Published in final edited form as:
Muscle Nerve. 2013 July ; 48(1): 32–54. doi:10.1002/mus.23807.

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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Disclosures: The authors take full responsibility for the contents of this article, which do not represent the views of the U.S. Department of Education, the National Institutes of Health, the Department of Veterans Affairs, or the U.S. Government. R.T.A. has served as a consultant for PTC Therapeutics, Inc. A.A. has nothing to disclose. P.R.C. is a consultant for ReveraGen Biopharma. A.C. serves as a consultant for GlaxoS-mithKline. T.D. has nothing to disclose. D.M.E. serves on the speakers bureau for and has received funding for travel and speaker honoraria from Athena Diagnostics, Inc., and also serves as a consultant for Acceleron Pharma, HALO Therapeutics, AVI Biopharma, the Gerson Lehman Group, and Medacorp. J.M.F. serves on a scientific advisory board for Prosensa, serves on the editorial board of *Neuromuscular* Disorders, and serves/has served as a member of the CINRG Executive Committee and as a consultant for Prosensa, GlaxoSmithKline, Genzyme Corporation, PTC Therapeutics, Inc., and Acceleron Pharma. E.K.H. is a member of the CINRG Executive Committee and has served as a consultant for Genzyme Corporation and PTC Therapeutics, Inc. J.J.H. has nothing to disclose. E.P.H. has served on advisory committees for AVI BioPharma, Inc., and as a consultant with Gerson Lehman Group, Medacorp, and Lazard Capital, and is a cofounder, board member, and shareholder of ReveraGen Biopharma. C.M.M has served on advisory committees for PTC Therapeutics, Inc., Sarepta Therapeutics, Inc., GlaxoSmithKline, plc, Prosensa, Halo Therapeutics, Shire HGT, and Novartis AG.
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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.

Keywords

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

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 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.

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 and the Brooke Upper Extremity Functional Grade. 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 clinicianrated 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 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 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 ≥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. The study PI and colleagues produced a profile of DMD 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. 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.

Acknowledgments

This project was funded through grants from the U.S. Department of Education/NIDRR (H133B031118 and H133B090001), U.S. Department of Defense (W81XWH-09-1-0592), the National Institutes of Health

(UL1RR031988, U54HD053177, UL1RR024992, U54RR026139, G12RR003051, 1R01AR061875, and RO1AR062380), and Parent Project Muscular Dystrophy.

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

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
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	+ All	5 min	2006–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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.			
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 2150 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
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)	+ Amb	10 min (unilateral)	2006–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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.			
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. 3—Joint is moved against gravity but not through the full available range of motion.	+ All	10 min	2006–2012 (Amb; bilateral) 2012–present (All; unilateral)

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	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. 9—Is in a wheelchair. 10—Is confined to bed.	+ All	2 min	2006–present
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 5ability to	+ Amb	15 min	2012–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	perform the test normally, 15 modified method or assistance to perform test, and 05 unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 (no impairment on these assessments).			
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 5 normal to 35 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
Time to walk/run 10 m or 30 ft[1,11,26]	Time to walk/run 10-m assessment is performed in	+ Amb	2 min	2006–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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.			
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	+ All	5 min	2006–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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]			
POSNA Pediatric Musculoskeletal Functional Health Questionnaire/Pediatric Outcomes Data Collection Instrument (PODCI).[55–59]	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: 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	+ All	15 min	2006–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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	+ All	10 min	2012–present

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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]			
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 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]	+ All	15 min (short forms)	2012–present
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	+ NonAmb all adults	10 min	2006–2012

Body structure/function	Description of measures	Standard protocol? Ambulatory/ non-ambulatory	Time required	Chronology
	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.			
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)	6			±	±	±	±	±	±	±		±	
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)					+								

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.
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]					+								
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 func-tional health questionnaire/ Pediatric Outcomes Data Collection Instru-ment (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, Hopital Pitie-Salpetriere, Paris, France; C. Berard; Hopital Femme Mere 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

STUDY COLLABORATORS (CINRG INVESTIGATORS)

Sundaram 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 Korn-berg, 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.

