FULL PROTOCOL TITLE

Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen

(Short title: FOR-DMD)

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SYNOPSIS

Study Title:

Duchenne muscular dystrophy: double-blind randomized trial to find optimum steroid regimen

Abbreviated title:

FOR DMD

EudraCT number: 2010-023744-33

Objective:

This is a multi-centre, double-blind, parallel group, 36-60 month study, comparing three corticosteroid regimens in wide use in DMD:

- daily prednisone (0.75 mg/kg/day)
- intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off)
- daily deflazacort (0.9 mg/kg/day).

Primary study objective: The proposed randomized controlled trial will compare 3 corticosteroid regimens to address the pragmatic hypothesis that daily corticosteroids (prednisone or deflazacort) will be of greater benefit in terms of function and subject/parent satisfaction than intermittent corticosteroids (prednisone).

Secondary study objectives: A second hypothesis is that daily deflazacort will be associated with a better side effect profile than daily prednisone. The study protocol includes standardized regimens for prevention/ treatment of predictable side effects of corticosteroid medication, as well as standards of care for the general management of DMD. The trial directly addresses the current chaos in prescribed treatment schedules; its results will have direct impact on the current and future management of boys with DMD throughout the world by providing the evidence base for rational clinical practice.

The results of the trial will allow the generation of clear and specific evidence-based guidelines for patient treatment.

Design and Outcomes:

The primary outcome variable will be a three-dimensional (multivariate) outcome consisting of the following three components (each averaged over all post-baseline follow-up visits through Month 36): (1) time to stand from lying (log-transformed), (2) forced vital capacity, and (3) subject/parent global satisfaction with treatment, as measured by the Treatment Satisfaction Questionnaire for Medication.

Secondary outcome variables will include regimen tolerance, adverse event profile, secondary functional outcomes including the 6 minute walk test, quality of life, and cardiac function.

The primary statistical analysis will consist of a global test of the null hypothesis that the corticosteroid regimens do not differ with regard to any of the three outcomes against the alternative that they differ (in the same direction) for all three outcome variables. The analyses will involve three separate pair-wise comparisons among the three treatment regimens using O'Brien's OLS statistics, each performed using a Bonferroni-corrected two-tailed significance level of 0.017. The analyses will be adjusted for covariates, namely country/region, baseline time to stand from lying, baseline FVC and initial weight band. A

sample size of 75 subjects per group (225 total) will provide adequate power to detect differences that are thought to be of minimal clinical significance between any two of the three treatment groups, assuming a 10% rate of subject withdrawal.

Interventions and Duration:

The trial will randomize 225 boys aged 4-7 years to 0.75 mg/kg/d prednisone; 0.75 mg/kg/d prednisone for 10 days alternating with 10 days off; or 0.9 mg/kg/d deflazacort. All boys will complete a minimum of 3 years (36 months) of treatment period with the option to remain on study drug (blinded) up to 60 months. Boys electing to continue in this trial beyond 36 months will continue on blinded treatment but only primary outcome and safety variables will be collected at visits in Years 4 and 5. Subjects choosing to participate for the full 60 months of the trial will be unblinded to treatment after completion of their 60-Month (5-Year) study visit.

Commercial stock prednisone and deflazacort differ from one to another in appearance and their use would prevent blinding of subjects, parents and physicians to the allocated treatment. To achieve double-blinding, a clinical trials supplies company will manufacture identical tablets of prednisone and deflazacort, and matched placebo (to maintain blinding in the 10 days off period, for the intermittent prednisone regimen). This medication will be presented in form of tablets for oral administration. This solution is preferred to over-encapsulation of commercial stock tablets, as the resulting capsules would be quite large, presenting potential difficulties in swallowing for the younger children.

Study drug will be presented in 20 day treatment wallets containing 2-6 tablets per day (i.e. a total of 40 to 120 tablets), depending on the weight band, in a blister pack. Dosage banding for different steroid regimens will be as follows:

Band	Weight range in kg	Weight used for calculation of dose per kg	Dose in mg based on 0.75mg/kg Prednisone	Number of tablets of Prednisone (5 mg) for this dose	Dose in mg based on 0.9mg/kg Deflazacort	Number of tablets of Deflazacort (6 mg) for this dose
A	13-19.9	13.33kg	10mg	2	12mg	2
B	20-25.9	20.00kg	15mg	3	18mg	3
C	26-32.9	26.67kg	20mg	4	24mg	4
D	33-39.9	33.33kg	25mg	5	30mg	5
E	40+	40.00kg	30mg	6	36mg	6

Bands represent weight ranges.

Each wallet will be labelled with a multilingual booklet label and a single panel variable label. The wallets will be collated into kits containing either 7 wallets or 13 wallets. Each kit will be labelled with a multilingual booklet and a single panel variable label. Six months after study enrollment ceases, only 13-wallet kits will be used for the remainder of the study.

Sample Size and Population:

Eligible boys will be those with confirmed DMD (defined as male with clinical signs compatible with DMD AND confirmed DMD mutation in the dystrophin gene [deletion/duplication of one or more exons, that are predicted as 'out-of-frame', or other mutations that are expected to preclude production of the dystrophin protein (i.e. nonsense mutation, deletion/duplication leading to a downstream stop codon)] ; age at least 4 years and under 8 years; ability to rise independently from 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 maintain reproducible FVC measurements.

Exclusion criteria: history of major renal or hepatic impairment, immunosuppression or other contraindications to corticosteroid therapy; history of chronic systemic fungal or viral infections; diabetes mellitus; idiopathic hypercalciuria; lack of chicken pox immunity (as demonstrated by absence of antibodies via titer) and refusal to undergo no more than two separate immunizations (should initial immunization fail to produce antibodies); evidence of symptomatic cardiomyopathy; allergy/sensitivity to study drugs or their formulations; current or previous treatment with corticosteroids or other immunosuppressive treatments for DMD or other recurrent indications ; inability to take tablets; allergy/sensitivity to study drugs or their formulations; severe behavioral problems, including autism; previous or ongoing medical conditions, medical history, physical findings or laboratory abnormalities that could affect safety or impair the assessment of study results; weight of less than 13 kilograms; exposure to any investigational drug currently or within 3 months prior to start study treatment, unless exposure to investigational drug is a result of participation in a clinical trial that has a concurrent participation in FOR-DMD agreement in place.

A sample size of 75 subjects per group (225 total) will provide adequate power to detect differences that are thought to be of minimal clinical significance between any two of the three treatment groups, assuming a 10% rate of subject withdrawal.

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Abbreviations

6MWT 6 minute walk test
AAN American Academy of Neurology
AE Adverse Event
BMC Bone Mineral Content
BMD Bone Mineral Density
CIDD Clinical Investigations of Duchenne Dystrophy
CRF Case Report Form
DMD Duchenne Muscular Dystrophy
DXA Dual Energy X-ray Absorptiometry
ENMC European Neuromuscular Centre
eCRFs Electronic Case Report Forms
EK Egen Klassifikation scale
FOR-DMD Finding the optimum regimen for DMD
FVC Forced Vital Capacity
GCP Good Clinical Practice
ICH International Conference on Harmonization
IRB Institutional Review Board
MedDRA Medical Dictionary for Regulatory Activities
MOO Manual of Operations
NCTU Newcastle Clinical Trial Unit
NIH National Institute of Health
PedsQL Paediatric Quality of Life Inventory
QoL Quality of Life
REC Research Ethics Committee
ROM Range Of Motion
RRS Revised Rutter Scale
SAE Serious Adverse Event
SDQ Strengths and Difficulties Questionnaire
SOP Standard Operating Procedure
SSC Study Steering Committee
SUSAR Suspected Unexpected Serious Adverse Reaction
TSQM Treatment Satisfaction Questionnaire (Medication)
VS Vital Signs

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1 STUDY OBJECTIVES

This investigator-initiated Phase III trial compares three steroid regimens for boys with Duchenne muscular dystrophy in regard to functional outcome and subject/parent satisfaction. The long-term objective of this trial is to identify the optimum steroid regimen for boys with Duchenne muscular dystrophy.

1.1 Primary Objective

The primary objective is to compare three most commonly in use corticosteroid regimens (0.75mg/kg/day prednisone; 0.75mg/kg/day prednisone 10 days on/10 days off; 0.9mg/kg/day deflazacort) in regard to functional outcome and subject/parent satisfaction. The primary outcome variable is a multivariate (3-dimensional) measure, comprising two dimensions of function (time to rise from the floor, forced vital capacity) and one of satisfaction (global treatment satisfaction). The null hypothesis states that the three corticosteroid regimens do not differ from one to another with regard to any of the three dimensions of outcome while the alternative hypothesis states that they differ (in the same direction) with regard to at least one of the dimensions of outcome.

1.2 Secondary Objectives

The secondary objectives are to compare the three corticosteroid regimens with regard to:

- Tolerability
- Adverse events
- Secondary functional outcomes and disease milestones
- Quality of life
- Cardiac function

2 BACKGROUND

2.1 Rationale

The study population for this study is boys with confirmed Duchenne muscular dystrophy (DMD - defined as male with clinical signs compatible with DMD AND a confirmed DMD mutation in the dystrophin gene (out of frame deletion or duplication or point mutation); aged at least 4 years and under 8 years old at randomization and able to rise independently from the floor at that time (see Sections 4.1 and 4.2 for full inclusion and exclusion criteria). The age range reflects the population for which advice on corticosteroid treatment is of maximal clinical relevance.

DMD is the most common childhood muscular dystrophy with a birth incidence worldwide of 1 in 3,500 live male births. It is an X-linked recessive disorder, affecting almost exclusively boys. Mutations (mainly deletions) in the dystrophin gene are responsible for the disease. There is a high rate of new mutations in the dystrophin gene and in many cases there is no prior history of the disease in the family; prevention strategies are therefore not feasible on a large scale basis. The natural history of the disease is devastating and currently there is no curative treatment. Untreated, boys with DMD become progressively weak during childhood and are no longer ambulatory at a mean age of 9 years. Confinement to a wheelchair is followed by the development of spinal curvature, respiratory failure and cardiomyopathy. Without intervention, the mean age at death is 19 years (Brooke, Fenichel et al. 1983; Brooke, Fenichel et al. 1989).

The progression and complications of DMD are remarkably predictable, with only minor variation from child to child. However, interventions designed to modify disease progression have slowly made an impact on survival and quality of life in DMD. With the provision of home nocturnal ventilation to ameliorate the impact of respiratory failure, survival is now common into the late twenties and thirties (Simonds, Muntoni et al. 1998; Eagle, Baudouin et al. 2002). Surveillance and early treatment of cardiomyopathy alters the natural history of this complication (Eagle, Baudouin et al. 2002; Bushby, Muntoni et al. 2003; Duboc, Meune et al. 2005). Spinal surgery for scoliosis in addition to these other measures also improves survival. The perspective on DMD is therefore changing to recognize that it is a condition compatible with survival into adult life (Bushby, Finkel at al. 2010).

This study will compare 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 will last for a minimum of 36 months for all subjects, and a maximum of 60 months for those recruited into the trial first and wishing to continue beyond 36 months. The longer duration of blinded intervention and follow-up for those subjects recruited early is in anticipation of the continued long-term unblinded follow-up of the full cohort of subjects at the end of this 3-5 year study.

Corticosteroids are the only pharmacological interventions currently available that increase muscle strength in DMD. The use of corticosteroids was first suggested in 1974. A recent Cochrane review, ENMC report, and AAN practice parameter identified six randomized controlled trials (RCTs) that provided reliable data on the benefit of daily corticosteroids in DMD over short periods, using change in muscle strength as the primary outcome measure (Bushby, Muntoni et al. 2004; Manzur, Kuntzer et al. 2008; Moxley, Ashwal et al. 2005). Both prednisone/prednisolone and deflazacort have been shown to increase muscle strength. Prednisone is the formulation of choice for this trial, since it was the more widely used formulation in previous trials. Two long-term cohort studies, reporting on the unblinded follow up of the children started on treatment in the original RCTs or subsequently, have shown substantial long-term functional benefits from the intervention: prolongation of ambulation into the mid-teens, reduction in the development of scoliosis, major preservation of

respiratory function and possible protection against the development of cardiomyopathy (Biggar, Gingras et al. 2001; Silversides, Webb et al. 2003; Biggar, Politano et al. 2004; Biggar, Harris et al. 2006).

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 designed either to give a lower dosage of corticosteroids or to allow “steroid holidays”, including, regimens that do not use corticosteroids every day. Only one of these latter regimens has been tested against placebo, while one other has been tested against daily corticosteroids; (Fenichel, Mendell et al. 1991; Sansome, Royston et al. 1993; Backman and Henriksson 1995; Carter and McDonald 2000; Connolly, Schierbecker et al. 2002; Dubowitz and Kinali 2002; Kinali, Mercuri et al. 2002; Merlini, Cicognani et al. 2003; Escolar, Hache et al. 2011). The long-term outcomes of these regimens are not clear; nevertheless, they are in regular and long-term use in clinics around the world. The lack of consistency in practice was documented by the ENMC survey of muscular dystrophy clinic physicians from the U.S., Canada, and Europe (Bushby, Muntoni et al. 2004): only 3 of 15 centers questioned use daily prednisone 0.75 mg/kg/day, 4 do not use corticosteroids at all, and 8 use lower dosage or intermittent prednisone or an alternative agent (deflazacort). Inconsistency of dosage was seen among and within different countries. It is therefore clear that there is equipoise concerning the optimum treatment regimen. If alternative regimens are not as effective as daily treatment, boys treated on these regimens may not be getting an adequate dosage. Patient and family questionnaires document high levels of frustration with the *status quo* and ask explicitly for more information to be generated to guide practice and inform families (Bushby, Muntoni et al. 2004). Despite the publication of consensus statements on this topic, patient experience continues to be that widely different corticosteroid regimens remain in use (source: PPMD conference July 2006; Griggs, Herr et al. 2013).

2.2 Supporting Data

2.2.1 Summary

The current trial addresses questions that have arisen in the context of five previous controlled clinical trials of corticosteroids in DMD conducted by the Collaborative Investigation of Duchenne Dystrophy (CIDD) study group (Brooke, Fenichel et al. 1987; Fenichel, Florence et al. 1991; Fenichel, Mendell et al. 1991; Griggs, Moxley et al. 1991; Griggs, Moxley et al. 1993).

2.2.2 Short-term effect of prednisone

2.2.2.1 Muscle strength

Average strength as ascertained by manual muscle testing was used as a primary outcome variable in all six (Beenaker et al. 2005) randomized controlled trials of prednisone/deflazacort in DMD. Each of 34 muscles was graded on a ten-point scale using a modification of the MRC grading system (Brooke, Fenichel et al. 1983). The scores were averaged across the 34 muscles to arrive at the average muscle strength score. This outcome variable was highly reproducible and was responsive to the treatment effects of prednisone in as little as 10 days (Griggs, Moxley et al. 1991). The relatively short duration of treatment in the CIDD studies made the use of functional outcomes, such as cessation of ambulation or decline in forced vital capacity, less practical as measures of efficacy, though improvement in these parameters was observed in secondary analyses. In the CIDD studies of prednisone, strength improvement reached a maximum by three months post intervention and was maintained (relative to placebo) at six months and 18 months. Comparison of the average muscle strength scores before and after six months of treatment showed a 4.8% decrease in the placebo group compared to a 6.7% increase in the 0.75 mg/kg/day prednisone group ($p < 0.0001$) (Fenichel, Mendell et al. 1991; Griggs, Moxley et al. 1991).

The results of the studies with daily prednisone (0.75 or 1.5 mg/kg/day) for six months indicated that treatment increased muscle strength and significantly slowed the progression of weakness. Alternate day prednisone was less effective than daily treatment (Fenichel, Mendell et al. 1991). A lower dosage of prednisone (0.30 mg/kg/day) was associated with significantly less improvement in strength but showed a lower frequency of side effects (e.g., weight gain) (Griggs, Moxley et al. 1991).

2.2.2.2 Functional measures

Short-term (6 months) CIDD group data included standardized timed function testing: time to arise from supine to standing, time to traverse 30 feet, time to climb 4 standard stairs. After 6 months of treatment, there was a highly significant difference between prednisone and placebo for each measure of function. The average time to arise from the floor, from supine to standing for the placebo group was 6.17 vs. 4.17 seconds ($p<0.0002$) for the 0.75mg/kg/day prednisone treatment group (Mendell, Moxley et al. 1989). Similar data were obtained in another trial (Griggs, Moxley et al. 1991).

2.2.2.3 Forced vital capacity (FVC)

Short-term (6 months) CIDD data on pulmonary function included standardized measurement of FVC. After 6 months of daily prednisone 0.75 mg/kg/day, FVC was 10.5% higher in the treated group than in the placebo group ($p<0.0004$) (Mendell, Moxley et al. 1989) Nearly identical improvement was noted in another trial (Griggs, Moxley et al. 1991).

2.2.2.4 Quality of Life

Data on quality of life are available only from one short-term (six months) randomized placebo-controlled, crossover study using intermittent Prednisone 0.75 mg/kg/day for 10 days per month. The QoL did not change significantly during the prednisone period. With every new measurement, however, subjects reported a slightly higher QoL, irrespective of given medication, resulting in an improvement in the emotional functioning and the total scale (Beenakker, Fock et al., 2005).

2.2.2.5 Side effects

Corticosteroids have a well documented range of side effects, not all of which have been reported in the DMD population. The most common side effects in the CIDD group 6-18 month studies were weight gain and cushingoid change in facial appearance. Even with 18 months of prednisone 0.75 mg/kg/day there was no significant increase in the number of subjects with hypertension, diabetes, gastro-intestinal (GI) bleeding, vertebral fractures, or cataracts. Behavioral change, acne, and GI complaints were of similar frequency in prednisone vs. placebo participants at both 6 and 18 months. Weight gain >20% occurred in 75% of prednisone-treated boys after 18 months vs. only 43% of placebo-treated boys. Longer term, open follow-up (3 years) of CIDD subjects indicated that weight gain remained a problem. In addition, asymptomatic cataracts and glycosuria appeared in 11% of subjects treated for 3 years (Fenichel, Florence et al. 1991).

2.2.2.6 Comparisons with deflazacort

The CIDD group working as part of a U.S./Canadian MD collaborative group compared prednisone with deflazacort and placebo for 6 and 12 months of follow-up. Prednisone 0.75 mg/kg/day and deflazacort 0.9 mg/kg/day had comparable effects on muscle strength, muscle function, and FVC. Side effects were less on deflazacort: weight gain (over baseline) on prednisone was 26.7% and on deflazacort 6.8 % (statistically significant, $p < 0.01$). Other studies of deflazacort showed similar results, but publication of randomized clinical trial data, especially over longer term treatment is lacking (Loftus, Allen et al. 1991; Angelini, Pegoraro et al. 1994; Bardare, Bianchi et al. 1994; Markham, Bryson et al. 1995; Reitter 1995; Lippuner, Casez et al. 1998; Biggar, Gingras et al. 2001).

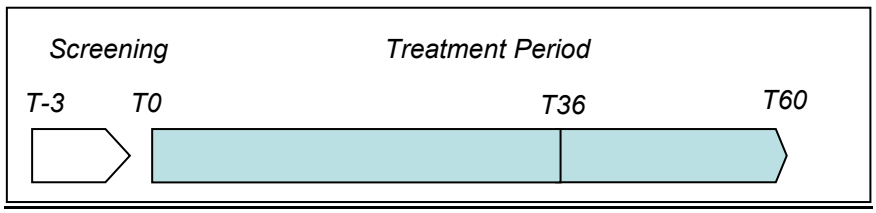
3 STUDY DESIGN

3.1 OVERVIEW

The study is an international, multicentre, randomized, double-blind controlled trial comparing three active corticosteroid regimens over three years of treatment: daily prednisone (0.75 mg/kg/day) versus intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off) versus daily deflazacort (0.9/mg/kg/day). All three regimens are in common use in boys with Duchenne muscular dystrophy. Prednisone is a corticosteroid licensed for use in a wide range of conditions. It has been shown to improve muscle function in boys with DMD. Prednisone, rather than prednisolone, is the formulation of choice for this trial for consistency and comparison with other trial data. Prednisone is not currently licensed for use in DMD and will therefore be considered an investigational medicinal product for the purposes of this trial. Deflazacort is a glucocorticoid derived from prednisolone, and is licensed in Europe for use in a wide range of conditions. Deflazacort is not currently licensed for the indication of muscular dystrophy and there has been less exposure of children to deflazacort compared to prednisone in clinical trials. Moreover, deflazacort is not approved for any indication in the U.S. Therefore for the purposes of this trial it will be considered an investigational medicinal product.

