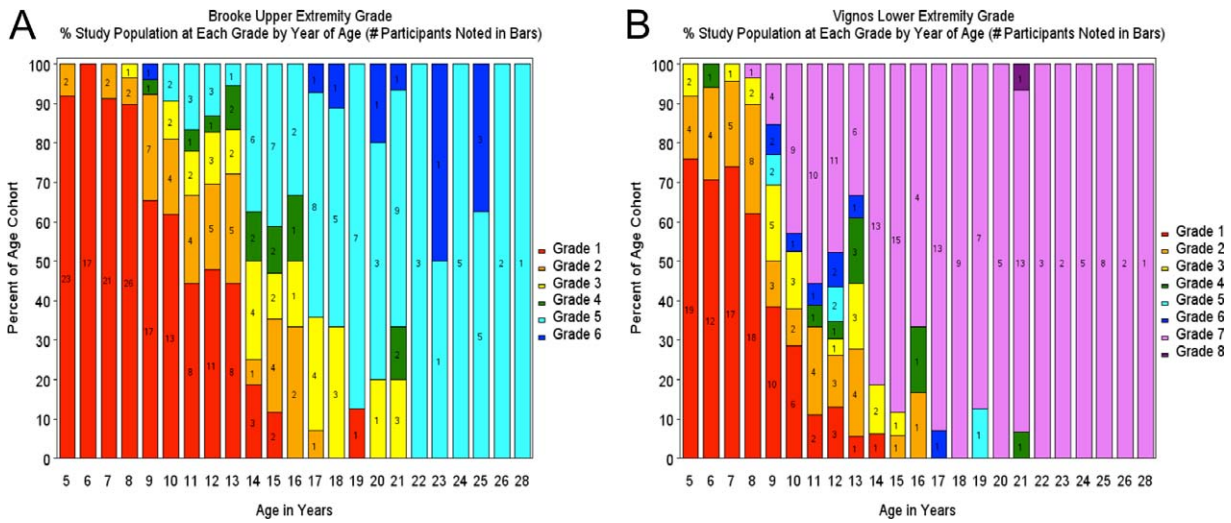

FIGURE 1. (A) Brooke upper extremity grade. **(B)** Vignos lower extremity grade. Percent study population at each grade by year of age (number of participants noted in bars).

and PFTs were summarized using box-and-whisker plots. PFTs were compared using Kruskal–Wallis exact tests. For the Brooke and Vignos functional tests, stacked bar graphs of the distribution of grade levels within each 1-year age group showed trends of loss of function with increasing age. Percentages of participants accomplishing each of the 6 levels in the combined scale described in timed function testing, functional grades, and functional milestone assessments (above) within each age group between the 3 GC-use groups were compared using an exact chi-square test with $P = 0.01$ for significance to account for 5 outcomes. Ordinal regression models were fit to both the Brooke and Vignos scales and the combined "milestone" scale as outcomes using age and GC grouping as predictors.

For the timed tests, if a participant was unable to perform a task due to weakness and was 4–18 years of age, we assigned an imputed value of zero velocity for that assessment in order to prevent a bias in the assessment of median velocity due to exclusion of those who could not perform the test. The resulting data are skewed due to having multiple zero-velocity observations, and therefore values were summarized using box-and-whisker plots.

The MMT was the only strength test assessed in a previous natural history cohort.[29] To compare the current natural history cohort with the previous Clinical Investigation of Duchenne Dystrophy (CIDD) cohort, we duplicated their methodology, calculating longitudinal rates of change from baseline to the 12-month visit. Thus, we calculated the mean and SD of the slopes based on each individual's regression line of change in MMT over 12 months, including all MMT assessments performed within the period. Thus, all participants with at least 2 MMT assessments and up to 5 assessments were included. Because the majority of our study population was GC treated and plots of MMT data versus age showed an apparent inflection point around 10 years of age, we further subdivided our analysis into 2 age groups of <10 years and ≥10 years, due to the observed increased rate of decline in the older age group.

RESULTS

Population Characteristics. Between May 2005 and July 2009, we enrolled 340 individuals with DMD (age range 2–28 years) and their primary caregiver(s) at 20 participating study centers. The median site enrollment was 14 participants (range 3–49 participants per site). At baseline, 210 of 340 (62%) participants were receiving GC therapy, 48 of 340 (14%) were past GC users, and 82 of 340 (24%) were GC-naive. At baseline, 194 of 340 (57%) participants were ambulatory.

