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# Developing Standardized Corticosteroid Treatment for Duchenne Muscular Dystrophy

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## Abstract

Despite corticosteroids being the only treatment documented to improve strength and function in boys with Duchenne muscular dystrophy (DMD) corticosteroid prescription is inconsistent and in some countries, corticosteroids are not prescribed. We are conducting a clinical trial that (1) compares the 3 most frequently prescribed corticosteroid regimes; (2) standardizes treatment of DMD complications; and (3) standardizes prevention of corticosteroid side effects. Investigators at 38 sites in 5 countries plan to recruit 300 boys aged 4–7 who are randomly assigned to one of three regimens: daily prednisone; daily deflazacort; or intermittent prednisone (10 days on/10 days off).

Boys are followed for a minimum of 3 years to assess the relative effectiveness and adverse event profiles of the different regimens. The primary outcome is a 3-dimensional variable consisting of log-transformed time to rise from the floor, forced vital capacity, and subject/parent satisfaction with treatment, each averaged over all post-baseline visits.

The study protocol includes evidence- and consensus-based treatment of DMD complications and of corticosteroid side effects.

This study seeks to establish a standard corticosteroid regimen for DMD. Since all new interventions for DMD are being developed as add-on therapies to corticosteroids, defining the optimum regimen is of importance for all new treatments.

### Keywords

Duchenne muscular dystrophy; Standards of Care; Prednisolone; Deflazacort; randomized

## Introduction

DMD is the most common childhood muscular dystrophy with a birth incidence worldwide of 1 in 5,000 live male births [1]. Mutations in the dystrophin gene are responsible for the

disease. Untreated, boys with DMD develop progressive weakness during childhood and become unable to walk at a mean age of 9 years. After boys require full-time wheelchair use, they develop scoliosis, cardiomyopathy and respiratory failure. Without intervention, the mean age at death is 19 years; increased survival has been reported over the past 20 years with cases of survival into the third and fourth decades now common, possibly due to application of standards of care including corticosteroids, cardiac and respiratory support and spinal surgery [2–8].

Prednisone and deflazacort increase muscle strength and function in DMD [9–11]. Multiple long-term unblinded and uncontrolled studies have shown major long-term functional benefits from corticosteroids [12–15]. Side effects are well documented; particular concerns in DMD include weight gain, behavioral disturbance, growth restriction, pubertal delay, and increased risk of vertebral fractures [14,16].

Since the initial publications on the use of corticosteroids in DMD, concerns about the side effects of daily regimens have led to the development of many alternative regimens with a lower dosage or intermittent corticosteroids; only one intermittent regimen has been tested against placebo, while one other has been tested against daily corticosteroids [17–25]. Compared to prednisone, deflazacort has been shown to be associated with less weight gain; however, published long-term randomized clinical trial data are lacking.

The long-term outcomes of the many different regimens (up to 29 identified) are not clear; nevertheless, these regimens are in regular use in clinics around the world [26–28]. Inconsistency of dosage was seen among and within different countries. It is therefore clear that there is overall uncertainty concerning the best treatment regimen. Not only is the best regimen unknown, but there has been no effort to standardize side effect prevention and management. Patients and families have documented high levels of frustration with the *status quo* and ask explicitly for more information to be generated to guide practice [10]. Moreover, the lack of consistency in the steroid prescription in DMD can complicate evaluation of efficacy and safety of other interventions.

Many potentially disease-modifying treatments for DMD are in development (clinicaltrials.gov). So far, all trials have been designed to allow co-prescription with corticosteroids rather than considering corticosteroids as an alternative treatment, though a novel dissociative steroid has shown some promise in this regard [29]. The long term utilization of corticosteroids as standard of care for DMD with or without co-prescription of other therapies is, therefore, likely to continue for the foreseeable future.

The FOR DMD study compares three corticosteroid regimens, taken orally in the morning in line with normal clinical practice for these drugs: (1) 0.75 mg/kg/day prednisone; (2) 0.75 mg/kg/day prednisone 10 days on/10 days off; and (3) 0.9 mg/kg/day deflazacort. The study treatment is planned to last for a minimum of 3 years for all subjects, and longer for those recruited into the trial first. This paper presents a summary of the trial objectives and design. The full protocol is attached as an e-supplement.