It is anticipated that it will take 3.5 years to enroll all 225 subjects. Those recruited and therefore completing the three years of treatment first will have the option to continue study medications in a blinded fashion until they have completed 5 years of treatment. Therefore, all subjects will receive a minimum of 36 months of study medication and up to a maximum of 60 months treatment. This study will determine the relative efficacy and sustainability of these regimens over a longer time period than has previously been addressed.

A unique feature of this trial, designed to make it truly relevant to clinical practice and standardized across such a large number of diverse sites, is the consideration given to standards of care, which might otherwise impinge on the outcomes of the trial, and the provision of clear guidelines to be applied across the trial population for the prophylaxis, monitoring and treatment of predictable corticosteroid related side effects / adverse events (Bushby K, Finkel R, 2010).



3.2 Primary outcome measures

The primary outcome variable will be a three-dimensional outcome comprising muscle function, respiratory function and treatment satisfaction (see below). The average changes over all post-baseline assessments during the three year follow-up period will be of primary interest.

3.2.1 **Muscle function** (time taken to rise from the floor, from supine to standing)

A highly relevant functional endpoint in DMD is loss of independent ambulation, and altering the age at which this occurs is a major goal of corticosteroid therapy. However, within the

three-five year time span of this trial, this milestone will not be reached by most subjects, who will be enrolled at age 4-7 years. The time taken to rise from the floor progressively deteriorates over time and the ability to rise from the floor is lost before the loss of independent ambulation (McDonald, Henricson et al., 2010). The measure of choice is therefore a marker of decline in muscle function – the time taken for the subject to rise from the floor, from supine to standing, captured as part of the North Star Ambulatory Assessment.

3.2.2 **Respiratory function** (Forced Vital Capacity – FVC)

As respiratory failure is a major cause of death in DMD (Phillips, Quinlivan et al. 2001), improvement of the course of respiratory function, as measured by forced vital capacity, is a marker for potential increase in the time until nocturnal ventilation is required, and indeed of longevity and quality of life. Because of the young age of the subjects specific procedures have been developed to ensure reliability of measurements and to aid cooperation with the test. Subjects may be sent home with practice aids to help reaching reliability and reproducibility of the FVC measures. Re-test can be performed at any time within the 90-day Screening Period.

3.2.3 **Parent/subject satisfaction with treatment** (global satisfaction rating from the Treatment Satisfaction Questionnaire for Medicine (TSQM))

Satisfaction with treatment is a patient-centered assessment of outcome, particularly relevant to a non-curative therapy applied in a chronic disease. The TSQM (Atkinson, Sinah et al. 2004) has been validated in chronic disease groups and can determine the subject/parent perceived balance of benefit and side effects that may be a major determinant of corticosteroid success in DMD. The TSQM is a 14-item instrument, yielding four subscale scores: global satisfaction; effectiveness; side effects; and convenience. In this trial, because of the young age of the subjects, the parent(s) will complete the TSQM. Feasibility of this as a proxy measure has been demonstrated at the University of Rochester (Herr, Hart et al. 2008).

3.3 Secondary outcome measures

The secondary outcome variables will include regimen tolerance, adverse event profile, secondary functional outcomes, quality of life, and cardiac function.

3.3.1 Tolerability

The key *s*econdary outcome variable ("tolerability") will be the ability to tolerate the starting regimen of corticosteroids, defined as completing 3-5 years of follow-up on study medication with no deviation from the initially prescribed dosage level (increases in dosage band to accommodate growth and weight gain are allowed).

3.3.2 Adverse events

A key factor to be taken into account in determining the most useful steroid regimen is the adverse event profile with the different regimens.

The rates of occurrence and/or severity of the following predictable adverse events (i.e., known side effects of corticosteroids) will be recorded.

- Behavior problems

- Bone fractures
- Cataracts
- Cushingoid features
- GI symptoms
- Hypertension
- Immune/adrenal suppression
- Slow growth (height restriction)
- Skin changes
- Weight gain
- Diabetes

Areas where side effects prophylaxis and management have been closely prescribed include behavior changes, bone health, weight gain, and ocular changes.

- **Behavior changes**

A feared but to date poorly quantified side effect of corticosteroids in DMD is altered behavior. Behavioral problems are also reported in this group of patients without steroid treatment (Hinton, Nereo et al. 2006). Two particular aspects of behavior were identified as being particularly important for study in this trial: emotional well being and behaviors within the ADHD spectrum. The PARSIII, Iowa Conners scales and Strengths and Difficulties Questionnaire (SDQ) will be used to capture and document behavior changes, both negative and positive. Moreover, emotional distress will be assessed using the Revised Rutter Scale (RRS).

- **Bone health**

Long-term corticosteroid treatment has been proven to induce loss of bone mass and to increase the rate of fragility fractures even in young patients (Crabtree, Roper et al. 2010). Corticosteroids affect bone metabolism and calcium homeostasis, inhibiting of osteoblast activity and intestinal calcium absorption, hampering renal handling of calcium, and suppressing secretion of gonadal hormones and growth hormone. The net result is an increased bone resorption. Concerns about bone health with and without corticosteroid treatment in DMD have recently been the subject of three workshops (Biggar, Bachrach et al. 2005; Quinlivan, Roper et al. 2005; Quinlivan, Shaw et al. 2010). To study the side effects of corticosteroid therapy on bone, the changes in bone density (as assessed by DXA scans), the frequency of fractures and the changes in bone turnover markers (in serum and urine) will be evaluated. For each fracture occurred during the study, the age, site, circumstances, treatment and outcome will be recorded. DXA scans will not be performed at recruiting sites in Germany, per local regulations.

All boys (with the exception of those in Germany) will have a lateral spine x-ray at their 36 Month visit. An ancillary collaboration with Dr. Leanne Ward (Medical Director of the Children's Hospital of Eastern Ontario - 'CHEO' - Bone Health Clinic) and Eric Hoffman, PhD (Vice President of Research, ReveraGen BioPharma) will allow for centralized reading of vertebral fractures in these de-identified spine images, once all FOR-DMD subject follow-up visits have been completed (i.e., upon FOR-DMD trial completion). Images will be uploaded by the study sites into the Ottawa Bone Health Portal - a centralized, password-protected database (subjects/families will be asked to provide verbal consent for this via telephone conversation with their local FOR-DMD site PI/study staff). The aim is to use the bone health data already collected in FOR-DMD (once published) to ultimately understand the relative impact of three difference conventional glucocorticosteroid prescriptions on bone health in boys with DMD compared to the novel dissociative steroid, vamorolone.

- **Weight gain**

The most common short and long-term side effect of corticosteroids is weight gain, especially in the age-range population recruited in this trial (Mendell, Moxley et al. 1989; Griggs, Moxley et al. 1991; Griggs, Moxley et al. 1993). Body weight will be strictly monitored in this trial and prophylactic measures have been planned with particular emphasis on advice on appetite control around the time that treatment is started. Advice on healthy eating will be reinforced at each follow up visit throughout the study.

- **Ocular changes**

Recent evidence indicates deflazacort may be more likely to cause cataracts and might also cause glaucoma in a larger population of patients. As a safety measure, and because study treatment assignment is blinded such that boys taking deflazacort cannot be identified until the entire study has been completed, all boys participating in the FOR-DMD trial will be strongly encouraged to have a through eye examination by an ophthalmologist upon their completion or withdrawal from the study. Recommended assessment includes visual acuity, intraocular pressure, slit-lamp lens exam and funduscopic exam (cup to disc ratio).

3.3.3 Secondary functional outcomes and disease milestones

3.3.3.1 The North Star Ambulatory Assessment (NSAA)

The NSAA was developed specifically to address the need for a reliable evaluation of motor ability in ambulant children with DMD between the ages of 4-7. The starting point was the original Hammersmith Scale of Motor Ability (Main, Kairon et al., 2003). The NSAA addressed concerns about this scale relating primarily to ceiling effects, grading and lack of standardized instructions. In addition clinically meaningful items related to the construct of ambulation in DMD boys were selected by a group of expert physiotherapists in DMD taking into consideration the natural progression (or potential improvement) of the disease in ambulant boys (Scott and Mawson, 2006). The NSAA encompasses the important disease milestones such as ability to rise from the floor and ability to walk as well as skills that may be achieved or maintained following the use of steroids such as running, walking, hopping, jumping and lifting the head from supine. The scoring system reflects the disease specific characteristic patterns of movement seen in DMD. Each individual item is scored on an ordinal (three point) scale based on key functional activities that accurately reflect the course of the disease. Further validation of the scale has taken place in a multicenter study where the reliability between evaluators has been shown to be very good (Mazzone ES, Messina S et al., 2009). Furthermore recent psychometric evaluation (Rasch analysis) of the scale using assessments from 187 ambulant boys with DMD living in the UK has shown that the scale measures what it intends to, i.e. its construct validity is good (Mayhew, Cano et al. 2011). Rash analysis has shown that the item grades are clinically relevant as well as distinct and ordered correctly.

The NSAA is also a secondary outcome in several international multi-center trials addressing the efficacy and safety of new therapeutic approaches (e.g. exon skipping).

Application of the NSAA will provide the following secondary outcome measures in addition to the total score of functional ability:

- Timed functional tests, comprising time to rise from the floor (a component of the primary outcome) and time to traverse (walk/run) 10 meters. Of primary interest will be the average value of these outcomes over all post-baseline visits over the three year follow-up period.
- Timed Function Test Grading of the 10 meter walk/run and the timed rising from floor will be assessed on a 6 point scale to differentiate those subjects with similarly fast times who may achieve a ceiling time.

- Documentation of additional motor skills that are not normally present in DMD - i.e., percentage of follow-up time over which the child is able to jump, run, hop, step up and down, and raise the head from supine.

The use of the NSAA will also allow us to capture disease milestones

- Time from randomization to loss of ambulation
- Time from randomization to loss of the ability to stand from lying
- Time from randomization to loss of the ability to rise from a chair
- Time from randomization to loss of the ability to get up and down one step

3.3.3.2 6MWT

The 6 MWT has been specifically adapted for use in patients with DMD and was the primary outcome in the phase 2b trial of PTC 124 (McDonald CM, Henricson EK, et al., 2009). The 6MWT will provide a measure of walking endurance compatible with daily life walking activity.

3.3.3.3 Range of motion (goniometry)

Many of the physiotherapeutic interventions relate to prevention of contractures particularly at the ankle joint. Documentation of range of motion at the ankle joint will ensure consistency of physiotherapy interventions in accordance with prescribed physiotherapy intervention and advice. Range of motion at the ankle joint will be measured with a standard goniometer. Training will be given and specific detailed instructions are included in the manual of operations.

3.3.4 Quality of Life

An additional domain of the secondary outcome measures for the trial will be quality of life. Most previous trials of corticosteroids in DMD have not included this element of treatment impact.

The PedsQL (Varni, Seid et al. 1999; Varni, Seid et al. 2001; Varni, Seid et al. 2002) is a modular measure for which a neuromuscular disease-specific module has recently been developed. Both the generic core module of the PedsQL and the disease-specific fatigue module will be used. The generic core module comprises 23 questions and the NMD-specific module comprises an additional 25 questions.

Quality of life will be measured both by child self-report (only in children aged 5 years and over, who have the required levels of literacy and intellectual capacity to respond) and by proxy (parent(s)/guardian(s)) report for all children. The average values of these outcomes over all post-baseline assessments during the three year follow-up period will be of primary interest.

3.3.5 Cardiac function

It has been established that even in this young age group of boys with DMD, there is a recognizable incidence of cardiomyopathy detectable on echocardiography and early treatment is indicated to slow its progression (Bushby, Muntoni et al. 2003; Duboc, Meune et

al. 2005). In this young population, earliest definite, echo detectable impairment of left ventricular function is defined as ejection fraction < 55% and/or fractional shortening < 28%. In the long term, the use of corticosteroid may have a cardio-protective effect (Silversides, Webb et al. 2003; Markham, Spicer et al. 2005). Cardiac status will be monitored by trans-thoracic echocardiogram and 12-lead ECG at screening and every two years to the age of 10 years, and annually thereafter, according to published guidelines (Bushby, Muntoni et al. 2003); Bushby, Finkel et al. 2010) If echocardiogram shows any impaired left ventricular function and/or or evidence of regional motion abnormalities (posterior wall), the interval between evaluations will be reduced and adequate treatment will be initiated if indicated accordingly with guidelines/standards of care.

3.4 Definition of end of study

The end of the study will be 30 days after the point at which the last enrolled subject completes the 36 month treatment period.

4 SELECTION AND ENROLLMENT OF SUBJECTS

4.1 Inclusion criteria

1) Evidence of signed and dated informed consent form indicating that the subject and his parents or guardian (according to local legislation) have been informed about all pertinent aspects of the study. *The child might be asked to give his assent, possibly in writing, if considered intellectually capable, in line with the legal requirements in the participating countries and with the permission of the parent(s)/guardian(s).*

2) Confirmed diagnosis of Duchenne muscular dystrophy defined as: Male with clinical signs compatible with DMD AND a confirmed DMD mutation in the dystrophin gene (deletion/duplication of one or more exons, that are predicted as 'out-of-frame', or other mutations that are expected to preclude production of the dystrophin protein (i.e. nonsense mutation, deletion/duplication leading to a downstream stop codon))

3) Age ≥ 4 years and < 8 years at time of randomization.

4) Ability to rise independently from floor, from supine to standing, as assessed at screening visit.

5) Willingness and ability to comply with scheduled visits, drug administration plan and study procedures (including laboratory tests, NSAA, 6MWT, ECG, Echo, wrist X-Ray, DXA, PedsQL and TSQM questionnaires) as assessed by the site investigator at the end of the screening period.

6) Ability to maintain reproducible FVC measurements. *Boys must have reproducible measurements of FVC. The boy will be observed to insure complete understanding of the instructions and that he has given maximal effort. If the values continue to increase, the boy may be learning and testing will continue, if necessary, beyond the 3 required trials until the boy reaches a plateau. To ensure the boy is capable of performing a reliable FVC, a SECOND FVC must be completed at the end of all other assessments at the Screening visit. To be eligible for randomization, there must be no more than a 20% difference between the best FVCs on the first and the second attempts. Additional FVC information is provided in the Clinical Evaluator Manual.*

4.2 Exclusion criteria

1) History of major renal or hepatic impairment, immunosuppression or other contraindications to corticosteroid therapy.

2) History of chronic systemic fungal or viral infections. *Acute bacterial infection (including TB) would exclude from enrolment until the infection had been appropriately treated and resolved.*

3) Diabetes mellitus.

4) Idiopathic hypercalcuria.

5) Lack of chicken pox immunity (as demonstrated by absence of antibodies via titer) and refusal to undergo no more than two separate immunizations (should initial immunization fail to produce antibodies).

6) Evidence of symptomatic cardiomyopathy at screening assessment. *Asymptomatic cardiac abnormality on investigation would not be an exclusion.*

7) Current or previous treatment (greater than four consecutive weeks of oral therapy) with corticosteroids or other immunosuppressive treatments for DMD or other recurrent indications (e.g., asthma).

8) Inability to take tablets, as assessed by the site investigator by the end of the screening period.
9) Allergy/sensitivity to study drugs or their formulations including lactose and/or sucrose intolerance.
10) Severe behavioral problems, including severe autism.
11) Previous or ongoing medical condition, medical history, physical findings or laboratory abnormalities that could affect safety, make it unlikely that treatment and follow up will be correctly completed or impair the assessment of study results, in the judgment of the site investigator.
12) Weight of less than 13 kilograms.
13) Exposure to any investigational drug currently or within 3 months prior to start of study treatment, unless exposure to investigational drug is a result of participation in a clinical trial that has a concurrent participation in FOR-DMD agreement in place.

4.3 Study enrollment procedures

4.3.1 Identification and recruitment methods

All of the centers participating in the trial are referral centers for the diagnosis and management of DMD and other pediatric neuromuscular disorders and are responsible for the diagnosis of DMD within a specific geographical/population area. All subjects fulfilling the age and diagnostic criteria will be identified either at diagnosis or through investigators' clinical databases, national and international registries or referrals, and potential eligibility for the study will be determined by reference to the inclusion and exclusion criteria (Sections 4.1. and 4.2 above) in so far as these are documented in the child's medical records. Those children appearing to meet study eligibility criteria based on the pre-screening review will be invited to attend for a screening visit. In advance of this visit, parents/guardians will be provided with written information about the trial in the local language (or a translation appropriate to their linguistic needs). This will be supported by information from local patient information groups who will be involved in publicizing the trial, where available. The trial information will be provided in a format for both parents (or guardians) and the boys themselves (at their parents' or guardians' discretion). This information will be supplied sufficiently far in advance of the screening visit, to allow parents/ guardians time to read and discuss the material with family members and health professionals, as desired. The opportunity to discuss the trial with a member of the study team will be also given (contact details will be provided with the study information sheets).

4.3.2 Consent and assent procedures

At the screening visit, the parent(s)/guardian(s) (with legal authority to consent on behalf of the child) and the child (at the discretion of the parents/guardians) will be given the opportunity to discuss the study with site personnel and to have any questions about the study answered. Only after their questions and concerns have been adequately addressed will their informed consent be sought. Consent and assent documents will be provided in the local language (or a translation appropriate to their linguistic needs). The procedure for obtaining informed consent and assent (e.g., whether one or both parents must provide consent) will be in line with the legal requirements in the participating countries; full details are given in the Manual of Operations. The consent form will be signed and dated by the parent(s)/guardian(s) and by the site Principal Investigator (or other member of the site investigation team who has been formally delegated this role – see the Manual of Operations). An original and two copies of the completed consent form will be made: one

copy to be given to the parent(s)/ guardian(s) along with a copy of the trial information sheet; the original will be filed in the Site Study File; one copy will be filed in the child's general medical records.

Where the child is intellectually capable of assenting (and in accordance with local regulations), and with the permission of the parent(s)/ guardian(s), the assent of the child himself will also be obtained, if possible in writing, copied and filed as for the consent form.

4.3.3 Documentation of outcomes of screening procedure

At the screening visit, subjects will be recruited following the provision of informed consent and assent (as described in Section 4.3.2). Since the assessment of eligibility may require the performance of procedures that are not part of normal clinical practice, informed consent will be sought prior to performing any study-related screening procedures. Eligibility of the child will then be re-assessed with reference to the inclusion and exclusion criteria (see Sections 4.1 and 4.2 above). For some of the criteria, a screening period of between 1 and 3 months will be required (e.g., to assess bone and cardiac status, compliance with evaluations and trial medication, and screening for prior exposure to chicken pox or immunization). [For further details of screening visit assessments, see Section 6 below and the Manual of Operations.]

Following consent procedures, the CRF 01 will begin to be completed by the site personnel, providing the following information:

- Subject identification number
- Subject initials
- Subject date of birth
- Date of screening (visit 1)

The subject study ID number is 8 characters, 5 characters are given to the site number and 3 characters for the subject number. The subject number at screening is preceded by S (6th character of full Study ID number) followed by 2 numbers (01-99) (e.g. DEU01S01 for the first subject screened at the first site in Germany). [If the subject is randomized the S will drop out and be replaced with an R and the 8 characters will be the unique subject identification number].

Following screening procedure, a screening log (CRF00) will be completed by the site study coordinator as part of the screening CRFs and transmitted to the MSG Coordination and Biostatistics Centers (Rochester) via a web-based system with user name and password access to maintain a central screening monitor. Upon confirmation of all subject eligibility requirements the subject can be randomized and the baseline visit can be arranged. Randomization should be completed via the web-based system at least 10 days prior the baseline visit in order to allow study drug supply to be shipped to the site in time (see section 4.3.4 below).

Subjects deemed to be ineligible may be re-screened if there are any changes in their eligibility status. Screening failures will be also recorded using the screening log, along with the reason for each invited child not participating (e.g., did not attend screening visit, ineligible due to concomitant illness, unwilling to consent due to preference for one drug regimen or other clinical trials or any other exclusion criteria).