Performance by Functional Grades and "Milestones." We obtained functional grades using the Brooke and Vignos scales in 80% of participants who were 4–6 years of age, and nearly 100% of participants who were ≥7 years of age. The percentage and number of participants at the Brooke upper extremity and Vignos lower extremity functional grades by year of age are shown in Figure 1. Examination of upper extremity grades (Fig. 1A) shows that there was little phenotypic variability in arm function at <9 years of age, with scores typically of grades 1 or 2. In participants between the ages 9 and 18 years, there was wider variability, with scores covering the entire range. Most participants >18 years of age scored at grade 5 or 6. Examination of lower extremity grades by age (Fig. 1B)

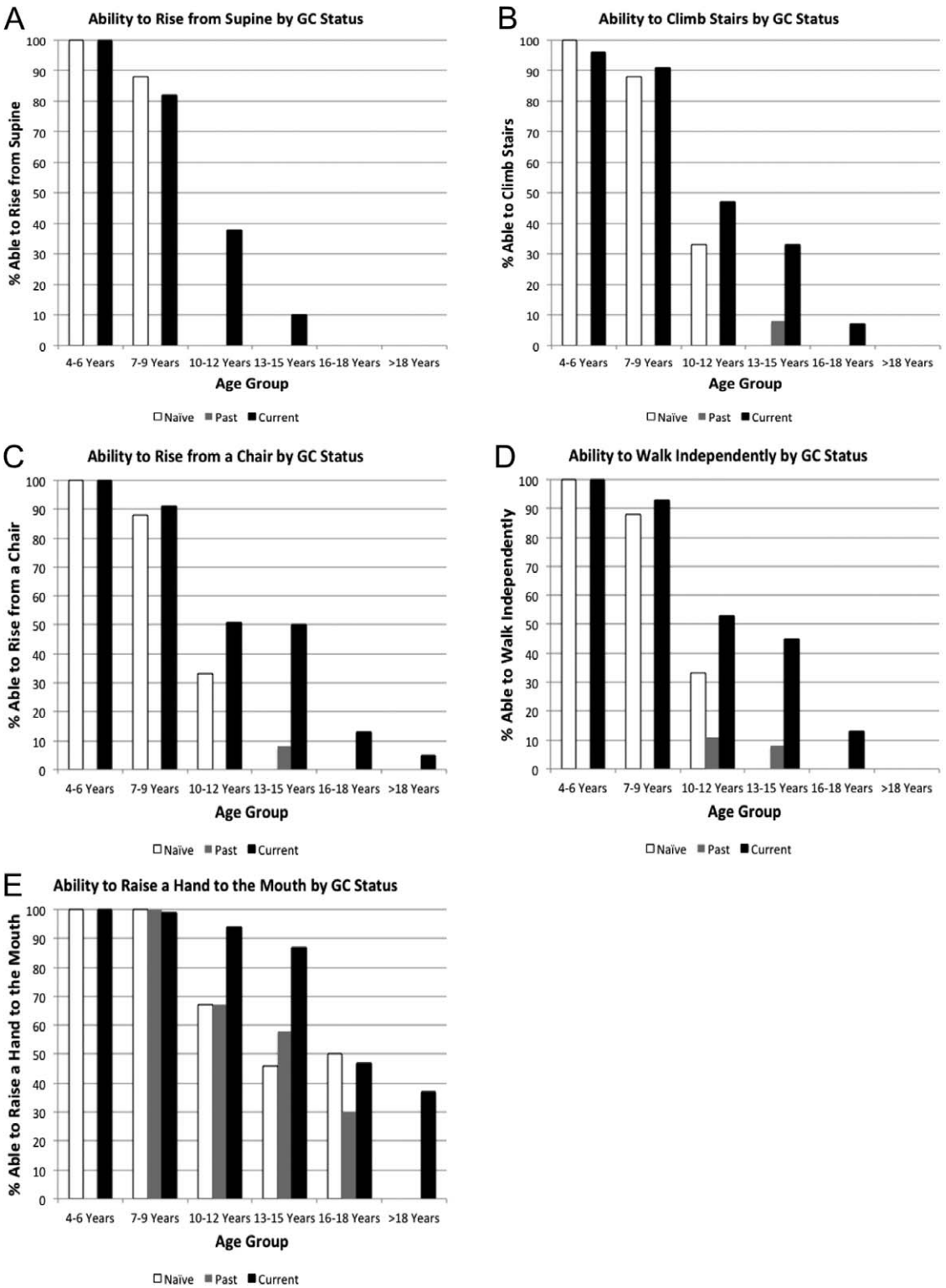

FIGURE 2. Ability to perform functional milestones by glucocorticoid status for: **(A)** standing from supine; **(B)** climbing stairs; **(C)** rising from a chair; **(D)** walking independently; and **(E)** raising a hand to the mouth. Numbers of participants (denominator) by age cohort in **(A)–(E)** who were GC-naive, current GC users, and past GC users (respectively) are as follows: 4–6 years ($N = 26, 27, 0$); 7–9 years ($N = 8, 68, 2$); 10–12 years ($N = 6, 47, 9$); 13–15 years ($N = 9, 30, 12$); 16–18 years ($N = 4, 15, 10$); >18 years ($N = 16, 19, 15$).

showed a similar pattern of disease progression, with notable differences between the ages of 9 and 13 years, coinciding with the typical pattern of transition from ambulatory to nonambulatory status. In the ordinal logistic regression models for the Brooke and Vignos scales, current GC-use participants predicted better upper and lower extremity function [odds ratios (ORs) 0.22 and 0.23 for 1

Table 1. Number of individuals with DMD with major clinical events by age group and glucocorticoid treatment status.