These findings were presented in part at the Proceedings of the American Academy of Neurology, April 2009 and April 2010, and the International Congress of Neuromuscular Disorders, July 2010.

The authors thank the patients and families who volunteered their time to take part in this project. We also thank Dr. Josh Benditt, Dr. Louis Boitano, Dr. David Birnkrant, Dr. David Connuck, Dr. Jonathan Finder, Dr. Veronica Hinton, Dr. Katherine Mathews, and Dr.

Richard Moxley for their expert advice during study development. We thank Dr. Susan Sparks and Erynn Gordon for their expert review of all DMD diagnostic test results. We also thank the dedicated CINRG members who continue to commit countless hours to this effort. The CINRG group is comprised of the following institutions and individuals: *University of California, Davis*: Michelle Cregan, Erica Goude, Merete Glick, Linda Johnson, Nanette Joyce, Alina Nicorici, Andrew Skalsky, Amanda Witt, Bethany Lipa; *Sundaram Medical Foundation and Apollo Children's Hospital, Chennai*: Suresh Kumar; *Holland Bloorview Kids Rehabilitation Hospital*: Laila Eliasoph, Elizabeth Hosaki, Angela Gonzales, Vivien Harris; *Alberta Children's Hospital*: Angela Chiu, Edit Goia, Jennifer Thannhauser, Lori Walker, Caitlin Wright, Mehrnaz Yousefi; *Queen Sylvia Children's Hospital*: Ann-Christine Alhander, Lisa Berglund, Ann-Berit Ekstrom, Anna-Karin Kroksmark, Ulrika Sterky; *Children's National Medical Center*: Marissa Birkmeier, Sarah Kaminski, Katie Parker; *Royal Children's Hospital*: Kate Carroll, Katy DeValle, Rachel Kennedy, Dani Villano; *Hadassah Hebrew University Hospital*: Adina Bar Leve, Itai Shurr, Elana Wisband, Debbie Yaffe; *Instituto de Neurosciencias Fundacion Favaloro*: Luz Andreone, Jose Corderi, Lilia Mesa, Lorena Levi; *Mayo Clinic*: Krista Coleman-Wood, Ann Hoffman, Wendy Korn-Petersen, Duygu Selcen; *University of Pittsburgh*: Hoda Abdel-Hamid, Christopher Bise, Ann Craig, Lauren Hache, Sarah Hughes, Casey Nguyen, Jason Weimer; *Washington University, St. Louis*: Paul Golumbak, Glenn Lopate, Justin Malane, Betsy Malkus, Kenkicki Nozaki, Renee Renna, Jeanine Schierbacker, Catherine Seiner, Charlie Wulf; *Children's Hospital of Virginia*: Susan Blair, Barbara Grillo, Karen Jones, Eugenio Monasterio; *University of Tennessee, Memphis*: Judy Clift, Cassandra Feliciano, Masanori Igarashi, Rachel Young; *Children's Hospital of Westmead*: Kristy Rose, Richard Webster, Stephanie Wicks; *University of Alberta*: Lucia Chen, Cameron Kennedy; *University of Puerto Rico*: Brenda Deliz, Sheila Espada, Pura Fuste, Carlos Luciano; *University of Pavia*: Luca Capone, *Niguarda Ca' Granda Hospital*: Maria Beneggi, Valentina Morettini; *Texas Children's Hospital*: Anjali Gupta, Robert McNeil; *University of Minnesota*: Amy Erickson, Marcia Margolis, Cameron Naughton, Gareth Parry, David Walk; *CINRG Coordinating Center*: Naomi Bartley, Paola Canelos, Robert Casper, Lauren Hache, Corinne Ingram, Fengming Hu, Mohammad Ahmed, Angela Zimmerman.