## Objectives and Hypotheses

This international multicenter randomized, double-blind, parallel group trial has three interrelated goals that aim to improve the care of boys with DMD: (1) Identifying which of the three most commonly prescribed corticosteroid regimens is best over the course of three years in terms of muscle and respiratory function and patient/parent satisfaction (a balance between side effects and efficacy); (2) providing data on the outcomes of standardized prevention of DMD complications; and (3) providing data on the prevention and management of corticosteroid side effects (comparing their success in the three different regimens).

### Primary hypothesis:

Daily corticosteroids (prednisone or deflazacort) will be of greater benefit in terms of function and subject/parent satisfaction than intermittent corticosteroids (prednisone).

### Secondary hypothesis:

Daily deflazacort will be associated with a better side effect profile than daily prednisone.

The study protocol includes standardized regimens for prevention/treatment of the predictable corticosteroid side effects, as well as standards of care for the management of DMD. The trial directly addresses the current inconsistency in prescribed treatment schedules; its results will have direct impact on the current and future management of DMD boys throughout the world by providing the evidence base for rational clinical practice.

## Eligibility Criteria

The trial aims to recruit corticosteroid-naïve boys soon after diagnosis (age 4–5) at 38 sites in five countries (United States, Canada, United Kingdom, Germany, and Italy). Boys up to age 7 years 11 months are eligible if they have not been started on corticosteroids previously. The investigators believe that it would be unethical to withhold corticosteroids completely from boys with DMD (hence, there is no placebo arm) but have equipoise with respect to the relative benefits and risks of the three regimens. Enrollment of boys from a relatively narrow age range and standardization of all aspects of treatment facilitate the assessment of the relative benefits and risks of the three regimens.

Eligible boys are those with confirmed DMD (defined as male with proximal muscle weakness and confirmed DMD mutation in the dystrophin gene); age at least 4 years and under 8 years; ability to rise independently from the floor; willingness and ability of parent or legal guardian to give informed consent; willingness and ability to comply with scheduled visits, drug administration plan and study procedures; and ability to provide reproducible forced vital capacity (FVC) measurements (< 15% variability between two repeated FVC measures). Detailed inclusion and exclusion criteria are reported in the e-protocol.

## Randomization and Enrollment

Following confirmation of eligibility, the child can be randomized into the study. The computer-generated randomization plan is stratified by country and includes blocking within country. Details regarding the randomization process are contained in the e-protocol.

## Interventions and Blinding

Commercial stock prednisone and deflazacort differ in appearance and their use would have prevented blinding of subjects, parents, and study personnel to the allocated treatment. To achieve double-blinding, a clinical trials supplies company (Catalent, Ltd.) manufactured identical tablets of prednisone and deflazacort, as well as matching placebo to maintain blinding in the 10 days off period for the intermittent prednisone regimen. Study drug is presented in 20 day treatment wallets containing 2–6 tablets per day, depending on the weight band of the subject. Dosage banding for different steroid regimens is reported in the protocol (supplement).

## Evaluation and Follow-up

All boys are followed for a minimum of 3 years on study medication. The maximum duration of blinded treatment is 5 years. A baseline visit is performed within 3 months of the screening visit; boys are then evaluated at Months 3 and 6, and then every 6 months until the end of the study. Details of the evaluations are provided in the e-protocol.

## Standardization of DMD Care

Consensus-based guidelines [8,9] for treatment of DMD complications and corticosteroid side effect prevention are detailed in the e-protocol and include standard protocols for assessment and advice regarding diet, behavior, physiotherapy, and cardiac surveillance. Interventions and dosage modifications are provided for management of specific adverse events including excessive weight gain, behavioral problems, bone abnormalities, slowing of growth, gastrointestinal symptoms, hypertension, glycosuria, cataracts, infections, and skin changes. For specific areas, such as bone health and behavior assessment, expert opinion was sought to address the lack of guidelines as part of the current standards of care. For other areas lacking in clear recommendations, such as management of steroid related side effects, consensus was reached among the clinical experts on the study Steering Committee.

## Primary Outcome Variable

The selection of the multivariate primary outcome was based mainly on its clinical relevance. The early trials of prednisone focused on strength, as measured by manual muscle testing (MMT), as the primary outcome variable [11–14]. The difficulties involved in standardizing strength evaluations (using either MMT or quantitative muscle testing), in addition to the uncertain clinical relevance of changes in strength, led to consideration of outcomes that were more closely tied to function and were relatively easy to measure. The primary outcome variable was chosen to be a three-dimensional (multivariate) outcome consisting of the following three components (each averaged over all post-baseline follow-

up visits through Year 3): (1) time to stand from lying (log-transformed), (2) FVC, and (3) subject/parent global satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM) [30].