Age group (years)	GC status	*n*	Fractures	Surgical contracture release	Surgical spine stabilization	KAFO for ambulation	Nutrition with PEG	Invasive ventilation	Noninvasive ventilation
4–6	Naive	26	2 (8)	0	0	0	0	0	0
	Current	27	3 (11)	1 (4)	0	0	0	0	0
7–9	Naive	8	0	0	0	0	0	0	0
	Current	68	8 (12)	2 (3)	1 (1)	0	1 (1)	0	3 (4)
	Past	2	1 (50)	0	0	0	0	0	0
10–12	Naive	6	1 (17)	3 (50)	0	1 (17)	0	0	0
	Current	47	7 (15)	9 (19)	0	5 (11)	0	0	0
	Past	9	4 (44)	1 (11)	0	0	0	0	0
13–15	Naive	9	2 (22)	1 (11)	3 (33)	0	1 (11)	0	0
	Current	30	10 (33)	5 (17)	1 (3)	2 (7)	0	0	0
	Past	12	5 (42)	3 (25)	4 (33)	1 (9)	1 (8)	0	1 (8)
16–18	Naive	4	3 (75)	0	2 (50)	1 (25)	1 (25)	0	2 (50)
	Current	15	8 (53)	5 (33)	5 (33)	5 (33)	1 (7)	0	3 (20)
	Past	10	5 (50)	6 (60)	5 (50)	1 (11)	1 (10)	0	3 (30)
>18	Naive	16	3 (19)	5 (31)	9 (56)	4 (25)	3 (20)	2 (13)	9 (56)
	Current	19	8 (42)	11 (58)	7 (37)	8 (42)	1 (5)	0	6 (32)
	Past	15	7 (47)	7 (47)	10 (67)	5 (33)	1 (7)	1 (7)	4 (47)

Data show number (%) of individuals. GC, glucocorticoid; KAFO, knee–ankle–foot orthoses; PEG, percutaneous endoscopic gastrostomy.

function level lower, confidence intervals (CIs) 0.1–0.42 and 0.47, respectively, $P < 0.001$ in both models] than GC-naive participants after controlling for age ($P < 0.001$). There were no significant differences between the GC-naive users and past GC users in the upper extermity, but past users had worse (OR for 1 function level lower = 4.5, CI 1.1–18.5, $P = 0.04$) lower extremity function than GC-naive participants.

Ability to perform functional "milestone" tasks by age group and GC treatment status is shown in Figure 2. Regardless of GC-treatment status, loss of functional abilities occurred in a predictable order beginning with loss of the ability to stand from supine and subsequent loss of stair climbing, loss of the ability to rise from a chair followed by loss of ability to walk, and finally loss of the ability to raise a hand to the mouth. However, across all ages >6 years, GC-treated subjects displayed preservation of function relative to previously GC-treated and GC-naive peers (exact chi-square *P*-values 0.0024–0.043 within each age group function level subgroup that had at least 5 participants able to achieve the function level, comparing the GC distribution between those who did and did not achieve the function level). In the ordinal regression model using the "milestone" combined Brooke and Vignos and timed function as the outcome variable, GC users had significantly better functional milestones than GC-naive patients [1-level worse milestone level OR = 0.34 (CI 0.17–0.67), $P = 0.0022$]. Past GC users had significantly worse functional milestone levels than GC-naive patients [1-level difference OR = 3.1 (CI 1.2–8.1), $P = 0.022$]. In those DMD patients aged ≥18 years treated long term with GCs, 37% maintained the ability to get the hand to the mouth and feed independently as compared with 0% of those who were steroid-naive and 0% of past steroid users.

Longitudinal Assessment of Modified MRC Manual Muscle Test Scores. The average MMT score at baseline was 6.7 (SD = 1.1) in those participants who could be assessed for this test. Analysis of averages of individuals' slopes of strength change in all ambulatory participants ≥5 years of age who were able to perform MMT evaluations at least twice during the 5 potential evaluations from baseline to month 12 ($n = 163$), including all evaluations done during the 12 months, showed an overall decrease of 0.22 (1.07) MMT unit/year. For those age <10 years, the decrease was 0.14 (0.96) MMT unit/year ($n = 115$), which is less than half the previously described rate of −0.4 (0.39) MMT unit/year,[29] albeit more variable. Of those individuals, 32% had a slope increase of >0.1 MMT unit/year vs. 15% as reported by Brooke *et al.*,[29] and 14% had a slope decrease of ≥1.0 MMT unit/year. For participants ≥10 years of age, the decrease was 0.42 (1.29) MMT unit/year ($n = 48$), which is consistent with previous reports.[29] Of these individuals, 17% had a slope increase of >0.1 MMT unit/year, and 13% had a slope decrease of ≥1.0 MMT unit/year. Approximately 75% of these participants were on GC therapy throughout the 12 months. Their results are comparable to the whole group, except for a somewhat decreased variability, and a slower decrease among participants ≥10 years of age.