4.3.4 Randomization procedures

Following consent and confirmation that the child is indeed eligible for the study, the child can be randomized into the study. Randomization should be performed at least 10 days prior the baseline visit (see Section 6 and the Manual of Operations) and will be achieved via a

web-based system with user name and password access. Randomization will be stratified by country. At the beginning of the trial, the clinical trials supply company will be provided with a list of allocations per country, corresponding to this randomization schedule.

Randomization will require the site investigator, or designee, to verify that the child meets the inclusion/exclusion criteria of the study, and to verify that the child has not already been randomized. CRF01 (Screening and Randomization Form) must be completed via the web-based system, so that the system can assign the subject to a treatment group.

When the site investigator/designee completes the randomization procedures via the web-based system, an e-mail report with the randomization number, the subject study ID number and the starting dose will be generated and sent to the site investigator, to the clinical trials supply company, the NCTU, the US Project Manager, and the MSG Coordination and Biostatistics Centers (Rochester) confirming enrollment into the trial. Following completion of randomization procedures, the subject study ID number will be 8 characters (5 characters given to the site number and 2 progressive numbering from 01 to 99 preceded by R which replaces the S given at screening) (e.g., DEU01R01). From the baseline visit, this number will be the unique subject identification number entered by the site on all subsequent worksheets and CRFs.

The randomization number will be assigned by the web-based system and will be only used for study drug supply and shipment. Once the information (randomization number, subject identification number and subject weight) have been received and reconciled (by reference to the randomization number), the clinical trials supply company will prepare a subject-specific kit of medication and ship it to the site (see Section 5.1.2 below).

Randomization procedures should be completed at least 10 days prior to the baseline visit in order to allow study drug supply to be shipped to the site in time to be provided to the subject by the site investigator at baseline visit.

4.3.5 Blinding

To achieve double-blinding, a clinical trials supplies company will manufacture identical tablets of prednisone and deflazacort, and matched placebo (to maintain blinding in the 10 days off period, for the intermittent prednisone regimen). Subjects, parents/guardians, site investigators and all other site study staff will not know which steroid regimen has been assigned and will remain blinded to the identity of the treatment assignment until the subject has reached their 36-Month Visit. The only exception to this is if study drug becomes temporarily unavailable (expired, compromised, etc.) for a period of more than 21 days, such that a subject requires a prescription of prednisone/prednisolone to bridge the gap of study drug unavailability and knowledge of who is on the intermittent treatment regime is required to ensure the subject's continued safety.

After the 36-Month Visit, if the subject desires to transition to a different clinical trial that does not allow for concurrent participation in FOR-DMD and for which the subject's treatment regimen must be known for inclusion, the FOR-DMD treatment blind will be broken. Furthermore if, after the 36-Month Visit, it is clinically warranted, the treatment blind will be broken. If the blind is broken for either of the reasons previously stated, the treatment regimen will be shared on a "need-to-know" basis only. The subject/family will be informed, and the site PI (if necessary), but the blind will be maintained for all other study staff. Additionally, the subject/family will be asked to not reveal their FOR-DMD treatment regimen with other members in the DMD community, either verbally or via social networking. Prior to completion of the Month 36 visit, the FOR-DMD treatment regimen will not be revealed to subjects/families, site investigators, or study staff unless warranted in a medical emergency.

Subjects who have their treatment blind broken at the 36-Month visit (or withdraw from taking study medication at any point in the trial), will be asked if they are willing to continue with

their FOR-DMD visits for follow-up, as per protocol. If they decide to continue receiving corticosteroids outside the FOR DMD trial, these can be prescribed by their local clinician as per local requirements.

Subjects electing to remain on blinded treatment after their 36-Month visit and until their study completion will have their treatment regimen revealed upon occurrence of the following: 1) completion of their 60-Month visit or 2) after data from all subjects have been collected and the database has been locked. Once a subject has completed his 60-Month visit, the treatment blind will be broken on a "need-to-know" basis only, as described above. Families will be asked not to share the treatment regimen with the DMD community or via social networking, so as not to potential unblind those still participating in the trial. Subjects or families who subvert the blind should be discontinued from the study.

4.3.6 Blinding and concurrent participation in other trials

Due to the longevity of follow-up in the FOR-DMD trial (up to 5 years), it is recognized that other trials for Duchenne muscular dystrophy (both investigator-led as well as industry-sponsored) will likely be initiated during this time period and may vie for subject participation. Some of these trials may be particularly appealing should they offer new, investigative treatments beyond a corticosteroid regimen. Nevertheless, for treatments currently under study/consideration, concomitant corticosteroid treatment is recommended.

If a FOR-DMD subject expresses interest in participating in a separate DMD trial, the site PI/study staff should notify the FOR-DMD Chief Medical Coordinator (CMC) and the Project Manager of the trial/sponsor in question. The CMC or Project Manager will contact the appropriate parties responsible for the other trial to determine if concurrent participation in two separate treatment trials would be feasible. In most cases, the concurrent trial would require knowledge of the potential subject's corticosteroid regimen as an inclusion criterion. The FOR-DMD Team will consider sharing a FOR-DMD subject's treatment regimen (break the treatment blind) only if an agreement has been reached with the other trial/sponsor to ensure that the unblinded information will remain protected and will in no way be revealed to the subject/family or study staff (PI, coordinator, etc.). If an agreement between the FOR-DMD Team and the specific trial/sponsor is not reached, and the subject chooses to enter the separate treatment trial, he will have the option to withdraw from the FOR-DMD study drug (following a medically-supervised study drug taper and arrangement for open-label treatment) and enter a different trial of his choosing, assuming he meets their eligibility requirements. The FOR-DMD subject will not be unblinded to FOR-DMD treatment regimen in order to meet eligibility criteria for another clinical trial (i.e., knowledge of corticosteroid regimen) until he has completed his Month 36 visit (3 year). After this milestone (36-Month visit), the subject's treatment regimen may be revealed if the subject expresses interest in another trial and knowledge of current treatment regimen is expressly required for participation in the other trial. In all cases, FOR-DMD subjects will be encouraged to continue their semi-annual FOR-DMD visits, if they are willing, regardless of whether they continue on FOR-DMD study drug or participate in another trial.

If the FOR-DMD Team and responsible parties from another DMD treatment trial agree that concurrent participation in both trials is feasible, all parties will adhere to a Standard Operating Procedure (SOP) regarding the transmission of FOR-DMD subject data (treatment regimen, subject ID, mutation type, etc.) (Manual of Operations, Appendix 14). Representatives from both FOR-DMD and the other trial will sign off on the SOP. Additionally, the FOR-DMD subject/guardian/legal representative will be asked to provide separate informed consent, indicating their desire to participate in another trial while remaining in FOR-DMD. The consent form will identify the FOR-DMD data that will be shared with the other trial. A copy of the consent form will be stored in the subject's FOR-DMD study file, as well as in the other trial's subject file.

5 STUDY INTERVENTIONS

5.1 Study Medication

5.1.1 Study medication administration

This study compares three active corticosteroid regimens over three years of treatment:

- daily prednisone (0.75 mg/kg/day)
- intermittent prednisone (0.75 mg/kg/day, 10 days on, 10 days off)
- daily deflazacort (0.9 mg/kg/day).

All regimens will be administered orally, in the morning at home, in line with normal clinical practice for the administration of corticosteroids for this indication.

As indicated above, dosage is a function of the child's weight. The initial dosage will be calculated from the child's pre-entry weight (assessed at the last screening visit), as per the weight bands in Table 5.1. The initial dosage will be adjusted as necessary according to weight change at the three-month visit and at each subsequent 6-month follow-up visit. If adverse events are encountered, dosage adjustments will be made as per the schedules described in Section 5.3 below. Deviation from the expected dosage per weight will be recorded as a failure of the initial regimen (tolerability).

Table 5.1 Weight bands of trial steroid regimens

Study drug will be presented in 20 day treatment wallets containing 2-6 tablets per day (a total of 40 to 120 tablets per wallet) for all regimens depending on the weight band. Weight banding for different steroid regimens will be as follows:

Band	Weight range in kg	Weight used for calculation of dose per kg	Dose in mg based on 0.75mg/kg Prednisone	Number of tablets of Prednisone (5 mg) for this dose	Dose in mg based on 0.9mg/kg Deflazacort	Number of tablets of Deflazacort (6 mg) for this dose
A	13-19.9	13.33kg	10mg	2	12mg	2
B	20-25.9	20.00kg	15mg	3	18mg	3
C	26-32.9	26.67kg	20mg	4	24mg	4
D	33-39.9	33.33kg	25mg	5	30mg	5
E	40+	40.00kg	30mg	6	36mg	6

Bands represent weight ranges.

Commercial stock prednisone and deflazacort differ from one another in appearance and their use would prevent blinding of patients, parents and physicians to the allocated treatment. To achieve double-blinding, a clinical trials supplies company will manufacture identical tablets of prednisone and deflazacort, and matched placebo (to maintain blinding in the 10 days off period, for the intermittent prednisone regimen). This medication will be presented in form of tablets for oral administration. This solution is preferred to over-encapsulation of commercial stock tablets, as the resulting capsules would be quite large, presenting potential difficulties in swallowing for the younger children

Each wallet will be labeled with a single panel variable label in the country specific language. Wallets will be packaged into 140-day (for first 2 x 3 months of study participation) or 260-day supplies (for remainder of study) for shipment purposes, by collation into kits containing either 7 cards or 13 cards. Each kit will be labeled with single panel variable label and an instruction sheet in the country specific language.

It is anticipated that it will take 3.5 years to enroll all 225 subjects required for this trial. Those recruited and therefore completing the three years of treatment first will have the option to continue study medications in a blinded fashion until they complete their 5-year visit. Therefore all subjects will receive a minimum of 36 months of study medication and up to a maximum of 60 months blinded treatment, unless premature discontinuation or withdrawal occurs.

Each enrolled subject will receive between 7 dispensing (subject recruited late in year 3) and 11 dispensing (subjects recruited at the beginning of year 1). Subjects recruited in the 1st quarter of year 1 will receive 2 x 140 days' supply (months 1-3 and 4-6) and 9 x 260 days supplies (months 7-12, 13-18, 19-24, 25-30, 31-36, 37-42, 43-48, 49-54, 55-60) and so on.

At the end of the study (30 days after the last enrolled subject has completed the 36 months of treatment period), subjects and their families may be asked if they would be willing to provide new informed consent to participate in a 5 year follow up study.

5.1.2 Interruption to study medication supply

If FOR-DMD study drug becomes unavailable to subjects for any reason (expiration, lost or compromised in some way, etc.), safety procedures should be followed to ensure an uninterrupted supply of corticosteroid treatment for subjects until replacement FOR-DMD study drug is provided. At no time should subjects take expired or compromised FOR-DMD study drug.

Upon notification that a subject's study drug is unavailable, the site investigator should prescribe (or arrange for provision of) daily prednisone or prednisolone (depending on the formulation available in their country) until the new study drug supply is provided to the subject. Dosage for each subject will be equivalent to the dosage of FOR-DMD study drug the subject is currently taking (based on weight band). This action should be documented in the subject study binder.

To ensure subjects do not take expired/compromised FOR-DMD study drug, site study staff (PI, coordinator, study nurse, etc.) will telephone FOR-DMD families to ensure that the boys are taking the prescribed prednisone/prednisolone daily and will arrange for the prompt return of the expired/compromised study drug (this should be documented in the subject binder). Expired/compromised drug should be returned to the study site for reconciliation and destruction. Should a family not comply with timely (within 7 days of compromise) return of expired/compromised study drug, a registered letter should be sent to the family address on record, requesting return of the product.

The choice of daily prednisone/prednisolone is based on two main factors:

●It is available in all participating countries (unlike deflazacort)

●Daily dosing is a safer choice for all subjects (as opposed to the intermittent, 10-day on/10-day off regimen), as it does not put participants at an increased risk of adrenal suppression

Safety Issues

Children taking corticosteroids, whether daily or intermittently, for longer than six weeks will have adrenal suppression and be at risk of adrenal crisis. This is an issue with all children, whether on the FOR-DMD protocol or undergoing usual clinical care.

For the 2/3 of FOR-DMD subjects randomly assigned to the (blinded) daily prednisone or daily deflazacort regime, there are no safety concerns associated with starting a daily prednisone/prednisolone regimen or with resuming FOR-DMD study drug, as appropriate doses of daily prednisone/prednisolone will be prescribed during the interval when FOR-DMD study drug is unavailable. When the new supply of FOR-DMD study drug is provided, subjects will switch back to their FOR-DMD drug wallets (Day 1) with no taper of the daily prescribed prednisone/prednisolone required.

The remaining 1/3 of FOR-DMD subjects assigned to the intermittent dosing regimen will switch to daily prednisone/prednisolone while study drug is temporarily unavailable and then will need to switch back to the intermittent study drug regime after a period of daily administration. This might put subjects at a potentially increased risk of adrenal crisis as they will have a period without corticosteroid treatment for 10 days at some point after resuming FOR-DMD study drug.

Both clinical and biochemical evidence of adrenal suppression has been well described in children following discontinuation of therapeutic doses of systemic corticosteroids.[1-4] Adrenal suppression has been demonstrated in children and adults exposed to courses as short as 5 days, however resolution after short courses typically takes less than 2 weeks.[5,6] Biochemical evidence of adrenal suppression following acute lymphocytic leukaemia induction therapy has been demonstrated in the majority of children immediately following one month of supra-physiological corticosteroids with recovery by 2 weeks in many, and ongoing suppression for up to 34 weeks in a subset.[7] A recent study of paediatric rheumatology patients who had received corticosteroids for a median duration of 40 weeks reported adrenal suppression in over 50% of patients, with time to recovery lasting beyond 7 months in half and up to 1-2 years in some.[8] Other studies have demonstrated duration of adrenal suppression beyond 18 months.[9] Adrenal crisis and death in addition to milder signs and symptoms of adrenal insufficiency are well documented in individuals with adrenal suppression related to systemic glucocorticoid therapy.[3,10-12] Risk factors for the development of symptomatic adrenal suppression in children receiving systemic corticosteroids remain unclear, however higher dose, longer duration and timing of administration of corticosteroids (evening >morning) are theoretical risks.[13,14]

There is little evidence available in children who are on chronic high doses of systemic corticosteroids and tapering, although current guidance is that if the child has been on chronic high dosage steroids for more than 3 weeks then the dosage should be tapered. Corticosteroids should be tapered or discontinued at a rate dictated by the underlying condition in order to maintain disease remission. In the case of DMD tapering and lowering the dosage below therapeutic levels could be detrimental to the participants in regards to motor function.

The following procedures should be followed in situations where FOR-DMD study drug is temporarily unavailable. In all scenarios below, all subjects will need close monitoring for any signs of adrenal suppression (with appropriate management, as noted below).

If FOR-DMD study drug will be resumed <u>within 21 days</u>

●The subject should begin daily dosage (based on weight band) of prednisone/prednisolone the morning after the last dosage of FOR-DMD study drug was taken

●When the new study drug supply is provided (no later than **Day 21**), subject should begin a new study drug wallet (beginning with “Day 1”) the morning after their last dosage of daily prednisone/prednisolone – this applies to **<u>ALL</u>** subjects, regardless of the FOR-DMD regime they are assigned (daily or intermittent)

If FOR-DMD study drug will be resumed <u>after 21 days</u>

If there is cause to believe that the FOR-DMD study drug will not be made available to the subject within 21 days, unblinding to the FOR-DMD treatment regime for subjects assigned to the intermittent regime should take place early enough to allow families to receive appropriate bridging prescriptions until FOR-DMD study drug is again made available.

●The subject should begin a daily dosage (based on weight) of prednisone/prednisolone the morning after the last dosage of FOR-DMD study drug was taken

●On **Day 22** (or as soon as the blinded regime is revealed)

→If unblinding reveals that the subject was on a daily drug regime, the boy should continue daily prednisone/prednisolone prescription until FOR-DMD study drug becomes available. The subject should take FOR-DMD study drug (once available) beginning on "Day 1" of the wallet, the morning after the last dosage of daily prednisone/prednisolone was taken

→If unblinding reveals that the subject was on an intermittent drug regime, the boy should be started on a prescribed intermittent regime of prednisone/prednisolone:

○Initial dosing should be **10 days OFF,** followed by 10 days of prednisone/prednisolone, continuing in this manner until FOR-DMD study drug becomes available (it is important to start with 10 days off to minimize risk of adrenal suppression)

○"Day 1" of the FOR-DMD study drug wallet should be started ONLY after the subject has completed a full cycle of '10 days off and 10 days on' of prescribed prednisone/prednisolone. The study wallet "Day 1" would then be started after the 10 days of prednisone/prednisolone has finished

Procedures to minimize risk

●The "I am on Steroids" card should be updated with the current prednisone/prednisolone dosage and families provided with guidelines for emergency management of adrenal symptoms

●Stress doses of steroids should be documented for each subject (i.e., "hydrocortisone 30 mg/m^2 in case of emergency"; see guidelines below)

Symptoms of Possible Adrenal Suppression Poor linear growth Poor weight gain Anorexia Nausea/vomiting Malaise/dizziness Weakness/fatigue Headache Abdominal pain Myalgia/arthralgia Psychiatric symptoms
Symptoms of Adrenal Crisis Hypotension (low blood pressure) hyponatraemia (low sodium levels), Hyperkalaemia (high potassium levels), Hypercalcaemia (high calcium levels), metabolic acidosis. Hypoglycemia (low blood sugar/seizure/coma)
Signs and Symptoms Associated with AS Cushingoid features

Guidelines

If a child is unwell, he will need to be reviewed for signs of adrenal suppression and given injectable steroids if appropriate. The child's GP or the study PI involved in the child's care should be contacted for advice. The child/subject may need to attend the Emergency Room to be assessed and given appropriate care.

If a child lives in a remote area that is far away from a hospital, the child may be supplied with an injectable form of steroid to use in the event of a vomiting illness (i.e., hydrocortisone 50-100mg per dose) or oral steroids to use as per the PI's discretion. This will enable families to treat potential steroid deficiency while on the way to the hospital or while waiting for help.

Surgical procedures will require steroid cover –all doctors should be made aware of the fact that the child is on steroids.

In Hospital

Blood gas, glucose and electrolytes should be measured as a priority. Obtaining blood for measurement of cortisol and ACTH should be considered. This is guidance; individual hospitals should follow their own SOP for adrenal crisis treatment.

If the child is hypotensive, 20ml/kg bolus of isotonic saline should be given to restore blood pressure.

If the child is hypoglycaemic, 5ml/kg of 10% dextrose or equivalent should be given, followed by a saline/dextrose infusion to prevent recurrence. Fluid shoe administered cautiously because patients may be relatively fluid overloaded at presentation.

Hydrocortisone should then be given in a dose of 50-100mg intravenously or intramuscularly (given it works more slowly) every 4 to 6 hours. In children <16kg, a smaller dose of 25mg every 4 to 6 hours can be given (or at a dose of 30mg/m^2 in divided doses).

The steroid regimen will need to be reviewed on regular basis although patients can usually return to oral medication when they are recovering.

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5.1.3 Supply, storage and return of study medication

At screening, a test packet containing placebo tablets will be provided by the site investigator to confirm the child's ability to swallow tablets. The initial test of swallowing ability will take place in the screening clinic, but children will be allowed to take additional placebo tablets home to try in a more comfortable environment, if they struggle with the swallowing test in clinic. At the beginning of the trial, the clinical trials supply company will provide each site with sufficient test packets for their anticipated recruitment numbers, with sufficient additional supplies to allow for a second test packet to be provided to each family if needed. These test packets will be stored in a locked cupboard, at normal room temperature.

At the baseline visit the site investigator, or designee, will explain to parents the use, storage, re-supply and return of the study medication.

Parents will be instructed to store study medication securely at room temperature. An "I am on steroids" card (in the local language) will be supplied and parents will be instructed that this should be carried at all times, and presented to their child's health care providers in the case of routine treatment or medical emergencies. The "I am on steroids" card must reflect the actual dose of study drug the subject is taking. Therefore, it needs to be updated when the subject moves to a different weight band (either up or down) during the study. This card should also be updated if study drug becomes temporarily unavailable such that a subject transitions to open label prednisone/prednisolone for a period of time. Site study staff will receive an electronic notification from the Data Management Team reminding them to update the subject's "I am on Steroids" card when a change in the study drug dose is requested..Parents will also be instructed to retain empty study medication wallets and to return these, and any unused medication, to the site at each follow-up visit.