Loss of ambulation is a major milestone in the lives of boys with DMD, and altering the age at which this occurs is a major goal of corticosteroid therapy. Since treatment-naïve boys will be enrolled between the ages of 4 and 7, however, this milestone would not be achieved in many participants within a 3–5 year follow-up period. For this reason, time to stand from lying was selected as a marker of the decline in muscle function that was responsive to prednisone treatment in the early randomized trials. Forced vital capacity (FVC) was selected as a marker of respiratory function since respiratory failure is a major cause of death in DMD [31]. The successful use of FVC in young boys (aged 5–10) with DMD has been documented [32].

Global satisfaction with treatment is a patient-centered assessment of outcome that is particularly relevant in the setting of a non-curative therapy applied in a chronic disease. The Global Satisfaction with Treatment subscale of the TSQM was selected as a measure of the subject/parent-perceived balance of benefit and side effects that may be a major determinant of corticosteroid treatment success in DMD. Although side effects are a major concern with chronic daily treatment with corticosteroids, the plans for rigorous standardized prophylaxis of adverse events specified in the protocol are hypothesized to mitigate the negative impact of adverse events on overall satisfaction with treatment.

In summary, the three components of the primary outcome variable represent different but important aspects of the benefits of corticosteroid treatment. A multivariate outcome variable is particularly useful in a disease such as DMD that affects multiple clinically relevant domains; selection of a single primary outcome variable may be arbitrary in this case. It also leads to a substantial reduction in the required sample size for the trial relative to that for a single outcome variable, particularly when the components of the multivariate outcome are not highly correlated and the difference between two regimens is consistent across all components. A potential criticism of this approach is that the power to detect differences between regimens may be compromised if the regimens do not differ on all components in the same direction. On the other hand, the requirement of clear and consistent evidence of a difference in regimens across the three components may be seen as an appealing characteristic of this approach [33].

## Secondary Outcome Variables

Secondary outcome variables include the following continuous variables, averaged across all post-baseline follow-up visits through Year 3: time to run/walk 10 meters, distance walked in 6 minutes, North Star Ambulatory Assessment total score [15], TSQM subscale scores (Effectiveness, Side Effects, Convenience), range of motion in the ankle joint, cardiac function (as measured by transthoracic echocardiography and 12-lead ECG), and quality of life as measured by the PedsQL [34,35] 23-item generic core module and a 25-item neuromuscular disease-specific module, both completed by subjects (age 5 and over) and their parent(s)/guardians. Other secondary outcome variables include times from

randomization to various disease milestones such as loss of ambulation, loss of the ability to stand from lying, loss of the ability to rise from a chair, and loss of the ability to climb stairs.

Safety outcomes include adverse events, with particular attention to the known side effects of corticosteroids. Bone health is monitored by dual energy x-ray absorptiometry (DEXA) and spinal and wrist radiography. The primary tolerability outcome variable is the ability to complete 3 years of follow-up on the originally assigned dosage (for body weight) of study medication.

## Statistical Analysis

The primary statistical analyses will be performed according to the intention-to-treat principle and will include all available data from all randomized subjects. Every effort will be made to retain subjects in the trial and to collect all data at every visit. If a subject cannot tolerate or refuses to continue receiving the study drug, for whatever reason, the subject is asked to continue to be followed and evaluated, and any out-of-protocol treatment received by the subject is recorded. If a subject withdraws from the study, attempts are made to bring the subject in for a final evaluation. Compliance with trial procedures, treatment modifications, dropouts, and reasons for treatment modification and subject withdrawal are carefully tracked throughout the study. Missing data will be accommodated using multiple imputation [36,37].

The primary statistical analysis will consist of a global test of the null hypothesis that the corticosteroid regimens do not differ in mean response with regard to any of the three outcomes against the alternative that they differ in mean response (in the same direction) for at least one of the three outcome variables. The analyses will involve three separate pair-wise comparisons among the three treatment regimens using O'Brien's ordinary least-squares (OLS) statistic [38] each performed using a Bonferroni-corrected two-tailed significance level of 0.017. The analyses will be adjusted for covariates, namely country/region, baseline log-transformed time to stand from lying, baseline FVC, and initial weight band. Comparisons between regimens with respect to each of the individual components of the primary outcome variable will be performed using O'Brien's tests and a closed testing procedure [39].