Table 2. Anthropometric measures: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

Age group (years)	Standing height (cm)		Ulnar length (cm)		Weight (kg)	
	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
4–6	107.9 (6.2)	53 (100)	16.4 (1.1)	51 (96)	20.2 (3.7)	53 (100)
7–9	123.1 (6.5)	68 (87)	19.1 (1.3)	78 (100)	27.6 (8.0)	78 (100)
10–12	132.4 (10.8)	27 (44)	21.3 (2.1)	62 (100)	41.9 (14.6)	62 (100)
13–15	136.7 (12.1)	15 (29)	23.3 (2.7)	51 (100)	51.6 (18.1)	51 (100)
16–18	145.0 (7.1)	2 (7)	25.5 (1.9)	29 (100)	62.9 (20.7)	29 (100)
>18	–	–	25.0 (2.0)	50 (100)	62.4 (27.3)	50 (100)

Feasibility and Cross-Sectional Characteristics of Common Clinical Trial Outcome Measures. ***Prevalence of Important Clinical Events.*** For both GC-treated and GC-naive study participants at the baseline evaluation, we assessed lifetime prevalence of events that often raise concern among families and health-care professionals when discussing the use of GC therapy and for interventions commonly used to maintain mobility and function. Table 1 shows information on the development of clinical events. Prevalence for all measures increased with age, as expected, but the number of individuals with events is small for all types of events. There were no significant differences in rates except for surgical stabilization in the 13–15-year-old group, where only 1 patient required this in the GC group ($n = 30$) compared with 3 patients in the naive group ($n = 9$) and 4 patients in the past-user group ($n = 12$) ($P = 0.013$).

Anthropometric Characteristics. Anthropometric characteristics by age group are shown in Table 2. Collection of weight data and ulnar length was feasible in the entire study cohort regardless of age. Standing height was reported only for those participants who could stand appropriately, and the decline in numbers with increasing age group was apparent (Table 2). No adult participant (>18 years old) was able to stand.

Timed Function Testing. Timed function test characteristics by age group are shown in Figure 3. Calculating TFT evaluation results as a distance over time velocity enabled the use of 0 as an attainable speed in all 3 measures, even in instances where the participant could not be assessed due to disease progression and was thus assigned an imputed velocity of 0. Zero velocities were imputed for 0–1 (0–2%) subject in the 4–6-year-old group, 8–15 (10–19%) subjects in the 7–9-year-old group, 34–44 (55–71%) subjects in the 10–12-year-old group, 37–48 (73–94%) subjects in the 13–15-year-old group, and 27–29 (93–100%) subjects in the 16–18-year-old group. As noted earlier, no participants could perform the tests in the >18-year-old group. Figure 3 also shows the consistent decrease in velocity with increasing age for all 3 tasks. After 9 years of age, very few participants were able to stand from supine without the aid of furniture or a person. In addition, very few were able to climb 4 stairs at that time. However, many were still able to walk 10 meters. Although the median pace (including the non-walkers as 0 velocity) in the 10–12-year-old age group was 0.0 m/s, 25% of participants were still walking at a pace of ≥1.0 m/s at that age.

Range of Motion. Passive range of motion (ROM) characteristics by age group are shown in Tables 3 and 4. Larger numbers in the positive direction indicate better ROM, whereas larger numbers in the negative direction indicate restricted ROM. Upper extremity ROM measures were obtained in 77% of study participants <7 years of age, in 100% of participants 7–9 years of age, and in 96–100% of participants ≥10 years of age (Table 3). Lower extremiy ROM measures were obtained in 91% of participants <7 years of age and in 100% of participants 7–9 years of age (Table 4). In ambulatory participants, ROM progressed toward 0 or negative values with increasing age.

Quantitative Muscle Strength. Skeletal muscle strength characteristics by age group are shown in Tables 5, 6, and 7. Participants >6 years of age were reliably able to perform quantitative grip strength testing (Table 5). Knee and elbow flexor and extensor strength data collection by quantitative isometric testing was possible in 72–81% of participants 4–6 years of age, and in 88–100% of those 7–9 years of age, depending on the muscle group assessed (Table 6). A smaller subset of older participants (52% of the 10–12-year cohort, 37% of the 13–15-year cohort, and 0% of those ≥16 years of age) were able to perform an assisted stand–pivot transfer utilizing the study-defined testing safety criteria and were thus able to provide strength testing data (Table 7).

Pulmonary Function. Pulmonary function characteristics by age group are shown in Table 8. Pulmonary function measures were feasible and performed in most participants aged ≥7 years (commonly appreciated as a lower age limit for reliability testing). FVC, FEV_1, and PEFR were obtained in 79–95% of study participants ≥7 years