When all entry criteria are met, and at least 10 days prior to the baseline visit subjects will be randomized via a web-based system (see Section 4.3.4). The clinical trials supply company will receive, by e-mail, notification of allocation, starting dose, country, study randomization number and subject identification number directly from the web-based system. The clinical trials supply company will look up the appropriate country -specific list of allocations, to identify the regimen to which the child has been allocated.

A subject-specific drug supply will be produced, labeled (with subject ID number and randomization number) and couriered to the pharmacy or clinic (according to local custom) at the recruiting site prior to the baseline visit for the subject. At baseline visit, the subject will be provided by the site staff with the first study drug supply (i.e. for months 1-3). Study medication will be initiated at home on the morning after the baseline visit. The initial drug supply will be sufficient (140 days) to allow for the 3-month visit to be carried out by the latest date permissible within the visit window (3 months ± 2 weeks from baseline).

At subsequent follow-up visits (3 and 6 months post-baseline, and the 6-monthly intervals thereafter), the need for dosage adjustment will be reviewed by the site investigator, taking into account weight gain (which may mandate moving to the next weight band – see Table 5.1 above) and side effects (which may mandate maintaining dose at the current level, or reducing to a lower weight band – see Section 5.3.3 below). The required dosage for the next treatment period (3 months for the 3-month visit, 6 months for all subsequent visits) will be communicated by the data system to the clinical trials supply company. The new subject-specific drug supply will be packaged, labeled (as described above) and couriered to the site. The site personnel will record the date and number of wallets (7 or 13) received on the Study Drug Adherence Record Subjects and will then courier the drug supply to the subject's home. Receipt of the shipment at the subject's home needs to be confirmed to the site by a phone call. If a subject lives in close proximity to the study site and the family is agreeable, they may visit the study site to physically pick up the new drug supply.

Study subjects will continue to take study medication from the previous dispensing until the new supplies arrive. They will also be instructed to complete the wallet in current use at the

time of receipt of the new supplies, to avoid overdoses in the intermittent regime group. (see the Manual of Operation for details). Subjects should only deviate from this schedule in the case of temporary unavailability of FOR-DMD study drug (See Section 5.1.2).

To allow for slippage on study visit dates (within the permitted visit windows, see Section 6.2), 140 days supply (i.e., 7 x 20-day wallets) will be provided for Months 1-3 and Months 4-6. Similarly, for all subsequent 6-month periods, 260 days supply (i.e., 13 x 20-day wallets) will be provided.

Used packaging and unused drug supply must be returned to the site at each visit, where it will be counted for adherence assessment. At each visit, the site investigator will provide the subject with study medications (from previous subject-specific supply brought to the visit) to be continued until the new supply is received at subject's home. The site personnel will record the number of wallets given to the subject on the Study Drug Adherence Form and will collect them at the subject's following visit.

Study personnel must ensure that study drug supply (prior to handing to family or returned unused) is kept in a secure locked area with access limited to authorized personnel until it is destroyed. Destruction can be performed at site or can be arranged via the Clinical Trials Supplies Company depending on local facilities.

Prior to destruction of the study drug sites must ensure that all personal identifiers are removed from the wallets (i.e. no subject names should be readable). For GCP, sites will also need to provide the study Sponsor with a certificate of destruction from the people responsible for this (either the Clinical Trials Supplies Company or the site pharmacy).

Study Drug Adherence logs and tracking records will be maintained by each site and the clinical trials supply company to ensure accountability for trial supplies at all times.

5.1.4 Adherence Assessment

Parents/guardians will be required to return all empty and unused drug wallets to the study site at each visit. Study staff will assess compliance with trial medication by reviewing the wallets and counting the returned tablets. This information will be reported on the Study Drug Adherence Log (see the Manual of Operation for details).

5.1.5 End of treatment period

For a given subject, study drug will be discontinued after completion of his 60-Month visit or - if the subject has not yet reached the 60-month visit - after the last enrolled subject completes the 36 month treatment period (see the Manual of Operation for details), unless the given subject chooses to withdraw from the trial prematurely. If a subject chooses to transition to another treatment trial after completion of his 36-month (3 year) FOR-DMD visit, the treatment blind may be broken and shared with the subject/family and PI. The subject may then transition to open-label corticosteroids. Additionally, if a subject has completed his 36-month visit and the clinical opinion of the PI is that breaking the treatment blind would be clinically warranted, then the subject may transition to open-label corticosteroids, if indicated. Corticosteroids are available on prescription and therefore at the end of the study treatment period subjects can continue to receive corticosteroids as per care recommendation.

5.2 Handling of Study Interventions

5.2.1 Unblinding

Every attempt should be made to preserve the integrity of study drug blinding. Prednisone and deflazacort are both corticosteroids with very similar side effect profiles, and therefore knowing which of these two drugs a child is receiving will not usually assist the decision making process for their management in the case of a medical emergency. All subjects will be provided with cards, to be carried at all times, stating “I am taking steroids” (in the local language) to be presented to medical staff in the event of routine treatment or a medical emergency. Moreover, the maximal dose of steroids that the subject might take according to his weight band will be recorded on the card by the site investigator or site staff to further reduce the need for unblinding. Information on the card will be reviewed at each study visit and updated each time a subject changes weight bands. There will, therefore, rarely be an indication for emergency unblinding. Experimental medications can usually be withdrawn without the need for unblinding in a subject experiencing an adverse event. Therefore in case of an adverse event which requires cessation of study treatment or medical interventions, the site investigator should provide adequate and necessary support to the subject without unblinding. However, an emergency unblinding procedure will be provided to allow site investigators to disclose a treatment assignment for an individual subject if clinical circumstances should require this. Each site will be provided with a patient-specific code-break envelope at the time of patient randomization, to be held in a central and readily accessible location at site, and with local Standard Operating Procedures in place for accessing and opening these envelopes (see the Manual of Operation for details). We expect the need to emergency code-breaks to occur only very rarely; for example, when the subject needs emergency surgery and information about all treatment interventions is requested. In the exceptional circumstance that knowledge of the study drug assignment appears essential for providing appropriate medical management, the site investigator should make every effort to contact the chief medical coordinator to discuss the rational for breaking the blind. If the site investigator still believes that unblinding is needed, or the chief medical coordinator and the study PIs are uncontactable (see the Manual of Operation for details), the site investigator will follow the established local SOP for accessing and opening the code-break envelope for the subject in question. After breaking the blind, the site staff should record details regarding the reasons for breaking the blind and any adverse events leading to the unblinding in the subject’s notes, appropriate worksheets and CRF. Once the blind is broken for a given subject, every attempt will be made to keep the subject in the study. If desired by the subject and his parents/ guardian(s) and clinically indicated, study medication might be continued. Even if the study medication is discontinued, for whatever reason, the child may continue to be followed-up in the study as per protocol, i.e., continue attending 6-monthly visits for evaluations off trial medication.

If a subject temporarily discontinues treatment due to an emergency but was not unblinded, study medication can be restarted (unless clinically contraindicated) and the subject can stay in the study.

Once a subject has completed his 36-month visit (year 3), the treatment blind may be broken under the following circumstances: 1) the subject desires to transition to a different treatment trial that does not allow for concurrent participation in FOR-DMD and for which the subject’s treatment regimen must be known in order to participate in the other trial, OR 2) the FOR-DMD PI believes knowledge of the FOR-DMD treatment regimen is clinically warranted (See Section 4.3.5 and Section 5.1.4, above).

The FOR-DMD subject will not be unblinded to FOR-DMD treatment regimen in order to meet eligibility criteria for another clinical trial (i.e., knowledge of corticosteroid regimen) until he has completed his Month 36 visit (3 year) unless an agreement is in place to allow concurrent participation in both trials.

5.3 Concomitant and supportive care

5.3.1 Concomitant and supportive care medications

Any treatment, including prescription and non-prescription drugs, herbal remedies and supplements that are taken by the subject during the study period, from screening to the end of the study, are considered concomitant medications and need to be collected and documented in the concomitant medication CRF page and in the subject's file by the study staff (see the Manual of Operation for details).

Concomitant treatment with Ataluren (Translarna) is allowed as it is not considered an investigational drug. Doses and start date of Ataluren/Translarna need to be recorded in the concomitant medication CFR page and in the subject's file.

The introduction of or dosage changes in any supportive care medication, and the reasons for its use in that subject, must be also reported.

Use of drugs for concomitant indications should take into account possible interactions with corticosteroids (as reported on the Summary of Product Characteristics).

Live vaccines should not be administered during corticosteroid treatment in accordance with the guidelines *http://www.cdc.gov/nip/recs/contraindications_vacc.htm*) and nonsteroidal anti-inflammatories should be avoided.

Use of dietary supplements and "health foods" (i.e. creatine, glutamine, coenzyme Q_{10}) will be discouraged though not prohibited. For subjects who are on dietary supplements, a stable regimen should be maintained during the whole study. Details of all concomitant medications and any supplements in use will be recorded at each visit as concomitant medications.

Subjects will be instructed about the importance of informing the clinical staff of the use of any drugs or remedies.

5.3.1.1 Calcium and Vitamin D

Adequate calcium and vitamin D intake is a first line prevention against the effects of long-term corticosteroid therapy on bone metabolism. Dietary counseling will be provided to recommend a daily intake of 1000 mg of calcium with the diet and 400-1000 IU of vitamin D with adequate supplements (e.g. cholecalciferol)(Bianchi, Morandi et al. 2011) (See below, and the Manual of Operations for details of dietary and Vitamin D supplementation advice). Vitamin D deficiency and insufficiency will be treated with higher doses of oral Vitamin D supplementation (e.g. cholecalciferol) (See below, and the Manual of Operations for details of dietary advice). These recommendations, and the recommendations for bisphosphonate therapy in the case of vertebral fractures are in keeping with expert guidelines (Bianchi 2005; Quinlivan, Roper et al. 2005).Quinlivan, Shaw et al, 2010). Initiation of any supplement should be noted on the concomitant medication log.

5.3.1.2 Bisphosphonates

Osteoporosis and fractures, particularly vertebral fractures, are recognized side-effects of long-term treatment with corticosteroids. A protocol for the management of bone health is in place in this trial; see Section 5.3.2.2.1 below and the Manual of Operations for further details. In children in whom vertebral fractures are diagnosed, bisphosphonate therapy (i.e., pamidronate, 0.5-1 mg/kg intravenously, every 4 months) will be initiated in consultation with a bone specialist. If bisphosphonate or other bone protection treatments are commenced, dose and starting date must be recorded as concomitant medication.

5.3.1.3 Cardiac health

A protocol for the management of cardiac health is in place in this trial in keeping with published expert guidelines (Bushby, Muntoni et al. 2003); Bushby, Finkel et al. 2010). Drug

interventions for cardiac events will be as follows, and should be initiated with consultation of a cardiologist.

- If left ventricular ejection fraction falls below 55% or fractional shortening below 28%, or regional motion abnormalities (posterior wall) are observed on echocardiogram, in the absence of symptoms, angiotensin converting-enzyme inhibitor [ACE] inhibitor therapy (e.g., perindopril 2 mg starting dosage) should be recommended.
- If ACE-inhibitor therapy is not tolerated (e.g., because of cough), an angiotensin receptor blocker [ARB] (e.g., irbesartan 75 mg starting dosage) should be substituted.
- If cardiac function continues to deteriorate asymptomatically despite the use of ACE inhibitor or ARB, the addition of a beta-blocking agent (i.e., bisoprolol 1.25 mg starting dosage; or metoprolol 25 mg 12-hourly starting dose; or carvedilol 3.125 mg hourly starting dosages; or similar agent) should be considered after optimum titration of ACE-inhibitor or ARB therapy for the weight of the subject.
- If any subject develops symptomatic left ventricular failure, diuretics (e.g., furosemide or bumetanide) and ACE-inhibitors or an ARB should be instituted, if the subject is not already taking them. Additional therapies should then be at the discretion of the physician in overall clinical charge of the subject.

If cardiac medications are commenced, dose and starting date must be recorded as concomitant medication.

5.3.1.4 Respiratory management

Accordingly with standards of care, DMD boys should receive 23-valent pneumococcal polysaccharide vaccine and annual immunization with trivalent inactivated influenza vaccine. Other vaccines might be administered in accordance with country-specific guidelines but live-vaccine should be avoided (see section 5.3.1 above). During an established infection, antibiotics are necessary, irrespective of oxygen saturation if positive evidence of an infection is established on culture and irrespective of culture results if pulse oximetry remains below 95% in room air. Any vaccines administered after enrollment in the trial should be noted as concomitant medications.

5.3.1.5 Infectious diseases

Contact with people with potentially serious infectious diseases, such as measles, meningococcal meningitis, etc. should trigger appropriate prophylaxis which may be provided by a family physician in line with standard guidelines for children on long term treatment with corticosteroids. The site investigator should be notified of all instances of exposure to potentially serious infectious diseases.

5.3.1.6 Trauma or surgical procedure

Additional steroid cover should be provided following trauma or in the event of elective or emergency surgery (see Manual of Operations for details).

5.3.2 Other supportive care interventions

5.3.2.1 Protocol driven management

Standard protocols (see the Manual of Operations for details) are in place in this trial for:

- Dietary assessment and advice

- Behavioral assessment and advice
- Physiotherapy assessment and management
- Cardiac surveillance and management

Interventions mandated by these protocols will be recorded; see the Manual of Operations for further details.

5.3.2.2 Management of predictable adverse events

Standard protocols (see Section 5.3.3.2 below and the Manual of Operations) are in place for the management of side effects of corticosteroid treatment. Specific interventions may be required and/or drug dosage may be adjusted, depending on the presence and severity of side effects. Details of dosage modifications, in the event of anticipated adverse events, are provided in Section 5.3.3.2 below.

5.3.2.2.1 Management of bone health

Prophylactic measures for the management of bone health will include standardized dietary advice on calcium intake and adequate vitamin D supplementation (see Manual of Operations for details). Limb fractures will be treated with early mobilization. As vertebral fractures are often asymptomatic or mildly symptomatic in children with DMD, high suspicion should be considered especially following falls. Lateral spinal X-Ray should be performed in case of suspected vertebral fracture. Vertebral fractures will be treated with bisphosphonates intravenously (see section 5.3.1.2 above). No steroid dosage adjustment is mandated by the occurrence of fractures.

5.3.2.2.2 Management of cataract development

The development of asymptomatic or symptomatic cataracts will trigger referral to an ophthalmologist for visual acuity measurement and subsequent follow up. No steroid dosage adjustment is mandated by the development of asymptomatic cataracts. Symptomatic cataracts will be treated as indicated in consultation with a specialist.

5.3.3 Concomitant Interventions

5.3.3.1 Prohibited Interventions

During the study period, subjects will be asked not to enroll in other clinical trials without consulting the site investigator. The study group will assess other trials enrolling during the period of this study and determine on a case-by-case basis whether or not enrolment in a specific trial may compromise the scientific integrity of this corticosteroid trial (See Section 4.3.6). However, subjects/parents will be at liberty to discontinue participation in this study if they so choose.

The study protocol must be followed for management of adverse events, study drug dosage adjustment and precautionary interventions in order to maintain the integrity of the study and of study results (see Manual of Operations for details). Any deviation from the protocol must be reported and documented.

5.3.3.2 Precautionary Interventions

The default is that subjects will be managed on an increasing dosage of corticosteroids (i.e, adjusted upwards for growth) according to weight (see Table 5.1 above), as measured at each follow-up visit. In the case of the development of predictable corticosteroid related side effects, or if the child has not passed a weight band bounder, dosage can be first maintained (that is, not increased for the normal increase in weight). Secondly, the dosage can be reduced to the band or (sequentially) bands below the one predicted for weight. Finally, the dosage can be stopped altogether (see Manual of Operations for details).

Lack of acceptability of the study medication to the family for whatever reason (to be recorded) will be a further reason for dose alteration/stopping even if the medical indications are not met. However, lack of acceptability of study medication to the family is typically not a medical emergency and should not warrant breaking the treatment blind.

5.3.3.2.1 Precautionary interventions in the event of behavior changes

An assessment of behavior, including completion of the PARSIII, Iowa Conners – Parent, SDQ and RRS (allowing quantification of the severity of changes) will be made at baseline and at all follow-up visits through Month 36. As a prophylactic measure, standardized behavioral advice will be provided to all families at the screening visit, at baseline and will be reinforced at all follow-up visits (see the Manual of Operations for further details). In the case of behavior changes that are noted but are not disruptive to family/school life, behavior advice should be reinforced and referral to a child psychologist for support should be considered. Where behavior changes are disruptive to family/school life, referral to a child psychologist should be considered and the following dosage adjustments and other interventions will be implemented:

- Steroid dosage not to be increased for weight if behavior changes persist despite behavioral advice.
- Steroid dosage to be reduced to a lower band if there is no improvement or behavior changes are disruptive to school/family life, despite not increasing the dosage.
- Steroid dosage to be stopped if there are severe behavior changes or they persist to be unacceptable disruption to school/family life. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.2 Precautionary interventions in the event of the development of Cushingoid appearance

At each visit, the child will be assessed for the development of Cushingoid appearance (see Manual of Operations for details of assessment). If Cushingoid appearance, unacceptable to the child/family develops, dosage adjustment will be as follows:

- Steroid dosage not to be increased for weight.
- Steroid dosage to be reduced to a lower band if Cushingoid appearance, unacceptable to the child/family, persists despite not increasing the dosage.
- Steroid dosage to be stopped if Cushingoid appearance, unacceptable to the child/family, persists on the lower dosage. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.3 Precautionary interventions in the event of gastrointestinal symptoms (abdominal pain, heartburn, GI bleeding)

Prophylactic measures will include advice to avoid non-steroidal anti-inflammatory drugs. In the event of gastritis/gastroesophageal reflux (GERD) symptoms such as heartburn, treatment with Ranitidine (or Proton-pump inhibitors) and antacid should be initiated. If GI symptoms persist despite treatment with Ranitidine (or Proton-pump inhibitors) and antacid, screening investigations for peptic ulcer disease, including red blood count and faecal occult blood testing, should be arranged. Study treatment dosage adjustment will be as follows:

- Steroid dosage not to be increased for weight and screening investigations for peptic ulcer disease should be initiated, if symptoms persist regardless treatment with Ranitidine (or Proton-pump inhibitors) and antacid.
- Steroid dosage to be reduced to a lower band if screening investigations for peptic ulcer disease are negative but GI symptoms cannot be satisfactorily controlled on

Ranitidine (or Proton-pump inhibitors) and antacid and persist despite not the dosage and

- Steroid dosage to be stopped if screening investigations for peptic ulcer disease are positive OR GI symptoms cannot be satisfactorily controlled on Ranitidine (or Proton-pump inhibitors) and antacid and persist on the lower dosage. Referral to a specialist should also be arranged. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.4 Precautionary interventions in the event of glycosuria

At each visit, a urinalysis will be performed to test for the presence of glycosuria. If glycosuria is detected (trace or greater), the urinalysis will be repeated within a week. If the second test confirms glycosuria, non-fasting (random) blood glucose should be checked within another week. If this too is abnormal, dietary advice should be reinforced and a fasting blood glucose test or 2-hour post-prandial test should be performed within 14 days. Further investigations (including HgbA1C) might be considered on individual subject based on the clinical judgment of the site investigator. In the event of elevated fasting blood glucose, or elevated post-prandial blood glucose, dosage modification will be as follows.