A sample size of 100 subjects per group (300 total) was chosen by simulation to provide > 80% power to detect differences that are thought to be of minimal clinical significance (approximately 0.5 standard deviation units for at least two components of the primary outcome variable) between any two of the three treatment groups, using O'Brien's OLS test and a two-tailed 0.017 level of significance. The rationale for the choices of effect sizes is described in detail in the e-protocol and was based on existing relevant literature [9,18,30,40]. The simulations were performed assuming various correlations among the three components of the primary outcome variable and a 10% rate of subject withdrawal.

## Data and Safety Monitoring

The trial is conducted in accordance with the Declaration of Helsinki and Good Clinical Practice and was registered at www.clinicaltrials.gov (identifier NCT01603407). All parents/

participants provide signed informed consent/assent before any study procedure is performed.

An independent NIH-appointed data and safety monitoring board (DSMB) reviews data on safety and trial performance at least twice annually. Since there is no placebo group, absolute adverse event rates will be interpreted in the context of those observed in previous clinical trials of prednisone [16–22]; in addition, the DSMB will assess comparisons among the 3 corticosteroid regimens. Since the trial is designed to address the relative long-term benefit vs. side effect burden of different corticosteroid regimens, there are no planned interim analyses for efficacy or futility.

## Ancillary Studies of Corticosteroid-Associated Bone Loss and Genomics

The rigorous evaluation and longitudinal follow-up of this large cohort of 4–7 year old boys with DMD provides opportunities to prospectively evaluate genetic modifiers, proteomic and metabolomic responses to corticosteroids, as well as the relative effects of different corticosteroid regimens on bone health. Companion studies funded by the Parent Project for Muscular Dystrophy, the Muscular Dystrophy Association, the Italian Telethon, and the Association Francaise contre les Myopathies are ongoing to address these issues.

## Discussion

In 1989, a randomized, placebo-controlled trial demonstrated that daily prednisone rapidly increased strength in boys with DMD [3]. Subsequent studies with prednisone established that the minimum dosage with the maximum benefit was 0.75 mg/kg/day; lower dosages were not as beneficial and a higher dosage (1.5 mg/kg/day) provided no additional benefit [18]. Alternate day treatment was demonstrated to be less effective than daily treatment [16]. Despite clear and consistent evidence of the benefits of corticosteroids in DMD, prescriptions remain highly variable from country to country, and within and between clinics [26]. There are some countries (e.g., China and France) and many clinics in which corticosteroids are infrequently prescribed. Survival has been prolonged from the late teens to the late 20s, with reported cases of survival above age 40, possibly due to the application of standards of care, including corticosteroid use. Factors possibly responsible for the delay in acceptance of corticosteroid use include concerns about side effects and lack of familiarity with means of preventing them; the stated desire of boys and their parents to “wait for curative treatment”; the fact that corticosteroid treatment is “off label” since no effort was made to secure regulatory approval for corticosteroid use; and uncertainty about the different regimes. Lifespan in cystic fibrosis (CF), another rare genetic disease, has improved dramatically by the reporting of outcomes and standardization of the approach to treatment, suggesting that a similar approach might improve care in DMD [41]. Both length and quality of life were found to differ between clinics, empowering patients to seek care from clinics with better outcomes and encouraging clinics with poor outcomes to adopt better approaches to treatment. Some building blocks are in place to try to move towards a CF-like model for DMD; care guidelines are published and many patient registries are in place, but the lack of a standardized model of care for corticosteroid treatment remains a barrier.

The FOR-DMD trial has the potential to accomplish the aims of identifying the most beneficial initial corticosteroid regimen and, simultaneously, establishing standards of corticosteroid side effect prevention and management, and of treatment of complications of DMD. Such standardization provides a basis for the development of different approaches to treatment and better methods to prevent corticosteroid side effects. With novel agents likely to include co-prescription with corticosteroids, the identification of a consistent standard of corticosteroid administration becomes arguably even more important: widely varying corticosteroid regimens make it more difficult to determine the benefits and side effects of any new treatment co-administered with corticosteroids.

There are other unresolved issues regarding corticosteroid use: (1) Is there a better schedule of administration? (2) Is there a modified corticosteroid with comparable benefit and fewer side effects compared to current formulations? (3) Must all new treatments be combination therapy with corticosteroids? This trial lays the foundation for addressing these and other questions.

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