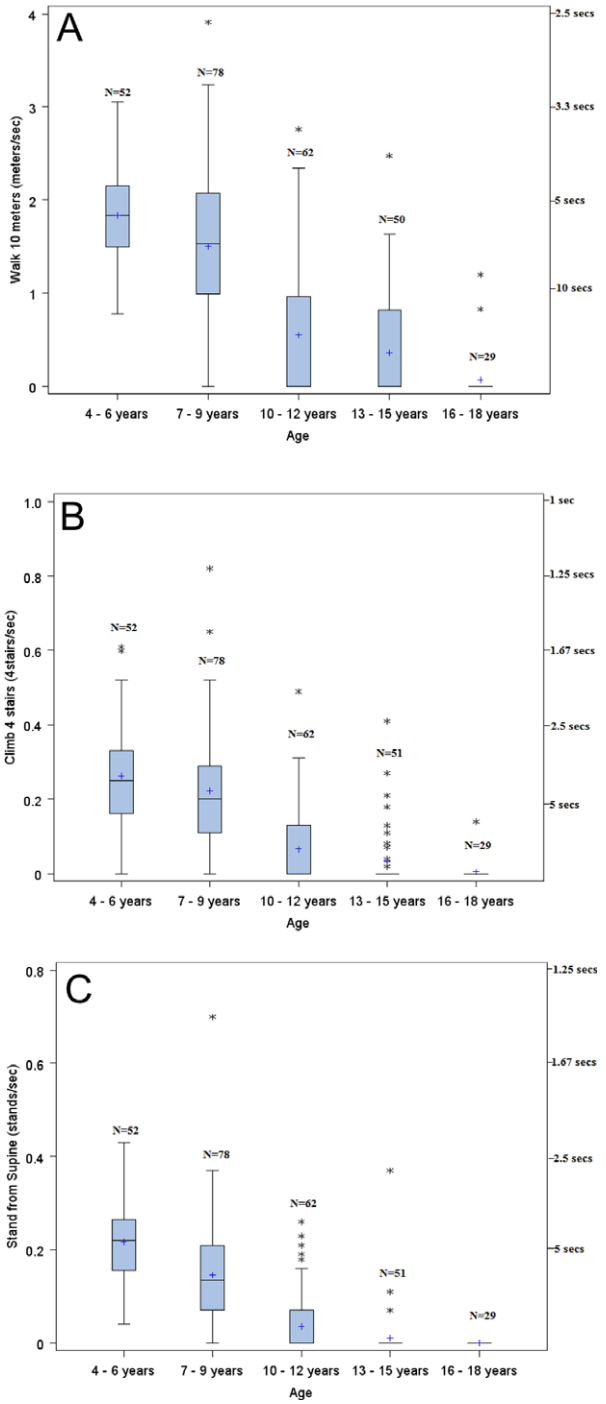

FIGURE 3. Timed function tests by age group for: **(A)** 10-m walk/run; **(B)** climb 4 stairs, and **(C)** stand from supine. The box-and-whisker figures show velocity; a velocity of 0 is imputed for all participants who could not perform the test. The limits of the box are the 25th and 75th percentile. The median (middle line) and mean ("+") are shown within the box. The whiskers are 1.5 times the interquartile length, starting from the edge of the boxes; asterisks indicate data values of outliers beyond the whiskers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

of age. MIP and MEP were obtained in 95–100% of study participants in the same age groups.

Table 3. Upper extremity range of motion: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	Wrist extension (°)		Elbow extension (°)	
Age group (years)	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
4–6	78.4 (23.2)	41 (77)	4.0 (5.9)	41 (77)
7–9	70.8 (26.1)	78 (100)	1.0 (5.9)	78 (100)
10–12	65.5 (27.1)	62 (100)	–3.8 (13.4)	62 (100)
13–15	57.7 (33.7)	49 (96)	–16.0 (22.5)	49 (96)
16–18	28.8 (43.3)	28 (97)	–28.6 (22.8)	29 (100)
>18	17.3 (41.8)	48 (96)	–42.9 (29.4)	50 (100)

Results show that MIP and MEP were already very compromised in the 7–9-year-old participants (mean 63% and 47% predicted, respectively), whereas FEV_1 and FVC were more modestly impacted. Percent predicted values for FVC by age and GC treatment status demonstrated higher overall function for GC-treated boys across the age groups 10–12 and 13–15 years and older, as shown in Figure 4 (*P*-values 0.0001–0.039 for all 5 PFTs in this age group, with the exception of MEP in the 10–12-year group, $P = 0.08$). By 16 years of age, all parameters were <50% of predicted values of healthy children and, by adulthood, all parameters were at approximately 25% predicted values of healthy adults. There was large variability in the pulmonary function results in the younger participants, which declined with advancing participant age. The range of results decreased; however, even among the adult participants there was substantial variability in the results of the pulmonary function evaluations.

DISCUSSION

Functional "Milestones" Preserved in GC-Treated Adolescents and Young Adults. The data demonstrate that our cohort exhibited significantly preserved functional "milestones" in the currently GC-treated participants, including the ability to stand from supine, climb stairs, rise from a chair, walk independently, and raise the hands to the mouth. This issue is especially compelling when considering the use of GC therapy in older and less functional nonambulatory patients, in whom there is a relative lack of efficacy and safety data

Table 4. Lower extremity range of motion: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	Knee extension (°)		Ankle dorsiflexion (°)	
Age group (years)	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
4–6	2.9 (5.8)	48 (91)	6.5 (7.1)	48 (91)
7–9	–1.8 (9.4)	78 (100)	–0.1 (10.7)	78 (100)

Table 5. Quantitative hand grip strength: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	QMT hand grip (lbs.)	
Age group (years)	Mean (SD)	*n* (%) studied
4–6	10.2 (3.6)	43 (81)
7–9	12.4 (5.5)	78 (100)
10–12	13.5 (7.3)	62 (100)
13–15	12.0 (8.1)	51 (100)
16–18	9.8 (8.4)	29 (100)
>18	5.7 (5.7)	50 (100)

that can be obtained from the literature. This point was highlighted by Bushby and colleagues in the recently published DMD care guidelines, which identify continued use of GC therapy in individuals who are nonambulatory with limited upper extremity function as an area in need of further research.[34] Although clinical trials have demonstrated increases in strength due to GC use in early and middle childhood, our observational data suggest that there may be significant long-term functional benefits associated with continued GC treatment during the preteen and teenage years, and even during adulthood. Prolonged ambulation, improved ability to perform positional transfers, and maintenance of self-feeding abilities are all expected to have a significant positive impact on functional activities of daily living and, subsequently, on health-related quality of life. Our data suggest that those who continue to receive GC therapy through their teenage years and even into adulthood may be more likely to preserve lower and upper extremity function compared with those who remained untreated. The interesting observation of significant functional deficits demonstrated between the past GC users relative to GC-naive patients is an area that will require further study using future longitudinal data.