- Steroid dosage to be reduced to a lower band in the event of fasting blood sugar > 110 (6.1 mmol/L) and < 126 mg/dl (7 mmol/L), or blood glucose two hours after a meal > 140 (7.7 mmol/L) and < 200 mg/dl (11.1 mmol/L) after dietary modification.
- Steroid dosage to be stopped in the event of the development of diabetes mellitus as defined by fasting blood sugar > 126mg/dl (7mmol/L) or blood glucose 2 hours after a meal > 200mg/dl (11.1 mmol/L). See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.5 Precautionary interventions in the event of hypertension (blood pressure elevation compared to age norms)

Blood pressure will be assessed at each visit and compared to age norms. Prophylactic measures will include standardized advice about dietary sodium intake. In the event of high-normal blood pressure (i.e., blood pressure in 90-99th centiles – see Manual of Operations for centile charts), the measurement will be repeated in a non-stress environment. Dietary recommendations (weight /sodium reduction) will be reinforced if high-normal blood pressure is persistent. In the event of confirmed hypertension (consistent and confirmed blood pressure equal to or above the 95th centile- see Manual of Operations for centile charts), repeat measurements will be made in a non-stress environment, on at least three separate visits, separated by 7 days apart or less if symptomatic. If there is continued evidence of significant hypertension on these repeat measurements, the child will be placed on a low sodium diet for 1 month (see MOO). Further investigations might be considered on individual subject based on the clinical judgment of the site investigator. If blood pressure is still elevated at repeat measurements after 1 month on low sodium diet, the following dosage adjustments will be made.

- Steroid dosage to be reduced to a lower band in the event of a consistent increase in systolic blood pressure of 5 mmHg over the 99th percentile or in diastolic blood pressure of 10 mmHg over the 99th percentile for age after sodium restriction. A night-time ACE-inhibitor should be added. If ACE-inhibitor therapy is not tolerated (e.g., because of cough), an angiotensin receptor blocker [ARB] (e.g., irbesartan 75 mg starting dosage) should be substituted.
- Steroid dosage to be stopped in the event of confirmed hypertension, defined as an increase in systolic blood pressure of 5 mmHg over the 99th percentile or in diastolic blood pressure by 10mmHg over the 99th percentile for age despite treatment. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids. If

hypertension persists despite stopping steroid treatment, referral to a specialist should also be arranged to exclude other possible causes of hypertension.

5.3.3.2.6 Precautionary interventions in the event of immune/adrenal suppression

Prophylactic measures against immune/adrenal suppression include: ensuring prior exposure to chicken pox/immunization (see Sections 4.2 and 6.2.1.1); tuberculosis prophylaxis according to local population guidelines in 'at risk' subjects; advice on promptly addressing minor infection; advice on corticosteroid cover in the case of illness, injury or surgery (see Section 5.3.1.6 above); guidelines regarding progressive reduction of steroids if discontinuation is required; disallowing live vaccines during treatment (see Section 5.3.3.1 above).

In the event of unusual infections or unusual responses to infection, initially there will be no steroid dosage modification. An unusually high frequency of infections/unusual organisms should prompt the seeking of advice from an immunology expert and steroid dosage adjustment as follows:

- Steroid dosage not to be increased for weight.
- Steroid dosage to be reduced to a lower band if an unusually high frequency of infections/unusual organisms persists despite not increasing the dosage.
- Steroid dosage to be stopped if an unusually high frequency of infections/unusual organisms persists on the lower dosage. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.7 Precautionary interventions in the event of skin changes

At each visit, an examination of the skin will be carried out. In the event of skin infections or acne, the condition will be treated as indicated, and there will normally be no steroid dosage modification. If skin changes (striae, acne, hypertrichosis) are unacceptable to the child/family dosage adjustment will be as follows:

- Steroid dosage not to be increased for weight.
- Steroid dosage to be reduced to a lower band if skin changes, unacceptable to the child/family persist despite not increasing the dosage.
- Steroid dosage to be stopped if skin changes unacceptable to the child/family persist on the lower dosage. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.8 Precautionary interventions in the event of slow growth (height restriction)

Height will be measured at each visit. If the change in height velocity consistent with predicted percentiles and pre-treatment height velocity, no steroid dosage modification will be required. If there is a failure to gain height, but this is not a cause of concern to child/family, no steroid dosage modification will be required. If a failure to gain height is observed and is unacceptable to child/family, dosage adjustment will be as follows:

- Steroid dosage not to be increased for weight.
- Steroid dosage to be reduced to a lower band if failure to gain height, unacceptable to the child/family, persists despite not increasing the dosage.
- Steroid dosage to be stopped if failure to gain height unacceptable to the child/family persists on a lower dosage. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.9 Precautionary interventions in the event of (excessive) weight gain

Weight will be measured at all visits and BMI (weight kg / height m^2) calculated. Weight gain is a known side effect of corticosteroids. Prophylactic measures against undesirable weight

gain will include standardized dietary advice at screening, at the baseline visit and at all follow-up appointments (see Manual of Operations) with particular emphasis on advice on appetite control around the time that corticosteroids are started. Dosage adjustment will be as follows:

- Steroid dosage not to be increased for weight in the event of annual weight gain > 1 and < 4 BMI units for subjects younger than 10 years, and of annual weight gain > 2 and < 4 BMI units for subjects older than 10 or if weight gain is unacceptable to the child/ family despite intervention. Dietetic advice will be reinforced.
- Steroid dosage to be reduced to a lower band in the event of annual weight gain ≥ 4 BMI units, despite dietary modifications or if weight gain is unacceptable to the child/ family despite intervention.
- Steroid dosage to be stopped if weight gain continues despite dosage reduction and/or weight gain is unacceptable to the child/ family despite intervention. See Section 5.3.3.2.10 below for procedures for discontinuation of corticosteroids.

5.3.3.2.10 Procedures in the event of the need to discontinue corticosteroids

Study medication should not be stopped suddenly. A tapered reduction in dosage is required to avoid risks of adrenal failure. The blinded nature of this study precludes the identification of which of the daily doses of tablets are active drug and which are placebo in the intermittent regime. Therefore, tapering of drug dosage will be obtained using daily corticosteroids (prednisone) on prescription, starting to the equivalent dose of prednisone according to the weight band (e.g. band A: 10mg, band B: 15 mg; band C: 20 mg) and progressively reducing of 5 mg every 14 days until the dose of 5 mg/day, then 2.5mg/day for 14 days before discontinuing study drug (see Manual of Operation for details).

Example: a boy on band C has to discontinue study drug due to a side effect which is unacceptable for the child and the family. Prednisone should be prescribed for the tapering and study drug discontinued. The initial dose of prednisone will be 15 mg/day for 14 days, followed by 10 mg/day for 14 days, than 5 mg/day for 14 days and then 2.5 mg/day for other 14 days and then discontinued.

Parents/guardians and the subject's physician have to be informed that risk of adrenal failure persists for months following discontinuation of steroids. Particular attention has to be given to symptoms and signs of adrenal insufficiency, including vomiting, hypotension, hypoglycemia, dizziness and altered consciousness. Parents will be instructed to promptly contact the child's physician or the local hospital if these symptoms should occur, for adequate advice and treatment.

A telephone call to the parent(s)/guardian(s) will be made 30 days after the scheduled date of stopping study medication to check on any persisting adverse effects of study medication. All adverse events possibly due to study medication will be monitored until resolved.

6 CLINICAL AND LABORATORY EVALUATIONS

6.1 Schedule of Evaluations

The schedule of evaluations is shown in Tables 6.1a and 6.1b

Table 6.1a. Schedule of clinical and laboratory evaluations

Visit	**Screening (T-3 to T-10 Days)**	**Baseline / Entry (T0)**	**Visit 1 (T3)**	**Visit 2 (T6)**	**Visit 3 (T12)**	**Visit 4 (T18)**	**Visit 5 (T24)**	**Visit 6 (T30)**	**Visit 7 (T36)[1]**	**Visit 8 (T42)**	**Visit 9 (T48)**	**Visit 10 (T54)**	**Visit 11 (T60)**
Study month	**-3 to -10 Days**	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Baseline data													
Informed consent	X												
Inclusion criteria	X	X[2]											
Exclusion criteria	X	X[2]											
Demography	X												
Medical history	X												
TB immunity	X	X[2]											
Chicken pox immunity	X	X[2]											
Ability to take tablets	X	X[2]											
Ability to comply with key study evaluations	X	X[2]											
Drug supply													
Establishment of starting drug dose	X[3]												
Randomization	X[3]												
Order trial drug	X[3]		X	X	X	X	X	X	X	X	X	X	X
Review drug dosage			X	X	X	X	X	X	X	X	X	X	X
Adherence assessment			X	X	X	X	X	X	X	X	X	X	X
Drug Dispensing		X	X	X	X	X	X	X	X	X	X	X	
Clinic based evaluations													
Height	X	X	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X
BP and other vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	**Screening (T-3 to T-10 Days)**	**Baseline / Entry (T0)**	**Visit 1 (T3)**	**Visit 2 (T6)**	**Visit 3 (T12)**	**Visit 4 (T18)**	**Visit 5 (T24)**	**Visit 6 (T30)**	**Visit 7 (T36)[1]**	**Visit 8 (T42)**	**Visit 9 (T48)**	**Visit 10 (T54)**	**Visit 11 (T60)**
Study month	**-3 to -10 Days**	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
General physical examination	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis – glucose/	X	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis – urinary calcium assessment	X				X		X		X		X		X
Urine specimen collection for bone metabolites		X			X		X		X				
Blood draw for hematology and chemistry	X				X		X		X				
Blood draw for 25-OH-D	X		X[2]		X		X		X		X		X
Blood draw for serum calcium metabolites	X				X		X		X				
Blood draw for bone metabolites		X[8]			X		X		X				
Blood draw for biobanking (optional – requires additional consent)		X[8]			X		X		X				
Skin examination		X		X	X	X	X	X	X	X	X	X	X
Eye examination[4]	X				X		X		X		X		X
Cushingoid features assessment		X	X	X	X	X	X	X	X	X	X	X	X
Details of concomitant meds	X	X	X	X	X	X	X	X	X	X	X	X	X
Details of adverse events		X	X	X	X	X	X	X	X	X	X	X	X
Assessments and advice													
Dietary assessment and advice		X	X	X	X	X	X	X	X	X	X	X	X
Behavioral assessment and advice		X	X	X	X	X	X	X	X	X	X	X	X
Physiotherapy assessment and advice	X	X	X	X	X	X	X	X	X	X	X	X	X

Visit	**Screening (T-3 to T-10 Days)**	**Baseline / Entry (T0)**	**Visit 1 (T3)**	**Visit 2 (T6)**	**Visit 3 (T12)**	**Visit 4 (T18)**	**Visit 5 (T24)**	**Visit 6 (T30)**	**Visit 7 (T36)[1]**	**Visit 8 (T42)**	**Visit 9 (T48)**	**Visit 10 (T54)**	**Visit 11 (T60)**
Study month	**-3 to -10 Days**	**0**	**3**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Functional assessments													
FVC	X	X	X	X	X	X	X	X	X	X	X	X	X
NSAA (includes timed rising from floor)[5]	X	X	X	X	X	X	X	X	X	X	X	X	X
6 MWT	X	X	X	X	X	X	X	X	X				
ROM at ankle joint assessment	X	X	X	X	X	X	X	X	X				
Questionnaire assessments													
Behavior scales (IOWA Connors & PARS III, SDQ, RRS)		X	X	X	X	X	X	X	X				
TSQM			X	X	X	X	X	X	X	X	X	X	X
PEDSQoL – parent		X			X		X		X				
PEDSQoL – child		X			X		X		X				
Blindedness Assessment[6]									X				
Investigations													
DXA[4]	X				X		X		X		X		X
Lateral spine X-ray[4]									X				
Wrist X-ray[4]	X								X				
Echo[4,7]	X						X		X		X		X
ECG[4,7]	X						X		X		X		X

1. T36 constitutes the “end of study” visit as it represents 36 months follow up which is the minimum envisaged. If a child withdraws from the study prematurely, every attempt should be made to complete the T36 assessments

2. Repeat evaluation only if indicated from screening investigations

3. Starting dose, randomization and trial drug ordering will be performed following screening procedures (and confirmation of subject’s eligibility) and at least 10 days prior the baseline visit

4. These evaluations are likely to require a separate visit and may be performed within the allowed time scale so that individual appointments are less burdensome for families. DXA will not be conducted at German sites.

5. If a child losses the ability to walk independently during the study period, the Egen Klassifikation scale (EK) will replace the North Star Ambulatory Assessment

6. If the subject withdraws from study medication before visit month 36 (T36), blindedness assessment should be performed at their first visit after study drug discontinuation

7. Echo and ECG at two-year intervals to age 10, then annually according to standard of care. So schedule of investigations needs to take into account the subject’s age.

8. Blood samples for bone metabolites and biobanking can be collected at baseline OR screening. If collected at screening with the other blood samples, the PI **MUST** ensure that the total dose of blood draw does not exceed the recommendation for research purposes (1-1.5ml/kg/day).

Table 6.1 b. *Between-visit phone calls*

Study month	1	2	4	5	9	15	21	27	33	37	39	45	51	57
Call[1]	X	X	X	X	X	X	X	X	X					

The site doctor or the site coordinator will phone calls between visits to monitor adverse events, concomitant medications, adherence to regimen, and any subject and parent concerns monthly during the first 6 months following baseline visit, then every 3 months through Month 36

6.2 Timing of Evaluations

6.2.1 Pre-Randomization Evaluations

6.2.1.1 Screening Period (T-3 to T-10 days)

The screening visit to determine eligibility will take place a maximum of three months and a minimum of 10 days prior to baseline/entry visit. Evaluations should be completed within this time frame; according to local facilities, they need not necessarily all take place at one visit. The screening will assess: whether the subject meets inclusion criteria and is not ruled out by any exclusion criteria, as well as establishing pre-intervention status for comparisons over time. Screening procedures will be performed after signed consent/assent form has been obtained.

The screening evaluations will record:

- Demographic details
- Medical history
- Concomitant medications
- Assessment of TB exposure / immunity (in 'at risk' children as identified through positive family history or at risk community, such as certain immigrant groups)
- Assessment of chickenpox exposure / immunity
- Ability and willingness to take tablets
- Ability and willingness to comply with key study evaluations (FVC, NSAA).
- Willingness and compliance to complete questionnaires (PedsQL and TSQM questionnaires). *If the subject and or parents/guardians illiterate, outcome measures which require reading will be read by study staff to the subject and answers recorded (a note to file should be inserted in the subject chart if this is the case).*
- Height and weight
- Blood pressure and other vital signs
- General physical examination
- Urinalysis for glycosuria. In the presence of glycosuria and an abnormal blood glucose test at the screening assessment, a fasting or 2 hours after a meal blood glucose should be obtained. Diabetes mellitus (fasting blood sugar > 126mg/dl or blood glucose 2 hours after a meal > 200mg/dl) would exclude the child from the trial.
- Urinalysis for urinary calcium assessment (urine calcium, urine creatinine, urine calcium/creatinine ratio). Hypercalcuria will be defined as a urine calcium (mg/dL)/ urine creatine (mg/dL) ratio >1.5. If hypercalciuria is detected, urinalysis will be repeated within a week for confirmation. Idiopathic hypercalcuria would exclude the child from the trial.

- Blood specimen for random glucose, full blood count, urea, creatinine, electrolytes, creatine kinase, 25-OH-D, calcium metabolites, triglycerides, cholesterol, LDLs, HDLs, gamma-glytamyl transpeptidase (gamma-GT) and conjugated bilirubin.
- Forced vital capacity (FVC) – 2 separate assessments (best of each assessment within 20% of each other)
- North Star Ambulatory Assessment
- 6MWT
- ROM at ankle joint assessment
- Physiotherapy assessment and advice
- Eye examination
- DXA scan (according to local custom and facilities, this may require a separate visit, but should be carried out prior to the child starting on study medication). DXA scan will not be collected at German sites
- Wrist X-ray (according to local facilities, this may require a separate visit, but should be carried out prior to the child starting on study medication)
- 12 lead ECG (according to local facilities, this may require a separate visit, but should be carried out prior to the child starting on study medication)
- Echocardiograph (according to local facilities, this may require a separate visit, but should be carried out prior to the child starting on study medication)

Once eligibility has been confirmed:

- Randomization, establishment of starting drug dosage (number of tablets according for body weight) and ordering of trial supplies (to be completed at least 10 days before baseline visit)

6.2.1.2 Baseline / Study Entry (T_0)

The baseline / study entry visit(s) will take place not more than three months and a minimum of 10 days after the screening/pre-entry visit. Evaluations should be completed within this time frame; according to local facilities, they need not necessarily all take place at one visit.

The baseline / study entry evaluations will include:

- Confirmation of eligibility criteria (review of inclusion and exclusion criteria)
- Confirmation of ability and willingness to take tablets
- Confirmation of ability and willingness to comply with key study evaluations (FVC, NSAA, questionnaires). *If the subject and or parents /guardians illiterate, outcome measures which require reading, will be read by study staff to the subject and answers recorded (a note to file should be inserted in the subject chart if this is the case).*
- Recording of concomitant medications
- Checking of chickenpox immunity (where immunity is unconfirmed at screening)
- Checking of TB immunity(in 'at risk' children as identified through a positive family history or at risk community, where immunity is unconfirmed at screening)
- Blood specimen for bone metabolites
- Blood specimen for biobanking (optional – requires additional consent)
- Urine specimen collection for bone metabolites
- Height and weight
- Blood pressure and other vital signs

- General physical examination
- Skin examination
- Examination of face and trunk for Cushingoid features
- Urinalysis for glycosuria and presence of red blood cells. In the presence of glycosuria, a random blood glucose test should be performed. If this too is abnormal, a fasting blood glucose or 2 hours after a meal should be obtained before proceeding with randomization. Diabetes mellitus (fasting blood sugar > 126mg/dl or blood glucose 2 hours after a meal > 200mg/dl) would exclude the child from the trial.
- Forced vital capacity
- North Star Ambulatory Assessment
- 6MWT
- ROM at ankle joint assessment
- Recording of adverse events
- Administration (parental completion) of behavior scales (PARS III, Iowa Conners – Parent, SDQ-Parent, RRS)
- Administration (parental and child completion) of PedsQL
- Dietary assessment and advice
- Behavioral assessment and advice
- Physiotherapy assessment and advice
- Drug dispensing and instruction for parents/guardians

6.2.2 On-Study Evaluations

The next 2 visits will take place 3 and 6 months post-baseline respectively, with a visit window of ± 14 days. Evaluation visits then continue at 6-monthly intervals, with a visit window of ± 30 days. Evaluations continue to a minimum of 36 months post-baseline, and up to a maximum of 60 months post-baseline, depending on how early in the study the subject was randomized and if they wish to continue in the trial beyond the 36-month visit. Evaluations need not necessarily all take place at one visit.

6.2.2.1 3-month follow-up visit (Follow-up visit 1 - T_3)

The 3-month follow-up evaluations will comprise:-

- Recording of concomitant medications
- Height and weight
-
- Blood pressure and other vital signs
- General physical examination
- Examination of face and trunk for Cushingoid features
- Blood draw for assessment of 25-OH-D (only in children found to be deficient at screening)
- Urinalysis for glycosuria.
- Assessment of forced vital capacity
- North Star Ambulatory Assessment
- 6MWT
- ROM at ankle joint assessment

- Administration (parental completion) of behavior scales (PARS III, Iowa Conners – Parent, SDQ-Parent, RRS)
- Parental completion of Treatment Satisfaction Questionnaire with Medicine (TSQM)
- Dietary assessment and advice
- Behavioral assessment and advice
- Physiotherapy assessment and advice
- Recording of adverse events
- Review drug dosage and order trial supplies
- Adherence assessment
- Drug dispensing

*6.2.2.2 Evaluations to be carried out every 6 months, **through Month 36** (Follow-up visits 2 to 7: T_6, T_{12}, T_{18}, T_{24}, T_{30}, T_{36})*

The following evaluations will take place every 6 months up to, and including, Month 36.

- Recording of concomitant medications
- Height and weight
- Blood pressure and other vital signs
- General physical examination
- Examination of face and trunk for Cushingoid features
- Skin examination
- Urinalysis for glycosuria
- Forced vital capacity
- North Star Ambulatory Assessment
- 6MWT
- ROM at ankle joint assessment
- Administration (parental completion) of behavior scales (PARS III, Iowa Conners – Parent, SDQ-Parent, RRS)
- Parental completion of Treatment Satisfaction Questionnaire with Medicine (TSQM)
- Dietary assessment and advice
- Behavioral assessment and advice
- Physiotherapy assessment and advice
- Recording of adverse events
- Review drug dosage and order trial supplies (not at 'last visit')
- Adherence assessment
- Drug dispensing (not at 'last visit')

*6.2.2.3 Evaluations to be carried out every 6 months, **after Month 36** (Follow-up visits 8 to 11: T_{42}, T_{48}, T_{54}, T_{60})*

Following completion of the 36-Month visit, the following evaluations will take place every 6 months for the remainder of the child's participation in the study.