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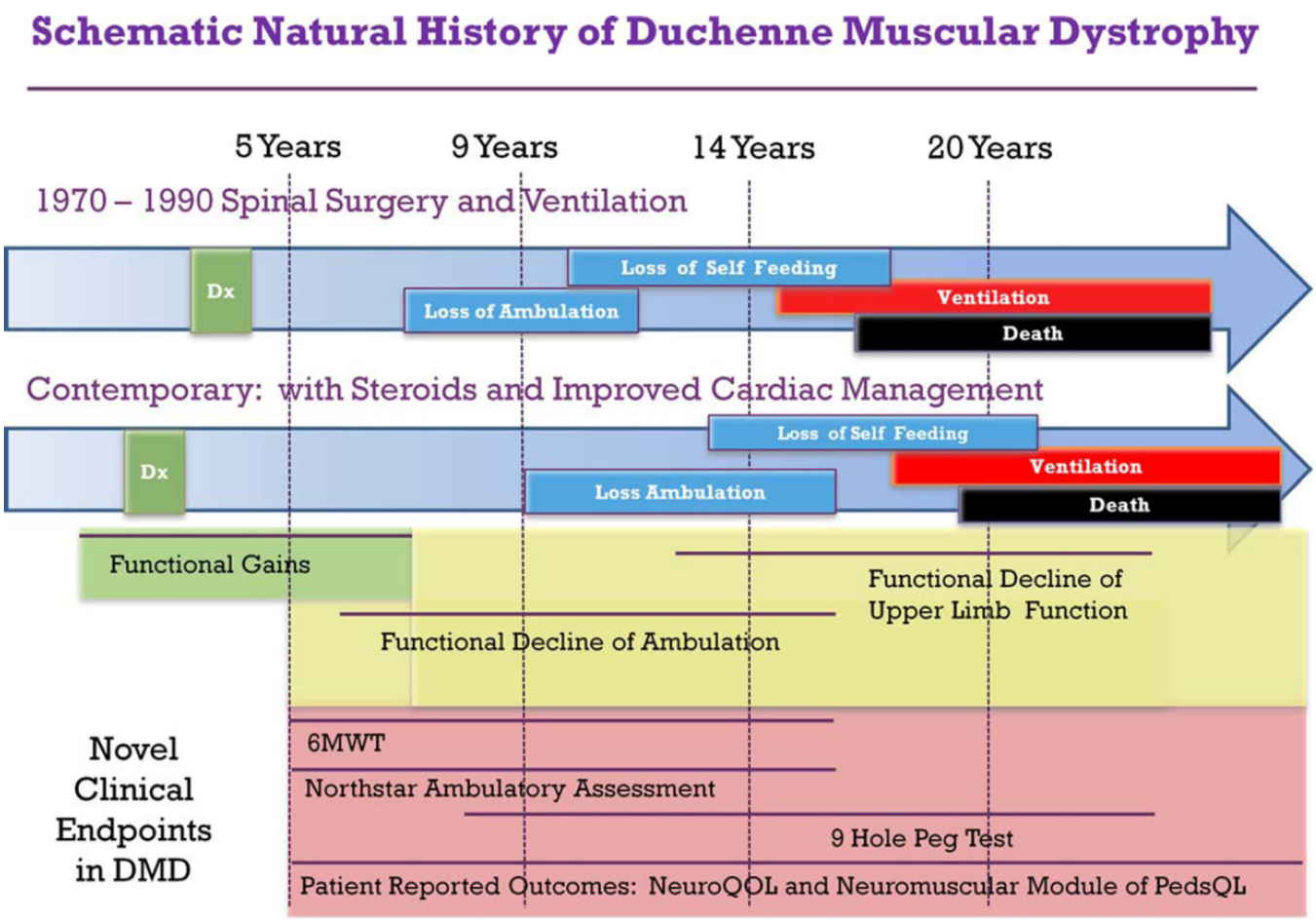

FIGURE 1.

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.]