Fractures in Cohort Rare and Unrelated to Steroid Use. There are lingering concerns among parents and practitioners about increased fracture risk due to GC use. Although reported instances of fractures were few, our cohort did not show substantive differences in fracture prevalence percentages between the GC-treated and GC-naive groups, even in those with continued GC therapy into their third decade. The prevalence of fractures in those <13 years of age is generally low, and in those >13 years it is comparable, regardless of GC status. A detailed description of other major risks of GC treatment, such as weight gain, cataracts, and behavioral changes, experienced by our cohort is beyond the scope of this investigation. These topics are addressed comprehensively in our companion study focusing on GCs in DMD.

One-Year Change in Manual Muscle Test Scores Decreased Compared with Previous Reports in Younger Steroid-Naive Patients. We compared our MMT score data over 12 months with findings by Brooke *et al.* in 1983.[29] Comparison with the CIDD cohort is not without challenges. Evaluation of that cohort occurred prior to the advent of molecular diagnostic criteria, and it is possible that even the very thorough clinical diagnostic criteria may have failed to exclude some individuals with milder phenotypes, such as those with intermediate or Becker-type dystrophinopathies, limb-girdle muscular dystrophies, or sarcoglycanopathies. Still, individuals with those diagnoses frequently have a slightly less aggressive clinical course. Therefore, had those individuals been excluded from the

Table 6. Quantitative muscle strength testing in children: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	QMT elbow extensor (lbs.)		QMT elbow flexor (lbs.)		QMT knee extensor (lbs.)		QMT knee flexor (lbs.)	
Age group (years)	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
4–6	7.0 (2.8)	38 (72)	7.6 (2.3)	41 (77)	15.5 (7.7)	41 (77)	9.7 (3.3)	40 (75)
7–9	6.0 (3.0)	68 (97)	8.0 (3.2)	68 (97)	10.9 (7.3)	68 (97)	12.1 (3.7)	68 (97)

Table 7. Quantitative muscle strength testing in preteens and teens able to perform assisted self-transfer: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	QMT elbow extensor (lbs.)		QMT elbow flexor (lbs.)		QMT knee extensor (lbs.)		QMT knee flexor (lbs.)	
Age group (years)	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
10–12	6.3 (3.7)	32 (100)	8.1 (3.8)	32 (100)	8.3 (6.4)	32 (100)	11.4 (7.0)	32 (100)
13–15	6.7 (3.8)	19 (100)	7.5 (3.8)	19 (100)	9.0 (4.5)	19 (100)	10.3 (6.8)	19 (100)