- Recording of concomitant medications

- Height and weight
- Blood pressure and other vital signs
- General physical examination
- Examination of face and trunk for Cushingoid features
- Skin examination
- Urinalysis for glycosuria
- Forced vital capacity
- North Star Ambulatory Assessment
- Parental completion of Treatment Satisfaction Questionnaire with Medicine (TSQM)
- Behavioral assessment and advice
- Dietary assessment and advice
- Physiotherapy assessment and advice
- Recording of adverse events
- Review drug dosage and order trial supplies (not at 'last visit')
- Adherence assessment
- Drug dispensing (not at 'last visit')

6.2.2.4 Evaluations to be carried out annually (Follow-up visits 3, 5, 7, 9 and 11: T_{12}, T_{24}, T_{36}, T_{48}, T_{60})

In addition to the evaluations to be carried out every 6 months (Section 6.2.2.2, Section 6.2.2.3 above), the following procedures will take place annually for the duration of the child's participation in the study (procedures no longer completed after Month 36 are noted).

- Eye examination (including a final, thorough exam by an ophthalmologist upon study completion or withdrawal)
- *Parental and child completion of PedsQoL (only through Month 36)
- Urinalysis for urinary calcium assessment (urine calcium, urine creatinine, urine calcium/creatinine ratio)
- Blood specimen for 25-OH-D
- Urine specimen collection for bone metabolites (only through Month 36)
- Blood specimen for random glucose, full blood count, urea, creatinine, electrolytes, creatine kinase, calcium, phosphate, and alkaline phosphatase, triglycerides, cholesterol, LDLs, HDLs (only through Month 36)
- Blood specimen for bone metabolites (only through Month 36)
- Blood specimen for biobanking (optional – requires additional consent)
- DXA

6.2.2.5 Evaluations to be carried out every two years, then annually (Follow-up visits 5, 7, 9 and 11: T_{24}, T_{36}, T_{48} & T_{60})

Echocardiograph and electrocardiography (12-lead ECG) should be conducted every two years until the child reaches the age of 10, annually thereafter, according to Standards of Care in DMD. More frequent visits can be arranged if clinically indicated.

6.2.2.6 Evaluations to be carried out at 36 months (Visit 7: T_{36})

In addition to the evaluations to be carried out every 6 months (Section 6.2.2.2, Section 6.2.2.3 above) and annually (Section 6.2.2.3 above), the following evaluations will take place at the 36-month visit (Visit 7) in all subjects to yield a consistent post-intervention status for comparisons over time.

- Blindedness Assessment
- Lateral spine X-ray
- Wrist X-ray
- Blood specimen for gamma-glytamyl transpeptidase (gamma-GT) and total bilirubin.

6.2.2.7 Between-visit phone calls

The site coordinator will make phone calls between visits to monitor adverse events, concomitant medications, adherence to regimen, and any subject and parent concerns monthly (+/- 7 days) during the first 6 months following baseline visit, and every 3 months (+/- 2 weeks) thereafter through Month 36.

6.2.3 Intervention Discontinuation Evaluations and Post-Intervention Evaluations

The study design compares three active corticosteroid regimens over three years of treatment. It is anticipated that it will take 3.5 years to enroll all 225 subjects. Those recruited and therefore completing the treatment first will have the option to continue their study medications in a blinded fashion until they complete their 5-Year visit. Therefore all subjects will receive a minimum of 36 months of study medication and up to a maximum of 60 months treatment – in other words, the period of study intervention ranges from 36 to 60 months post-baseline.

If trial medication is prematurely stopped at the instigation of the site investigator or family, for whatever reason, the child should continue to be followed-up in the study as per protocol, i.e., continue attending 6-monthly visits for evaluations off trial medication. The trial medication field of the worksheet/CRF should reflect the decision to discontinue trial medication. The date and reason for discontinuation should be recorded. Trial medication should not be stopped suddenly. A tapered reduction in dosage is required to avoid risks of adrenal failure. For details of how to taper dosage, see Section 5.3.3.2.10 above.

If a child discontinues from both medication and follow-up, a full 'final visit' should be performed where possible. This will comprise the elements of Visit 7 (T_{36}) and recommendation that the boy have a final, thorough eye examination. In the case of premature discontinuation from medication and follow-up, a telephone call to the parent(s)/ guardian(s) will be made 30 days after the last visit to check on any persisting adverse effects of study medication.

6.2.4 Final Evaluations

Because of the variable duration of participation in the study (36 to 60 months) any visit from Visit 7 (T_{36}) to Visit 11 (T_{60}) may represent the 'final visit' for a given subject. A thorough eye examination by an ophthalmologist will be strongly advised at this final visit for subjects who have already completed Visit 7 (T_{36}) or whose designated final visit is Visit 7 (T_{36}). As indicated in Section 6.2.3 above, in the case of premature discontinuation from both medication and follow-up, a full 'final visit' should be performed where possible, including the

elements of Visit 7 (T_{36}), as described in Section 6.2.2.5 above, if the subject has not already had his visit 7.

A telephone call to the parent(s)/guardian(s) will be made 30 days after the final visit to check on any persisting adverse effects of study medication.

6.3 Special Instructions and Definitions of Evaluations

6.3.1 Informed Consent

Potentially eligible subjects and their parents or guardians (with legal authority to consent on behalf of the child as described in Section 4.3.2 above) will be invited by letter (and by phone if considered appropriate) to attend a screening visit. The invitation to attend will include a Subject Information Sheet (including a child-friendly version) and contact details of the investigator site.

At the screening visit, the parent(s)/guardian(s) and the child (at the discretion of the parent(s)/guardian(s)), will be given the opportunity to discuss the study with site personnel and to have any questions about the study answered. Only once their questions and concerns have been adequately addressed will their informed consent be sought. The procedure for obtaining informed consent (e.g. whether one or both parents must provide consent) will be in line with the legal requirements in the participating countries; full details are given in the Manual of Operations.

The consent form will be signed and dated by the parent(s)/ guardian(s) and the site Principal Investigator (or other member of the site investigation team who has been formally delegated this role – see the Manual of Operations). An original and two copies of the completed consent form will be made. One copy of the completed consent form will be given to the parent(s)/ guardian(s), along with a copy of the trial information sheet; the original will be filed in the subject's Study File; one copy will be filed in the subject's general medical records.

Where the child is intellectually capable of assenting, and with the permission of the parent(s)/ guardian(s), the assent of the child himself will also be obtained, if possible in writing, copied and filed as for the consent.

At the screening visit, subjects will be recruited following the provision of informed consent/assent (as described in Section 4.3.2 above). Since the assessment of eligibility may require the performance of procedures that are not part of normal clinical practice, informed consent will be sought prior to performing any study-related screening procedures. Eligibility of the child will then be re-assessed with reference to the inclusion and exclusion criteria (see Sections 4.1 and 4.2 above).

If any modifications are made to the study that change the content of the information of the consent, then the subject and the parent(s)/ guardian(s) will be presented with the new information and asked to go through the written consent process again at the next visit.

6.3.2 Documentation of Duchenne Muscular Dystrophy (DMD)

All subjects recruited to this study will have a confirmed DMD (defined as male with clinical signs compatible with DMD AND confirmed DMD mutation in the dystrophin gene (deletion/duplication of one or more exons, that are predicted as 'out-of-frame', or other mutations that are expected to preclude production of the dystrophin protein (i.e. nonsense mutation, deletion/duplication leading to a downstream stop codon). A written copy of a genetic report of this information will be kept in the subject's study file.

6.3.3 Demographic Data

At the screening visit, basic demographic data will be recorded by reference to the medical records and questioning of parent(s)/guardian(s). See the Manual of Operations for details of the variables to be recorded.

6.3.4 Medical History

At the screening visit, a medical history will be recorded by reference to the medical records and questioning of parent(s)/guardian(s). Required details include: family history of DMD, diabetes and tuberculosis; birth history; medical history of the child, including any significant prior medical conditions and affected organs and systems; allergies and immunization history, with particular attention to TB immunity (if the subject has been exposed to risk), chicken pox immunity, allergies to corticosteroids and sucrose/lactose intolerance; achievement of developmental milestones; fracture history. Particular attention will be paid to those variables defining inclusion and exclusion criteria for the trial, and those indicative of contra-indications to or suggestive of the need for special precautions in the use of corticosteroids. See the Manual of Operations for details of the variables to be recorded.

6.3.5 Treatment History

At the screening visit, a history of medical and other treatments for DMD will be recorded, by reference to the medical records and questioning of parent(s)/guardian(s).

Current or previous treatment (greater than four consecutive weeks of oral therapy) with corticosteroids or other immunosuppressive treatments for DMD (or for other recurrent indications, e.g., asthma) will be grounds for excluding the subject from the study.

Particular attention will be paid on any anti-epileptic drugs as they might have an impact on bone mass.

Details of previous medication for DMD or other medical conditions will be recorded as will details of any surgical interventions for DMD-related conditions (e.g. spinal surgery, tendon lengthening) and of physiotherapy interventions (e.g. use of splints). See the Manual of Operations for further details of the variables to be recorded. Such complications would not be expected in this population of 4-7 year old boys with DMD.

6.3.6 Concomitant Treatments

At the screening visit and all subsequent visits, details of concomitant medications (for DMD and for other conditions) will be recorded. Concomitant medications will include prescribed medication, over-the-counter purchases, vitamin supplements, herbal and homeopathic remedies. Details to be recorded will include: name of drug (generic name/active ingredients of drugs should be recorded, except in case of combination products); indication; start and (if applicable) stop dates; dose size; dose frequency. Parent(s)/guardian(s) will be asked to bring to the visit all medications in current use, in their packages, to facilitate accurate recording of the name and dosage of concomitant medications. See the Manual of Operations for further details of how to record this information.

At the baseline visit and each follow-up visit, details of non-drug concomitant interventions for DMD will also be recorded. Standard protocols (see the Manual of Operations for details) are provided for dietary, behavioral and physiotherapy assessments and management, and for the management of: side effects of corticosteroid treatment, infectious diseases, trauma or surgical procedures, bone health, cardiac surveillance and management. Interventions mandated by these protocols will be recorded; see the Manual of Operations for further details. Orthopedic interventions for contracture management are infrequent in this age group. If an orthopedic procedure is performed for a child in the study the purpose and outcome will be carefully recorded. In accordance with the Standards of Care (Bushby,

Finkel et al. 2010) surgical interventions should be performed only after a multidisciplinary discussion. The Site Principal investigator should take part in the discussion to preserve the integrity of the study.

Concomitant treatment with Ataluren (Traslarna) is allowed but must be recorded in the concomitant medication log with the specific dosage and start date.

Concomitant participation in another study with investigational drugs might be possible, but it must be first discussed with the Chief Medical Coordinator and with the Project Manager. If a subject is enrolled in another clinical study, the investigational product should be recorded on the concomitant medication log with specification of the study protocol, starting dose and dosage. This information should also be entered on CRF81.

6.3.7 Study Intervention Modifications

Drug dosage will be determined at least 10 days prior to the baseline/study entry visit, by reference to the subject's weight (see Section 5.1.1 above) in order to allow study drug supply to be shipped to the site in time. Drug dosage will be reviewed and, if necessary, adjusted at each follow-up visit (Section 5.1.2). Dosage will normally be adjusted upwards for weight gain (see Table 5.1 above). The actual weight band and whether an increase has been made will be recorded at each follow-up visit.

If adverse events are encountered, dosage adjustments will be made as per the schedule described in Section 5.3. Deviation from the expected dosage per weight will be recorded, with an indication of whether this involves holding dosage steady (i.e. not increasing in line with the expected dosage per weight) or reducing to a lower weight band.

6.3.8 Clinical Assessments

6.3.8.1 Height, weight, BP and other vital signs

Height, weight, blood pressure and pulse rate will be recorded at screening and all subsequent visits. See the Manual of Operations for details of how to take and record these measurements.

6.3.8.2 Physical examination

A complete physical examination will be recorded at screening and at all subsequent visits. It will consist of a medical exam of organs and systems [head, eyes, ears, nose and throat (HEENT), lungs (auscultation), cardiovascular (heart auscultation and peripheral pulse), abdomen/GI, lymph nodes, musculoskeletal, neurological, spine, genitourinary/renal, skin/ mucosa, endocrine and extremities]. See the Manual of Operations for details of how to perform and record this examination.

6.3.8.3 Skin examination

Skin changes (striae, cutaneous/oral infection, acne, hypertrichosis) will be recorded by clinical observation at the baseline / study entry visit and at 6 monthly visits thereafter. See the Manual of Operations for details of how to perform and record this examination, and for how to manage cutaneous side-effects of corticosteroids.

6.3.8.4 Eye examination

An eye examination will be performed by a qualified eye care practitioner/optometrist at screening and annually thereafter to exclude cataracts and glaucoma (see the Manual of Operations for details of how to record this examination). Any suspicion of cataract will indicate referral for visual acuity assessment by an ophthalmologist. A thorough eye examination by an ophthalmologist will also be strongly recommended for each boy upon his study completion or withdrawal from the trial (see CRF 32).

6.3.8.5 Cushingoid signs

An assessment of Cushingoid appearance (face and trunk) will be made by clinical observation at the baseline/study entry visit and at each follow up visit. See the Manual of Operations for details of how to perform and record this examination, and for how to manage the development of Cushingoid signs.

6.3.8.6 Pulmonary function

Forced vital capacity will be measured at the screening visit (to confirm ability to comply with this evaluation, as it comprises part of the primary outcome), at the baseline/study entry visit and at each follow up visit. At screening, to ensure the boy is capable of performing a reliable FVC, a SECOND FVC must be completed at the end of all other screening assessments. To be eligible for randomization, there must be no more than a 20% difference between the best FVCs on the first and the second attempts. See the Manual of Operations for details of how to perform and record this evaluation.

6.3.8.7 Assessments of physical function

The assessment of motor skills (jumping, hopping, ability to lift the head from supine) and timed functional tests (time to stand from lying time to traverse 10 meters) will be assessed in the context of the North Star Ambulatory Assessment. This will be performed at screening to confirm eligibility to participate (by reference to the inclusion criterion of ability to rise independently from the floor) and ability to perform the assessment (since time to rise from the floor comprises part of the primary outcome).

Timed Function Test Grading of the 10 meter walk/run and the timed rising from lying will be assessed on a 6 point scale to differentiate those subjects with similarly fast times who may achieve a ceiling time.

The 6MWT will provide a measure of walking endurance compatible with daily life walking activity. ROM at the ankle joint will be also performed as part of the assessment of physical function to ensure consistency of physiotherapy interventions in accordance with prescribed physiotherapy intervention and advice. The North Star Ambulatory Assessment (NSAA), time functional tests, 6 MWT and ROM of ankle joints will be performed at screening, at the baseline/study entry visit and at each follow up visit up to and including Month 36. See the Manual of Operations for further details of how to perform and record these evaluations. If a subject losses the ability to walk independently during the study period, the Egen Klassifikation scale (EK) will replace the North Star Ambulatory Assessment (see the Manual of Operations for further details).

The assessment of physical function (including the North Star Ambulatory Assessment, time functional tests and the 6MWT) will be video-recorded for quality-control purposes (See the Manual of Operation for further details). A separate consent will be obtained for this video-recording.

6.3.8.8 DXA scans and lateral spine and wrist X-rays

Data on bone mass, density and body composition (fat and fat-free mass) will be collected by DXA in the screening period (depending on local facilities, this may require an additional visit but should be completed prior to starting study medication) and annually thereafter. For further details of how to perform and record these evaluations, and the management of bone health, please see the Manual of Operations.

Copy of the DEXA scan should be sent to “Instituto Auxologico Italiano IRCCS, Milano” for quality control and future references (see the Manual of Operations for further details). Site staff should provide copies of the DEXA scan to their site monitor during scheduled annual

visits. The monitor will then gather the reports from all sites and forward them to the EU or North American Project Manager, as appropriate, who will in turn send the reports on to Istituto Auxologico Italiano (care Dr Maria Luisa Bianchi).

Wrist x-rays will be performed in the screening period (depending on local facilities, this may require an additional visit but should be completed prior to starting study medication) and the 36-month visit.

Vertebral fractures will be recorded in medical history if detected during screening period and as adverse events if detected following baseline (see Section 7.1.1 below). A lateral spine X-Ray will be performed at the 36-month visit to verify absence of asymptomatic vertebral fractures. Upon study completion, these spine images will be de-identified and uploaded by each site (with the exception of those in Germany) to a secure, password protected database for central analysis, provided verbal consent has been granted by the subject/family.

6.3.8.9 Echocardiogram and ECG

Cardiac status will be assessed in the screening period (depending on local customs and facilities, this may require an additional visit but should be completed prior to starting study medication) by standard trans-thoracic echocardiogram and 12-lead electrocardiograph (including rhythm strip). Repeat echocardiograms and ECGs will be required every two years until the child reaches the age of ten years and annually thereafter or at the onset of cardiac signs and symptoms if they occur earlier according with the standard recommendations in DMD. Increased cardiac surveillance should be arranged if clinically indicated and if abnormalities of left ventricular function are detected on Echocardiogram. These assessments will also be performed at the 36-month visit. The ECGs and the Echocardiograms must be manually reviewed and interpreted by medically qualified personnel. The findings will be categorized as: normal; abnormal but not clinically significant; abnormal and clinically significant. An ECG or Echocardiogram result that is abnormal and clinically significant will be recorded in medical history if detected during screening period and will be considered as adverse events if detected following baseline (see Section 7.1.1 below). Adequate management should be initiated if any abnormalities of clinical significance will be detected (see section 5.3.1.3). Site staff should provide copies of the ECG to their site monitor during scheduled annual visits. The monitor will then gather the reports from all sites and forward them to the University of Rochester (see the Manual of Operations for further details) for future references. Echocardiograms on trial subjects must be retained for at least five years after study completion in a way that allows them to be readily available for independent re-evaluation by trial investigators. For further details of how to perform and record these evaluations, please see the Manual of Operations.

6.3.9 Laboratory Evaluations

6.3.9.1 Urinalysis

A urine sample for urinalysis will be taken at the screening visit, at the baseline visit, and at all follow-up visits. Urinalysis will include analysis for glucose, blood and protein. Results will be recorded and categorized as: normal; abnormal but not clinically significant; abnormal and clinically significant. If glycosuria is detected (trace or greater) the urinalysis should be repeated within a week. If the second test confirms glycosuria, non-fasting (random) blood glucose should be checked within another week. If this too is abnormal, dietary advice should be reinforced and a fasting blood glucose test or 2-hour post-prandial test should be performed within 14 days. See the Manual of Operations for details of how to manage glycosuria finding.

A urinalysis result that is abnormal and clinically significant will be considered as an adverse event, recorded as such and monitored until the event has resolved or stabilized at a level acceptable to the site Investigator. For further details of how to perform and record this

evaluation, and how to manage observed glycosuria or hematuria, please see the Manual of Operations.

6.3.9.2 Chicken pox and TB immunity

At screening, a blood sample will be taken for antibodies (IgG) to Varicella Zoster virus to confirm immunity. If antibodies are not detected, immunization before starting the trial will be advised and the immunization status will be re-checked prior to randomization (see Manual of Operation for details). Lack of willingness to immunize a child who is not already immune to chicken pox will be a reason for exclusion of the child from the trial. If after two immunizations the child still does not show antibodies (IgG) to Varicella Zoster, the case should be discussed with the Chief Medical Coordinator. Assessment of TB exposure will be performed in order to identify “at risk” children (positive family history, at risk community such as certain immigrant group). In an “at risk” child, an immunization before starting the trial will be required and the immunization status will be re-checked prior to randomization (see Manual of Operation for details). Lack of willingness to immunize a child with a risk of TB who is not already immune to TB will comprise a reason for exclusion of the child from the trial.