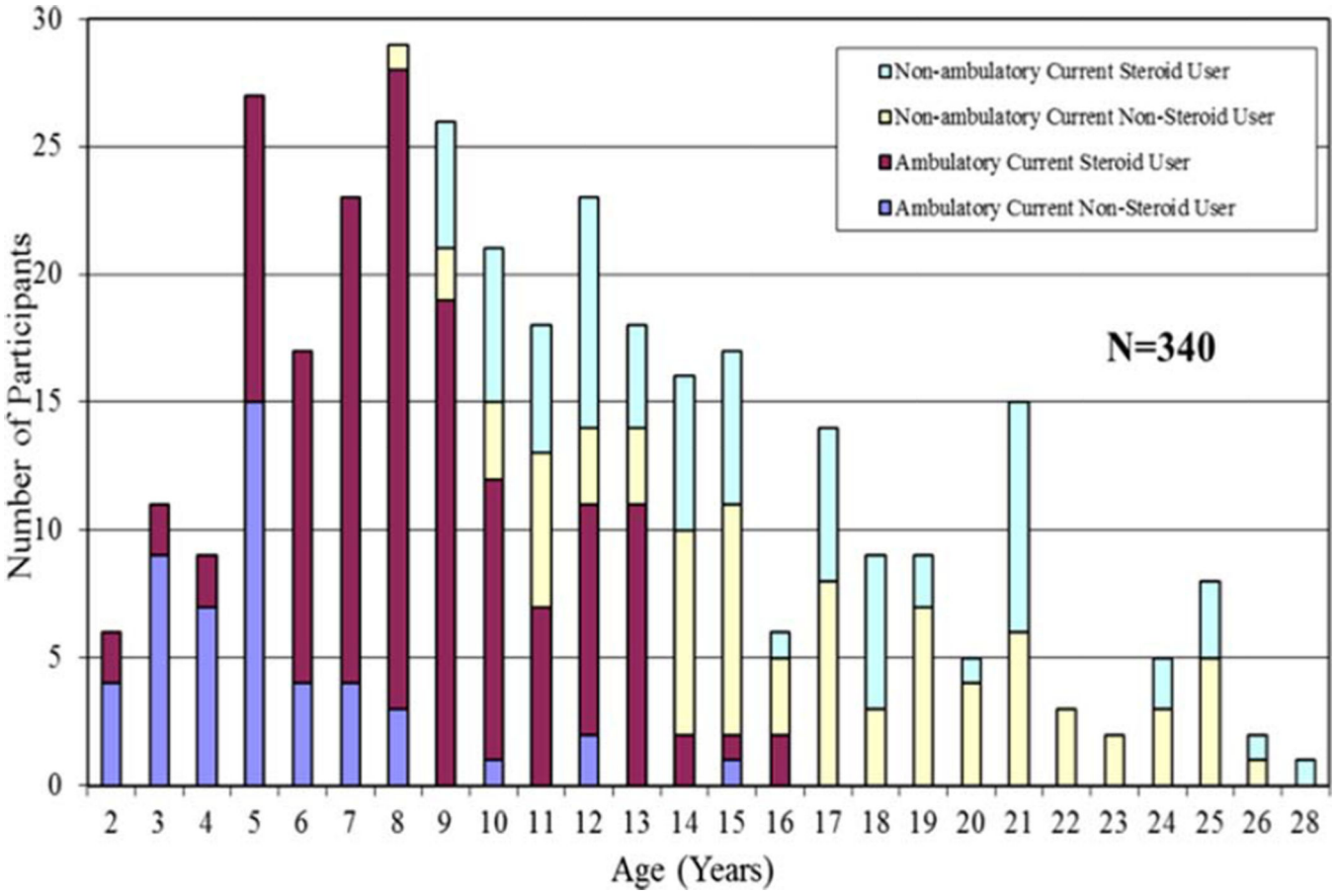

FIGURE 2.

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.]

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)	6	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	6 All	Chart Review
Cardiac: Echocardiography	6 All	Chart Review
Cardiac: Holter Monitoring	6 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	**Standard Protocol? Amb / Non-Amb**	**Time Required**

Body Structure / Function	**Standard Protocol? Amb / NonAmb**	**Time Required**
• **Satisfaction**		
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 [62–96]	+ 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; 1: administered to all; 6: Physician's Descretion; Amb: ambulatory; Non-Amb: non-ambulatory. For compete details see Appendix 2.

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-NaTve 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%)