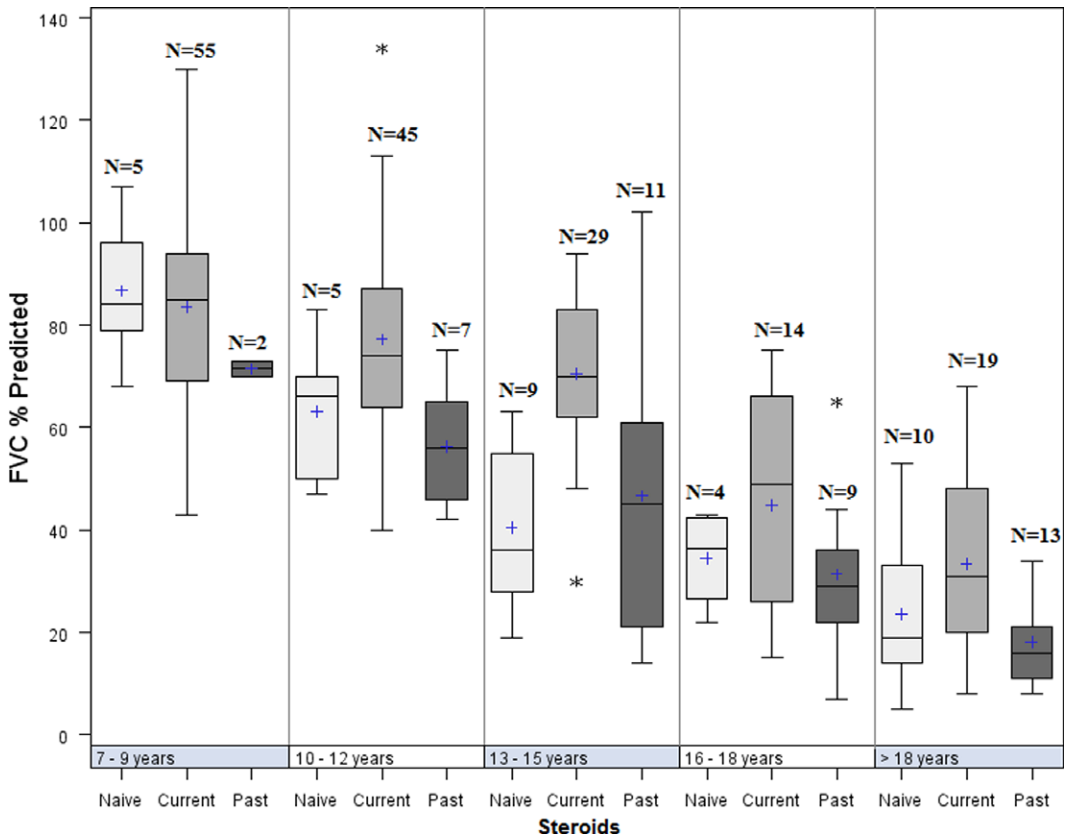

FIGURE 4. Percent predicted forced vital capacity by age and GC treatment groups. The limits of the box are the 25th and 75th percentile. The median (middle line) and mean (+) are shown within the box. The whiskers are 1.5 times the interquartile length starting from the edge of the boxes; the asterisks are data values of outliers beyond the whiskers. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

study, the reported clinical course could have been even more severe, which would have increased the magnitude of difference in our observations. Alternately, given the lack of molecular diagnostics, individuals in the CIDD cohort may have been identified later in the course of their disease, or they could have been more severe and identified earlier. Thus, the younger individuals in the CIDD cohort could have displayed a more severe course, thus creating a recruiting bias that would emphasize differences with our cohort. Regardless of the impact, those possibilities underscore the need for study of a cohort defined using more contemporary diagnostic standards.

Despite the challenges in interpretation, we propose that our study cohort demonstrates that individuals with DMD today who are <10 years of age are declining in strength and function at a rate that is less than half of that previously described. The increased variability of disease progression can be explained in part by the mix of GC-treated and GC-naive individuals in our sample, as well as by the greater proportion of children who demonstrated increased MMT scores. The functional significance of the reduced rate of progression we attribute to widespread GC use in early and mid-childhood is that children with DMD today are likely to have a much higher

Table 8. Pulmonary function testing: mean, standard deviation (SD), and number (%) who performed each study by age cohort.

	FVC % predicted		FEV_1 % predicted		PEFR % predicted		MIP % predicted		MEP % predicted	
Age group (years)	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied	Mean (SD)	*n* (%) studied
7–9	83.5 (17.3)	62 (79)	85.1 (19.9)	62 (79)	73.2 (21.7)	62 (79)	62.8 (21.5)	74 (95)	46.6 (19.6)	76 (97)
10–12	73.4 (18.8)	57 (92)	73.3 (16.9)	57 (92)	70.0 (18.5)	57 (92)	51.0 (15.8)	61 (98)	36.7 (16.4)	60 (97)
13–15	59.7 (21.8)	49 (96)	60.0 (21.5)	49 (96)	59.9 (18.1)	49 (96)	42.7 (16.3)	51 (100)	30.3 (13.0)	51 (100)
16–18	38.9 (18.8)	27 (93)	40.5 (19.7)	27 (93)	39.7 (18.8)	27 (93)	28.3 (11.6)	29 (100)	18.8 (10.2)	28 (97)
>18	26.4 (15.2)	42 (84)	28.1 (15.6)	42 (84)	29.6 (16.9)	41 (82)	23.7 (14.7)	48 (96)	16.3 (10.8)	48 (96)

degree of functional ability and participation during critical periods of childhood development. Maintaining a higher degree of strength and function when entering the adolescent growth spurt may be associated with improved spine stability and a reduced need for spinal instrumentation and fusion, improved pulmonary function capacity due to preservation of thoracic musculature and structure, prolonged preservation of self-care abilities, and overall reductions in developing secondary medical conditions. These alterations in the natural history of DMD would be expected to ultimately lead to improved survival characteristics. Individuals in our cohort who were $\geq$10 years of age demonstrated an overall decrease in strength consistent with, but more variable than data from Brooke and colleagues.[29] This suggests that early GC treatment maximizes functional preservation and raises the baseline level of strength and function through the adolescent transition, even if the overall rate of progression of weakness during the second decade of life is similar to that seen in previous reports.

Due to the previously documented increased sensitivity of other methods compared with MMT[32,33] and the challenges of maintaining consistency of MMT in international multicenter clinical trials, the trend has been to power clinical trials on the basis of other clinical endpoints. The changing natural history of DMD due to GC therapy appears, at least from the perspective of MMT, to have resulted in smaller-than-expected 1-year changes in the younger patients and increased variability due to differing rates of disease progression that could significantly impact clinical trial results using the measure. Future data from this natural history study characterizing QMT and TFT and recently added endpoints, such as the 6-minute walk test (6MWT),[35,36] the North Star Ambulatory Assessment,[37–39] and the 9-Hole Peg Test,[40,41] will thus be critical for the design of future clinical trials and will supplement the emerging literature on comparative endpoints from smaller populations, which has been showing a high degree of agreement between outcome measures.[38,39]