6.3.9.3 Serum chemistry and hematology

Non-fasting blood samples for serum chemistry (including glucose, electrolytes, urea, creatinine, creatine kinase, triglycerides, cholesterol, LDLs, HDLs) and hematology (including white blood cell count with differential, hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total red cell count and platelet count) will be collected and evaluated at the screening visit and annually thereafter, up to and including Month 36 (Visit 3, 5, 7). Gamma glytamyl transpeptidase and total bilirubin will be also performed on blood samples at screening and at end of study visit. All clinical laboratory test results will be entered into the data system directly from the printed lab reports, or first transcribed to the lab worksheet and then entered. All results will be recorded and/or entered in standard units as displayed on the lab reports (the local laboratory range of each value will be held on file centrally). The actual result and units for each test will be captured, as well as indicator flags for out of normal range values and whether or not they are deemed by the site Principal Investigator to be clinically significant. All results will be interpreted and categorized using the following categories: normal; abnormal but not clinically significant; abnormal and clinically significant. Any laboratory test abnormality considered clinically significant will be confirmed by repeat testing. A laboratory test result that is abnormal and clinically significant on re-testing will be considered as an adverse event, recorded as such and monitored until the event has resolved or stabilized at a level acceptable to the site Principal Investigator. For further details of how to perform and record these evaluations, please see the Manual of Operations.

6.3.9.4 Blood samples for 25-OH-D, serum calcium, phosphate, and alkaline phosphatase

A blood sample for serum calcium, phosphate and alkaline phosphatase will be taken at the screening visit and annually thereafter, up to and including Month 36. A blood sample for 25-OH-D will be taken at the screening visit and annually thereafter throughout the subject’s participation in the trial. If deficiency or insufficiency is detected in 25-OH-D, it will be corrected by a vitamin D supplement (see the Manual of Operations) and noted as a concomitant medication. A blood test for 25-OH-D will be repeated at the 3 month visit in children shown to be deficient or insufficient at screening, and provided with Vitamin D supplementation, in order to verify normalization of the serum levels.

For further details of how to perform the evaluations and on the management of bone health, please see the Manual of Operations.

6.3.9.5 Urinalysis for urinary calcium assessment

At the screening visit (i.e., before starting corticosteroid therapy, calcium or vitamin D) a urine sample will be collected and analyzed for urinary calcium, urine creatinine and urine calcium creatinine ratio to exclude the presence of hypercalciuria. Urinalysis for urinary calcium assessment will be repeated annually following the screening visit (visit 3, 5, 7, 9 and 11).

Hypercalciuria in children is defined as urinary calcium excretion > 4 mg/kg/24 hours. Since collecting urine for 24 hours could be inconvenient and unsuitable for children, an approximate value will be obtained from an extemporaneous urine sample., Hypercalciuria is defined as a urine calcium (mg/dL)/urine creatine (mg/dL) ratio >1.5. Detection of hypercalciuria will be confirmed by repeat testing. If the second test confirms hypercalciuria, urinalysis on 24 hours urine sample will be arranged. Diet and calcium supplement will be reviewed. Further investigations might be considered on individual subject based on presence of symptoms and clinical judgment of the site investigator. For further details of how to perform this evaluation and interpret and manage the findings, please see the Manual of Operations.

6.3.9.6 Blood and urine samples for bone metabolites

Non-fasting blood and urine samples will be collected at the baseline and annually thereafter, up through and including Month 36 (Visit 3, 5, 7) for the following markers of bone formation and resorption:

- for bone formation: serum osteocalcin and bone specific alkaline phosphatase (BSAP)

- for bone resorption: serum crosslinked C-telopeptide of Type I Collagen (CTx); urinary crosslinked C-telopeptide of Type I Collagen; crosslinked N-telopeptide of Type I Collagen (NTx); serum receptor activator of nuclear factor kappa-B ligand (RANKL) and serum osteoprotegerin (OPG).

Samples will be sent to Dr ML Bianchi, “Instituto Auxologico Italiano IRCCS, Milano”, Italy for analysis. More details about sample collection, processing and shipment are provided in the Manual of Operations.

6.3.10 Additional Evaluations

6.3.10.1 Dietary assessment and advice; behavioral assessment and advice; physiotherapy assessment and management

Standard protocols for (a) dietary assessment and advice; (b) behavioral assessment (including parental completion of the PARSIII, Iowa Conners – Parent, SDQ and Rutters) and advice; (c) physiotherapy assessment and advice will be followed in this trial. An assessment of dietary status and of behavior will be made at the baseline/study entry and at all follow up visits. Behavioral management will be provided as indicated by the findings on assessment. Please see the Manual of Operations for further details. A standard of physiotherapy care for boys aged 4-12 with DMD will be instituted at all sites. Physiotherapy assessment and advice including ROM at ankle joint using a goniometry will be performed at screening, at the baseline/study entry visit and at all follow up visits (ROM and 6MWT will not be performed after Month 36). Compliance with the prescribed program will be assessed at each follow up

appointment. Further details of physiotherapy assessment and management are provided in the Manual of Operations.

6.3.10.2 Adverse events

Adverse events must be assessed and documented at baseline and all subsequent visits. Participants will also be asked about any adverse events during the in between visit phone calls. A structured record of adverse events and reactions (see Section 7 for further details) will be made by reference to medical records and questioning of parent(s)/ guardian(s). See the Manual of Operations for further details.

6.3.11 Questionnaires

6.3.11.1 Treatment Satisfaction

Satisfaction with treatment will be measured at all post-baseline follow-up visits using the Treatment Satisfaction Questionnaire for Medication (TSQM) (Atkinson, Sinah et al. 2004). The TSQM consists of 14 Likert-scale items that yield four subscale scores: Effectiveness, Side Effects, Convenience, and Global Satisfaction (the latter being a component of the primary outcome variable for the proposed trial). There is not a child-report version of the TSQM available. Therefore, the parent(s)/guardian(s) will be asked to report from their perspective of the boy's treatment. TSQM is available in all languages relevant for this study. See the Manual of Operations for further details of how to administer and score the TSQM.

6.3.11.2 Behavior

Four instruments, for completion by the parent(s)/guardian(s) will be used for (1) behavior assessment screening and (2) evaluation of behavior change. These are (a) the Iowa-Conners Parent Checklist , a scale focusing on ADHD symptomatology; (b) the PARS-III, a scale designed to measure psychosocial adjustment of children with chronic physical illnesses (Stein and Jessop 1990; Collett, Ohan et al. 2003; Collett, Ohan et al. 2003; Witt, Kasper et al. 2003); Hendriksen JG et al. 2009); (c) the Strengths and Difficulties Questionnaire, a scale focusing on inattention, peer relationships and pro-social behavior (Hysing M, et al. 2009; Read J, et al. 2010); (d) the Revised Rutter scale to assess emotional distress. Each instrument will be completed by the parent(s)/guardian(s) at the baseline/study entry visit and at each follow-up visit through Month 36. See the Manual of Operations for further details of how to administer and score these instruments.

6.3.11.3 Quality of Life (PedsQL)

QoL will be measured at the baseline/study entry visit and annually thereafter through Month 36. The QoL instrument to be used in this trial is the PedsQL (Varni, Seid et al. 1999; Varni, Seid et al. 2001; Varni, Seid et al. 2002), the generic core and the NMD-specific module. Versions of the PedsQL for completion by the subject (for children aged 5 and over) and for the parent(s)/guardian(s) acting as a proxy for the child are available. When the child is capable of self-completing an age-appropriate version he will do so. In all cases, regardless of the child's capability to self-complete, the parent(s)/guardian(s) will complete the appropriate proxy version. If possible the same parent/caregiver should complete the questionnaires at all visits. See the Manual of Operations for further details of how to administer these instruments.

6.3.12 Blindedness Assessment

At Visit 7 (T36), parents/guardians will be asked to provide their opinion regarding which treatment and regimen (Prednisone versus Deflazacort; daily regimen versus intermittent regimen) their child has been taking during the study. The site Principal Investigator and Clinical Evaluator will be also asked to give their independent opinion. If a child prematurely discontinues from study medication (whether he continues follow up visits or is withdrawn from study medication and from the study), blindedness assessment should be performed at the time the medications are withdrawn.

6.3.13 Adherence Assessments

At Visit 1 (T3) and at all subsequent follow-up visits, used, unused and empty trial drug (including the packaging) will be returned to the site investigator. The number of returned used packaging and unused tablets will be recorded. Instances of non-compliance (number of missed doses) will also be recorded. See the Manual of Operations for further details of this evaluation.

6.3.14 Between visit phone calls

The site coordinator will make phone calls between visits to monitor adverse events, concomitant medications, adherence to regimen, and any subject and parent concerns monthly (± 7 days) during the first 6 months following baseline visit, then every 3 months (± 14 days) through Month 36. All adverse events and concomitant medications will be recorded on worksheets and subject's study file.

6.4 Off-Intervention Requirements

A telephone call to the parent(s)/guardian(s) will be made 30 days after the scheduled date of stopping study medication, to check on any persisting adverse events. All adverse events possibly due to study medication will be monitored until resolved.

6.5 Biobanking

Samples should be collected for biobanking from as many subjects as possible at screening/baseline and annually thereafter. Standardized protocols for collecting, processing and storing the samples can be found for example at http://www.eurobiobank.org/en/documents/sops.htm. A separate consent will be required for collecting these samples, and the consent will be very broad so as not to restrict the use of the samples for future approved research projects. However, it will be explained to the subjects and their parents/guardians that the samples will be for research purposes, not for commercial use. Specimens will be stored in the biobanking facility in Newcastle upon Tyne, UK that is set up such as the EuroBioBank (cf. www.eurobiobank.org), with the stipulation that the samples be made available to all approved researchers. Possible future research includes proteomics and biomarker studies.

Some blood samples will be processed by the centers locally to produce serum, but those blood samples from which DNA or RNA will be extracted, will only be collected by the centers but not be processed by them. The serum samples and the blood samples for later DNA or RNA extraction can be initially stored locally at the centers but will have to be shipped to the biobanking facility in Newcastle upon Tyne for processing. There are protocols available that are to be followed by the centers for these serum, plasma, DNA and RNA samples.

7 MANAGEMENT OF ADVERSE EVENTS

7.1 Definition and grading of adverse events

7.1.1 Defining ‘adverse event’

An **adverse event** (AE) is any untoward medical occurrence in a subject that occurs during the conduct of a clinical study of a pharmaceutical product, even if that event does not necessarily have a causal relationship to the study drug. This can, therefore, be any unfavourable and unintended physical sign, symptom, laboratory parameter, or disease entity that develops or worsens in severity during the course of the study, whether or not considered related to the study drug.

Accordingly, an adverse event in the context of this study will include any of the following that occur after the consent has been signed:

- Intercurrent illnesses
- Physical injuries. Note: in case of injury, the outcome of the injury should be reported as AE (i.e. fracture following a fall). If a medical condition is known to have caused the injury or accident (i.e. dizziness causing a fall), this should also be reported as AE.
- Adverse events that are suspected (possibly) to be related to study medications
- Adverse events (possibly) related to concomitant medications
- Significant worsening (change in nature, severity, or frequency) of the disease under study (DMD) or other pre-existing conditions
- Drug interactions
- Adverse events occurring during diagnostic procedures
- Adverse events occurring during or as a result of study evaluative procedures
- A laboratory or diagnostic test abnormality occurring after the start of the study (once confirmed by repeat testing) that results in the withdrawal of the subject from the study, requires medical treatment or further diagnostic work-up, or is considered by the site investigator to be clinically significant. Abnormal laboratory determinations at the screening visit that preclude a subject from entering the study or receiving study drug are not considered adverse events, but will be captured in order to monitor data from screen failures.
- Abnormalities in physical examination or vital signs that require clinical interventions or further investigations (after repeated confirmatory test) or are considered by the site investigator to be clinically significant.
- ECG and Echocardiogram abnormalities that require clinical intervention or further investigations unless they are associated with an already reported clinical event.
- FVC abnormalities that require clinical interventions or further investigations unless they are associated with an already reported clinical event.

Pre-existing conditions should be recorded at screening in the appropriate worksheets and CRF (medical history) but should not be reported as adverse events unless the condition worsens (increases in frequency and/or severity). Diagnostic and therapeutic invasive and non-invasive procedures (including surgeries) should not be reported as adverse events. However, the medical condition for which the procedure was performed should be recorded if it meets criteria for an adverse event.

7.1.2 Defining ‘serious adverse event’

Adverse events are classified as either serious or non-serious. A **serious adverse event** (SAE) is any adverse event occurring at any dose, which results in any of the following outcomes or actions:

- Death
- A life-threatening adverse event (i.e., the subject was at immediate risk of death from the event as it occurred); does not include an event that, had it occurred in a more severe form, might have caused death
- In-patient hospitalization or prolongation of existing hospitalization (a hospitalization scheduled before enrolment for an elective procedure or treatment of a pre-existing condition, which has not worsened during participation in the study will not be considered a serious adverse event.). Treatments in the emergency room for procedures that do not require admission to the hospital and observational durations in the emergency room for less than 24 hours will be not considered serious.
- A persistent or significant disability/incapacity (i.e., a substantial disruption of one’s ability to conduct normal life functions)
- A congenital anomaly/birth defect
- Any other important medical event that the site principal investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. These events may not result in death, be life-threatening, or require hospitalization, but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

An adverse event that does not meet any of the criteria for seriousness listed above should be regarded as a non-serious adverse event.

7.1.3 Grading of severity of adverse events

The severity of adverse events will be graded, whenever possible, according to the MedDRA.

If a MedDRA criterion does not exist, the severity of each adverse event must be recorded using the following categories:

- **Mild (grade 1)** No limitation of usual activities (no need of medical interventions)
- **Moderate (grade 2)** Some limitation of usual activities (medical intervention might be required)
- **Severe (grade 3)** Inability to carry out usual activities (medical intervention and/or close follow-up likely needed)
- **Life-threatening (grade 4)** Potential threat to life
- **Fatal (grade 5)** Death

Severity is not equivalent to seriousness. Severity is a measure of intensity; therefore a severe reaction may not be a serious reaction. A headache may be ‘severe’, i.e. may limit ability to carry out usual activities, but not constitute a ‘serious’ adverse event as defined in Section 7.1.2 above. Severity is judged by the parents/guardians according to impact of AE on the subject’s usual activities.

7.1.4 Relationship of an adverse event to study medication

An **adverse reaction** (AR) is an untoward or unintended response to an investigational medicinal product (i.e. study medication or associated placebo) related to any dose administered.

A **suspected unexpected serious adverse reaction** (SUSAR) is a serious (by SAE standards, as listed above) adverse reaction, the nature of which is not consistent with the applicable product information (see Section 5.3.3.2).

For each adverse event, the site investigator (or another medically qualified individual at the site with delegated responsibility) must define and record the relationship to the study drug as one of the choices on the following scale:

- **DEFINITE: Causal relationship is certain** (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, other causes have been eliminated, and the event must be definitive pharmacologically or phenomenologically.
- **PROBABLE: High degree of certainty for causal relationship** (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable, and other causes have been eliminated or are unlikely).
- **POSSIBLE: Causal relationship is uncertain** (i.e., the temporal relationship between drug exposure and the adverse event onset/course is reasonable or unknown, and while other potential causes may or may not exist, a causal relationship to the study drug does not appear probable).
- **UNLIKELY: Not reasonably related, although a causal relationship cannot be ruled out** (i.e., while the temporal relationship between drug exposure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study drug)
- **NOT RELATED: No possible relationship** (i.e., the temporal relationship between drug exposure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study drug is implausible)

7.2 Recording and reporting adverse events

7.2.1 Adverse event recording

For the purpose of adverse event recording, the study period is defined as that time period beginning with the day the informed consent is signed and end of the study for the subject concerned.

The site investigator has to report all directly observed and all adverse events spontaneously reported by parents/caregivers. Moreover, at each visit after consenting and at each telephone contact with the parent/guardian, the site investigator must query for adverse events by asking an open-ended question such as “What unusual symptoms or medical problems has your child experienced since the last visit?” All reported or observed signs and symptoms will be recorded individually, except when considered multiple manifestations of a medical condition or disease state. A precise diagnosis will be recorded whenever possible. When such a diagnosis is made, all related signs, symptoms, and laboratory test findings will be collectively recorded as a single diagnosis on the Adverse Events worksheet and CRF.

The clinical course of each adverse event that is active at the final visit will be monitored at suitable intervals until resolution or stabilization, a determination of a cause unrelated to the study is made, or the subject is referred to the care of a local physician.

The relationship to study drug, and seriousness of each adverse event as judged by the site investigator must be recorded on the adverse events worksheet. The severity, onset date, stop date, and outcome of each adverse event must be also recorded on the CRF, as must any action taken with the study drug in response to the adverse event.

Classification of an adverse event as serious or non-serious determines the reporting procedures to be followed. Procedures for adverse event reporting are further described in Section 7.2.2 below and in the Manual of Operations.

7.2.2 Adverse Event Reporting

Anticipated adverse events are described in Section 7.3 and 7.4 below, including how these events should be classified and graded and further details on adverse events reporting are provided in the Manual of Operations. A Flowchart of the Process appears below.

Classification	Reporting time	Reporting action
Serious	Within 24 hours	Fax or email of the SAE form to the NCTU Complete CRF 30 & subject's study file
Non-serious	Per CRF submission procedure	Record and submit information on appropriate CRFs

SAE forms should be sent preferably by fax to +44 (0) 191 222 8901 marked "For the attention of the FOR-DMD Trial Manager". If no fax is available the SAE form can be sent electronically to for.dmd@ncl.ac.uk.

More contact details for AE and SAE reporting are listed in the Manual of Operations.

Adverse events will assessed by the site study staff at each visit by recording all voluntary complaints of subjects and by assessment of the clinical features. Adverse events will also be collected monthly during the first 6 months following baseline visit and every 3 months thereafter during "in between visit" phone calls. The NCTU will receive information about serious adverse events (SAEs), and will be responsible for disseminating information about SAEs to those concerned. An SAE is defined in Section 7.1.2 above.

The study will comply with FDA and EU Clinical Trials Directive requirements and International Conference on Harmonization (ICH) GCP guidelines regarding reporting of AEs and SAEs to the appropriate regulatory and ethical authorities including definition of which SAEs require expedited reporting and the timelines and mechanisms for expedited reporting. Where the requirements vary between participating countries, the most stringent requirements will be followed.

Upon occurrence of an SAE the site principal investigator or a person at site with delegated responsibility will be required to complete an SAE report form. They must also complete the adverse event CRF (CRF 30) and subject's study file. The SAE report form should be signed by the site principal investigator; however if the site investigator is unable to sign at the time of the event, the clinical staff member reporting the SAE should sign the form. All SAE report forms must be faxed or emailed to the NCTU within 24 hours of the investigator learning of the event The NCTU will confirm notification of receipt of SAE with sites via email or phone

call. For any SAE report forms, the NCTU will liaise with the chief medical coordinator or the independent medical monitor.

Parents/caregivers should be encouraged to promptly inform the site investigator about possible serious adverse events (e.g. hospitalization). However, in the event that the site investigator does not become aware of the occurrence of a serious adverse event immediately, the site investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the adverse event.

Follow up information and outcome of the serious adverse event should be documented as "follow up" in the SAE report form and has to be sent to the NCTU by fax or e-mail. Follow-up information will be required if further information become available after completion of the initial SAE form. Ongoing SAE will be monitored by the site principal investigator until resolution. Follow –up SAE form should be sent to the NCTU every 15 days as update for ongoing SAEs until closed. The Chief Medical Coordinator in consultation with the site principal investigator will decide if and when and ongoing SAE should be closed if the event is not resolved.

If available to the site at the time, supportive documents (i.e. discharge letter, laboratory and diagnostic test results) might be sent with follow up SAE forms. These supportive documents should be redacted in order to obscure subject's identification details (e.g. name and surname, address). Only subject identification number and initials should be provided. The information in the Adverse Event page of the CRF and the SAE report form must match or be reconciled.

See the Manual of Operations for contact details and further information regarding serious adverse event reporting.

Each serious adverse event report received from the site principal investigator must be evaluated by the chief medical coordinator or the independent medical monitor. The chief medical coordinator will be responsible for confirming relatedness of the event to the study drug, in consultation with the independent medical monitor and the study principal investigators if required. The chief medical coordinator will also be responsible, after discussion with the independent medical monitor and the study principal investigators, to established expectedness of each SAE. If no agreement regarding expectedness will be reached, the DSMB will be provided with an unbiased written report of the event and queried to make final decision.

If immediate reporting to the relevant IRB/REC is required by national legislation or custom, the appropriate IRB/REC will be notified by the site investigator in accordance with the relevant IRB/REC guidelines.