Clinical Trial Outcome Measures are Feasible and Continuous across a Wide Range of Ages and Functions. Current natural history data pertaining to clinically meaningful endpoints are critical when considering the design of clinical trials for individuals with DMD. This investigation has presented a cross-sectional overview of our study cohort at their baseline evaluations. Examination of the data in Tables 2 through 8 show that means and standard deviations of commonly used measures varied across age groups, as did the proportion of the population who were able to complete those measures. From a feasibility standpoint, we found that commonly used clinical trial endpoints measuring overall physical and pulmonary function can be implemented across most ages and stages of disease severity. However, with the exception of quantitative grip testing, we observed limitations due to contractures and positioning in current testing methods for both MMT and QMT, which restricted evaluations to ambulatory and mildly to moderately affected nonambulatory patients.

Our data further suggest that some outcome measures should be expected to show longitudinal changes that are increasing, stable, or decreasing, depending on the age of the participant. This is illustrated by comparing quantitative muscle strength tests in the 4–6-year and 7–9-year age groups, where stable elbow flexor strength and increasing knee flexor and hand grip strength were consistent with the concept that, in younger children, deterioration of strength can be outpaced by normal growth and motor development. The implication is that consideration should be given to the design of trials with respect to stratification factors, wherein different groups are expected to progress at different rates depending on their age, developmental level, or stage of disease, thus leading to differing clinically important effect sizes. Also of note are those adolescents described in Table 7, who retained a higher degree of function. They are capable of testing using the current manual and quantitative strength testing methods. They do not, however, represent the entire population at those ages. Current strength testing methods could remain a useful tool in the context of a clinical trial directed specifically at such a group of individuals. Our data also reveal that there were gaps in current assessment techniques, which limits their utility in boys who are not able to transfer to an examination table. Modifying existing strength testing protocols will allow for inclusion of a broader sample of nonambulatory DMD participants in future studies. As we explore new endpoints for use in clinical trials, we should strive to develop assessments that maintain continuity of measures across the entire population whenever possible.

The underlying causes of variability in DMD disease progression, outcome measure performance, and degrees of response to GC therapy across the current survivable lifespan are still not well understood. In patients with similar diagnostic and clinical characteristics, DMD progresses at different rates, and there are few reliable ways to predict its clinical course. As a result, researchers have seen such variability reduce the statistical power to detect treatment differences in clinical trials. Because DMD is a rare disease with a limited

patient population, increasing planned sample sizes is not often the optimal choice. Consistent with providing input to a personalized medicine approach, future analyses of longitudinal data sets will facilitate identification of factors that explain variability in progression and treatment response and optimization of selection of study cohorts and clinical trial outcome measures. One such way to reduce heterogeneity in study populations in clinical trials is to include metrics of functionality as eligibility criteria, and to consider stratification by age or function-related groups. Specific measures for a trial should be chosen based on their ability to reveal a "decline phase" within a specified age range or level of function.[42]

In conclusion, for the individuals in our cohort, use of GCs into adolescence confers a higher level of function—one that is likely to have a significant, positive, long-term impact on functional ability, independence, health-related quality of life, and survival. Through an analysis of the first complete year of data on 340 boys and young men with DMD using the same techniques as the widely cited CIDD natural history study,[29] we found that rates of progression in our cohort in early and middle childhood decreased to less than half the rate described in the late 1980s prior to routine use of GC therapy. These results, based on analyses of currently used clinical trial outcome measures, show that GC treatment contributes to a "new natural history" that alters the characteristic progression of DMD. This decreased rate of strength loss and improved function creates a wider age range where existing validated clinical trial outcome measures are feasible, and also underscores the need for development of additional clinical trial measures that can be applied continuously across ages and stages of disease.

APPENDIX

Study Collaborators (CINRG Investigators). *Sunaram Medical Foundation and Apollo Children's Hospital:* V. Vishwanathan, MD, S. Chidambaranathan, MD; *Holland Bloorview Kids Rehabilitation Hospital:* W. Douglas Biggar, MD; *Alberta Children's Hospital:* Jean K. Mah, MD; *Queen Sylvia Children's Hospital:* Mar Tulinius, MD; *Children's National Medical Center:* Robert Leshner, MD, Carolina Tesi-Rocha, MD; *Royal Children's Hospital:* Andrew Kornberg, MD, Monique Ryan, MD; *Hadassah Hebrew University Hospital:* Yoram Nevo, MD; *Instituto de Neurosciencias Fundacion Favaloro:* Alberto Dubrovsky, MD; *Mayo Clinic:* Nancy Kuntz, MD, Sherilyn Driscoll, MD; *Washington University, St. Louis:* Anne Connolly, MD, Alan Pestronk, MD; *Children's Hospital of Virginia:* Jean Teasley, MD; *University of Tennessee, Memphis:* Tulio Bertorini, MD; *Children's Hospital of Westmead:* Kathryn North, MD; *University of Alberta*: Hanna Kolski, MD; *University of Puerto Rico:* Jose Carlo, MD; *University of Pavia and Niguarda Ca' Granda Hospital:* Ksenija Gorni, MD; *Texas Children's Hospital:* Timothy Lotze, MD; *University of Minnesota:* John Day, MD.

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