Study principal investigators and the chief medical coordinator will determine reporting status of the SAE (e.g., whether expedited reporting is required). If the SAE requires expedited reporting, study principal investigator through the NCTU will contact the appropriate regulatory authority (FDA or equivalent) within 7 days of first knowledge of the SAE with a complete report to follow initial notification (an additional 8 days). For non-expedited reporting, the appropriate regulatory authority will be notified within 15 days. The study principal investigators will independently perform final adjudication with respect to the relationship of the SAE to study drug. The NCTU Trial Manager will ensure appropriate communication of the SAE and related correspondence from the regulatory authority to the Data and Safety Monitoring Board (DSMB) as well as to the site principal investigators to submit to their respective IRBs/RECs, if required, and will also ensure that those SAEs which require entry on to the Eudravigilance database are so entered.

The independent medical monitor (IMM) and the chief medical coordinator will be responsible for monitoring conditions and progress of enrolled subjects. The independent medical monitor and the Chief Medical Coordinator will receive 6- month cumulative reports of AEs from the MSG-CC. The IMM will communicate with the chief medical coordinator and the study principal investigators for any new safety concerns to be raised with the DSMB.

The MSG-CC will be responsible for overseeing the preparation of (blinded) reports to the NINDS DSMB as well as interim communications through the principal investigators to program staff, should more frequent notification of safety issues be required. The IMM will be blinded as well, unless circumstances arise that the DSMB feel are necessary for unblinding.

7.3 Expected adverse events

7.3.1 Expected adverse events related to study medication

Both prednisone and deflazacort are well established drugs and the side-effect profiles are well understood. Not all of these effects have been observed in children.

There is extensive documentation of the side effects of short-term corticosteroids in boys with DMD. The effects of prednisone have been reported for 6 month and 18 month trials of daily prednisone as well as for longer term uncontrolled studies. There are also data for long-term (up to 2 years) use of deflazacort in small numbers of boys. There is relatively little short-term or long-term data for the intermittent prednisone regimen.

On the basis of these studies in DMD, mild side effects of corticosteroids are expected in a majority of subjects in both daily treatment groups and in some of the intermittent treatment groups. These include weight gain, cushingoid facial appearance, other manifestations of changes in fat distribution, excessive hair growth, and/or behavioral changes. Moderate side effects are expected (on the basis of these previous studies) to occur infrequently and include principally behavioral changes. Other mild side effects may be observed: acne, asymptomatic cataracts, glycosuria, loss of bone mineralization, abdominal striae, elevation of systolic or diastolic blood pressure. These side effects did not occur in a significant number of subjects treated with daily prednisone for up to 18 months and were infrequent in boys treated for 36 months.

There were no significant serious side effects in boys treated for up to 18 months with daily prednisone. Longer duration treatment is associated with symptomatic cataract, symptomatic fractures, secondary loss of bone mineralization, risk of infection, diabetes, hypertension, pancreatitis, glaucoma, congestive heart failure.

All adverse events will be monitored and recorded and may prompt dosage changes.

7.3.2 Expected adverse events related to other study procedures

During the collection of blood samples, boys may experience pain or bruising at the site. Localized clot formation and infections may occur, but this is rare. Fainting rarely occurs during or shortly after having blood drawn.

DXA / X-ray involve minimal exposure to radiation.

The other study procedures are not anticipated to cause adverse events.

7.4 Management of adverse events

A unique feature of this trial is the close attention paid by the planning groups to issues of baseline standards of care which might otherwise impinge on the outcomes of the trial as

well as clear guidelines to be applied across the trial population for the prophylaxis, monitoring and treatment of predictable corticosteroid-related side effects. Areas where side effect prophylaxis and management have been closely prescribed include behavior changes, bone health, and management of weight gain, due to their high occurrence in previous studies.

7.4.1 Behavioral problems

A feared but to date poorly quantified side effect of corticosteroids in DMD is altered behavior, in particular emotional lability and behaviors within the ADHD spectrum. Behavioral problems are also reported in this group of patients without steroid treatment (Hinton, Nereo et al. 2006). As a prophylactic measure, standardized behavioral advice will be provided to all families at the baseline visit and will be reinforced at all follow-up visits. In the case of behavior changes that are noted but are not disruptive to family/school life, consideration will be given to the provision of child psychology support. Where behavior changes are disruptive to family/school life, steroid dosage adjustments will be made as described in Section 5.3.3.2.1 above.

7.4.2 Bone health

Bone thinning and subsequent fracture are recognized side effects of long-term corticosteroid use. Prophylactic measures to ameliorate the risk of these adverse events will include dietary counseling, including advice on a daily intake of 1000 mg of calcium with the diet and 400-1000 IU of vitamin D with adequate supplements (e.g. Cholecalciferol). Further vitamin D supplements will be recommended for subjects who show evidence of vitamin D deficiency or insufficiency until further monitoring (see Manual of Operation for details). Vertebral fractures will be treated with bisphosphonates intravenously (see 5.3.1.2 above). All supplements initiated should be noted on the concomitant medication log.

7.4.3 Weight gain

Weight gain is a common side effect of corticosteroids. Weight will be measured at all visits and BMI (weight kg / height m^2) calculated. Prophylactic measures against undesirable weight gain will include standardized dietary advice (see Manual of Operations) with particular emphasis on advice on appetite control around the time that corticosteroids are started. In the event of annual weight gain > 1 and < 4 BMI units for subjects younger than 10 years and > 2 and < 4 BMI units for subjects older than 10, dietetic advice will be reinforced, and there will be no steroid dosage modification. In the event of an annual increase in BMI of ≥ 4 units, despite dietary modifications, or if weight gain is unacceptable to the child/ family despite intervention, steroid dosage will be reduced to a lower band. In the event of continued weight gain despite dosage reduction and/or where weight gain is unacceptable to child/family despite intervention, steroid dosage will be stopped. See Section 5.3.3.2.9 above.

7.4.4 Cataracts

There is an increased risk of cataracts in individuals on long-term corticosteroids which is often asymptomatic. The development of asymptomatic or symptomatic cataracts will trigger referral to ophthalmologist for visual acuity measurement and subsequent follow up.

7.4.5 Cushingoid appearance

The development of a Cushingoid appearance (Cushingoid facial appearance, other fat disposition) is a common side effect of corticosteroids. At each visit, the child will be assessed for the development of Cushingoid appearance (see Manual of Operations for

details of assessment). If Cushingoid appearance unacceptable to the child/family develops dosage adjustment will be as described in Section 5.3.3.2.2 above.

7.4.6 Gastrointestinal symptoms (abdominal pain, heartburn, GI bleeding)

Prophylactic measures against the anticipated side effect of gastrointestinal symptoms will include advice to avoid non steroidal anti-inflammatory drugs. In the event of gastritis/gastroesophageal reflux (GERD) symptoms, treatment with Ranitidine (or Proton-pump inhibitors) and antacid should be initiated. If GI symptoms persist despite treatment with Ranitidine (or Proton-pump inhibitors) and antacid, dosage, adjustment will be as described in 5.3.3.2.3 above.

7.4.7 Glycosuria

There is an increased risk of glycosuria and diabetes mellitus in patients on long-term corticosteroid therapy. At each visit, a urinalysis test will be performed to test for the presence of glycosuria. If glycosuria is detected (trace or greater), the urinalysis will be repeated within a week. If the second test confirms glycosuria, non-fasting (random) blood glucose should be checked within another week. Dietary advice should be reinforced and a fasting blood glucose test or 2-hour post-prandial test should be performed. In the event of elevated fasting blood glucose, or elevated post-prandial blood glucose, dosage modification will be as described in Section 5.3.3.2.4 above.

7.4.8 Hypertension

Blood pressure will be assessed at each visit and compared to age norms. Prophylactic measures will include standardized advice about dietary sodium intake. In the event of high-normal blood pressure (i.e., blood pressure in 90-99th centiles – see Manual of Operations for centile charts), the measurement will be repeated in a non-stress environment. Dietary recommendations (weight /sodium reduction) will be reinforced if high-normal blood pressure is persistent. In the event of confirmed hypertension (consistent and confirmed blood pressure equal or above 95th centile - see Manual of Operations for centile charts), repeat measurements will be made in a non-stress environment, on at least three separate visits, separated by 7 days apart. If there is continued evidence of significant hypertension on these repeat measurements, the child will be placed on a low sodium diet for 1 month (< 2.3 g sodium or 100 meq/day). If blood pressure is still elevated at repeat measurements after 1 month on low sodium diet, drug dosage will be adjusted as described in Section 5.3.3.2.5 above.

7.4.9 Immuno/adrenal suppression

The long-term use of corticosteroids can lead to immunosuppression. Contact with people with potentially serious infectious diseases, such as measles, meningococcal meningitis etc., should trigger appropriate prophylaxis (which may be provided by a family physician). Prophylactic measures against immune/adrenal suppression include: ensuring prior exposure to chicken pox/immunization; tuberculosis prophylaxis according to local population guidelines in ‘at risk’ children’; pneumococcal vaccination and annual flu vaccination; advice on corticosteroid cover in the case of illness, injury or surgery (see Section 5.3.1.6 above); disallowing live vaccines during treatment (see Section 5.3.1 above).

In the event of unusual infections or unusual responses to infection, initially there will be no steroid dosage modification. An unusually high frequency of infections/unusual organisms should prompt the seeking of advice from an immunology expert and steroid dosage adjustment as described in Section 5.3.3.2.6 above.

7.4.10 Skin changes

Skin changes, including acne, abdominal striae and hypertrichosis are recognized side effects of corticosteroids. At each visit, an examination of the skin will be carried out. In the event of skin infections or acne, the condition will be treated as indicated, and there will normally be no steroid dosage modification. If skin changes are unacceptable to the child/family dosage adjustment will be as described in 5.3.3.2.7 above.

7.4.11 Slow growth

Growth retardation is a recognized side effect of corticosteroids. If there is a failure to gain height, but this is not a cause of concern to child/family, no steroid dosage modification will be required. If a failure to gain height is observed and is unacceptable to child/family, dosage adjustment will be as described in 5.3.3.2.8 above.

7.5 Possible benefits

Subjects in the trial may benefit from frequent examinations by neuromuscular specialists, by application of standards of care for physiotherapy, cardiac follow up and respiratory care, from receiving (in all three arms of the trial) an active treatment for the management of DMD and from the application of explicit protocols for side effect prophylaxis and management.

8 INTERVENTION DISCONTINUATION

8.1 Criteria for treatment interruption

The principal criteria for discontinuation of intervention (i.e. withdrawal from study medication) are the experience of significant and persistent adverse events, even following dose modification as described in Section 5.3.3 above.

Study medication should not be stopped suddenly. A tapered reduction in dosage is required to avoid risks of adrenal failure. Procedures for achieving a tapered reduction are described in Section 5.3.3.2.10 above.

After discontinuation of study medication due to adverse events, the subject will be asked to continue follow up visits until the end of the study.

8.2 WITHDRAWAL OF SUBJECTS FROM THE STUDY

All subjects who start the study should remain in the study whenever possible. However, reasons for withdrawal include:

- Any subject or his parents/guardian have the right to withdraw from the study at any time without giving a reason
- The site investigator, in consultation with the chief medical coordinator, may withdraw any subject from the study if in their opinion this is in the best interest of the subject
- Any subject who becomes significantly non-compliant with study procedures, study follow-up and treatment should be withdrawn from the study if the circumstances increase risk to the subject.

In case of withdrawal from the study, continued corticosteroids treatment (commercial prescription) is not forbidden; however, it would be important to reinforce risk of treatment without adequate follow-up.

Study medication should not be stopped suddenly upon study withdrawal. A tapered reduction in dosage is required to avoid risks of adrenal failure. Procedures for achieving a tapered reduction are described in Section 5.3.3.2.10 above.

8.3 Procedures for maintaining involvement of subjects in follow-up activities

In the case of treatment discontinuation due to an adverse events or withdrawal of a subject from the study for whatever reason, a discontinuation worksheet should be completed by the site principal investigator and the chief medical coordinator should be informed (by email or phone call) within 5 working days. In addition, the site staff should record details regarding the reason of treatment interruption/withdrawal in the subject's notes and in the appropriate case report form (CRF81).

If study medication is prematurely discontinued at the instigation of the site investigator or family, for whatever reason (interruption or withdrawal), the child will be asked to continue to be followed-up in the study as per protocol, e.g., continue attending 6-monthly visits for evaluations off trial medication. The trial medication field of the worksheet should reflect the decision to discontinue trial medication. The date and reason for discontinuation should be recorded. If the subject is withdrawing from FOR-DMD study medication to participate in another clinical trial that does not allow for concurrent participation in FOR-DMD, the name of the trial should be noted in the "Notes" section of CRF81. Trial medication should not be stopped suddenly. A tapered reduction in dosage is required to avoid risks of adrenal failure. For details of how to taper dosage, see Section 5.3.3.2.10 above.

If a child prematurely discontinues from both medication and follow-up, a full ‘final visit’ should be performed if possible. This will include the elements of Visit 7 (T_{36}), as described in Section 6.2.2.5 above, as well as strong recommendation for the boy to have a thorough eye examination by an ophthalmologist. In the case of premature discontinuation from medication and follow-up, a telephone call to the parent(s)/guardian(s) will be made 30 days after the last visit to check on any persisting adverse events. Adverse events possibly due to study medication will be monitored until resolved.

9 STATISTICAL CONSIDERATIONS

9.1 Analysis of the primary outcome variable for efficacy

9.1.1 Primary statistical model

This trial is designed primarily to compare three corticosteroid regimens with regard to efficacy as measured by (1) time to stand from lying (log-transformed) averaged over all post-baseline visits during the three-year follow-up period (subjects no longer able to perform the task at a particular visit will be assigned the largest observed time in the sample), (2) forced vital capacity (FVC) averaged over all post-baseline visits during the three-year follow-up period, and (3) subject/parent global satisfaction with treatment, as measured by the TSQM (completed by the parent), averaged over all post-baseline visits during the three-year follow-up period. These outcomes represent different but important aspects of the expected benefits of corticosteroid treatment. The primary statistical analysis will treat this as a multivariate (3-dimensional) outcome and will consist of global tests of the null hypothesis that the regimens do not differ with regard to any of the three outcomes against the alternative that they differ (in the same direction) for all three outcome variables, performed separately for each of the three pair-wise comparisons among the three corticosteroid regimens.

The rationale for using a multivariate outcome is two-fold: the selection of a single primary outcome variable would be arbitrary, and the use of three outcome variables that are expected to similarly reflect differences between treatment regimens will be more powerful in detecting group differences than the use of a single outcome variable. A potential criticism of this approach is that the treatment groups may differ on some, but not all, outcomes in the same direction, in which case the power of the test may be compromised (see Section 9.6 below). One treatment regimen would be preferred over another only if there is consistent and persuasive evidence of this across the three outcomes, so if this is not the case the compromise in power may be seen as an appealing characteristic of this approach.

The test that will be used is based on the OLS (ordinary least-squares) statistic first proposed by O'Brien (O'Brien 1984). For a two-group comparison, this statistic is essentially an unweighted sum of the standardized two-sample statistics used for comparing the groups on each individual outcome. The analyses will involve three separate pair-wise comparisons among the three treatment regimens; each will be performed using a Bonferroni-corrected two-tailed significance level of 0.017 (this is two-tailed because it is not clear *a priori* which of the two regimens being compared will be superior, but it is expected that the superior regimen will be superior with respect to all three components of the outcome variable). The analyses will be adjusted for covariates, namely country, baseline time to stand from lying, baseline FVC, and initial weight band. This will be accomplished by using the adjusted treatment group means and corresponding estimated variance-covariance matrix from the appropriate multivariate analysis of covariance model in constructing the OLS statistic (Dallow et al., 2008). In order to ensure consistency of direction of the outcomes (i.e., higher values are "good" for all outcomes), the negative of time to stand from lying will be used for the formal statistical analyses.

It should be emphasized that interpretation of these tests will be in terms of the global three-dimensional outcome and that these tests do not identify the component on which the treatment groups differ. Follow-up analyses of the individual component outcomes, using a closed testing procedure, will also be performed in order to aid in the interpretation of the results of the global test for the multivariate outcome. This procedure will involve performing treatment group comparisons with regard to the three possible bivariate outcomes (time to stand from lying and FVC, FVC and TSQM, time to stand from lying and TSQM) as well as the individual outcomes. A treatment group comparison for an individual outcome will be considered to be statistically significant (at the 0.017 level) only if it is significant for the

trivariate outcome as well as for the bivariate outcomes of which the individual outcome is a component. It must be borne in mind, however, that the power to detect group differences for each of the individual outcomes will typically be lower than that for the multivariate outcome.

9.1.2 Adjustment for baseline characteristics

If clinically important differences are found among the three groups at baseline, particularly with regard to important variables such as age, the primary analyses will be repeated after statistically adjusting for these differences. These analyses, however, will be considered to be secondary.

9.1.3 Model assumptions

The underlying assumptions of the multivariate analysis of covariance model will be thoroughly checked (normality, linearity, etc.), and remedial measures (e.g., transformations) will be taken if serious violations of these assumptions are detected. Data from previous trials conducted by the CIDD group suggest that the model assumptions should be reasonable for the time to stand from lying and FVC components of the primary outcome variable (after transformation and averaging over time). The relatively large sample size (225 subjects) should also alleviate potential concerns about the multivariate normality assumption.

9.1.4 Primary strategy for the treatment of missing data

The primary analyses will be performed according to the intention-to-treat principle and will include all randomized subjects. Every effort will be made to retain subjects in this study and to collect all data at every visit. If a subject cannot tolerate or refuses to continue receiving the study intervention, the subject will continue to be followed and evaluated if willing, and any treatment received by the subject will be recorded. If a subject drops out, attempts will be made to bring the subject in for a final evaluation. Compliance with trial procedures, dosage modifications, dropouts, and reasons for dosage modification and subject withdrawal will be carefully tracked throughout the study. Multiple imputation will be used to accommodate missing data in the primary statistical analysis. A key assumption underlying this analysis is that the missing data are “missing at random” (MAR), i.e., the probability that the responses are missing for a subject depends only on the set of observed data for that subject and not on the specific missing values that were not obtained (Little and Rubin, 2002).

If a subject is missing a response at a particular visit, missing data will be imputed using a multivariate regression-based imputation model that is a natural extension of that often used in the univariate case (Little and Yau 1996). For subjects with complete data up to a particular visit, a multivariate multiple regression model will be fitted that includes the (3-dimensional) outcome at that visit as the dependent variable and (3-dimensional) outcomes at previous visits, treatment group, and country as independent variables. Separate models will be similarly constructed for each visit. Using these regression models, a missing value for a subject at a particular visit will be imputed as a draw from the predictive distribution given the outcomes at previous visits (some possibly imputed), treatment group, and country; as in the univariate case, the imputed value will be the predicted value from the multivariate multiple regression model with an appropriate amount of “noise” added according to the residual covariance matrix of the imputation model (Little and Yau 1996). This will be done sequentially starting with the Month 3 visit. This process will be repeated 100 times, resulting in 100 complete analysis data sets. The analyses will be performed separately for each of the 100 complete analysis data sets and the results will be combined into one multiple imputation inference (estimated treatment effect and associated p-value) using established methods (Li et al., 1991; Schafer, 1997). This regression-based imputation strategy reflects the within-subject correlations for each outcome over time as well as the correlations among the three components of the outcome variable.

This approach to imputation should be superior to other strategies such as carrying forward the last available observation, which often yields unrealistic imputed values. The use of multiple imputation also avoids the problem of artificially increasing power through data imputation associated with single-imputation methods because it accounts for the uncertainty associated with the imputation (Schafer 1997; Little and Rubin 2002). Also, sensitivity analyses that make different assumptions (other than MAR) regarding the missing data mechanism can be accommodated using the multiple imputation approach (Carpenter et al., 2013; O'Kelly and Ratitch, 2014). Such analyses will be performed, and it is hoped that the overall conclusions regarding the relative efficacy of the different regimens will not depend greatly on the imputation strategy used, particularly if subject dropout is minimized.

9.2 Analysis of the secondary outcome variables for efficacy

9.2.1 Analysis of continuous outcome variables

Analyses of the secondary outcome variables for efficacy thought to be approximately normally distributed, such as time to go 10 meters (log-transformed), 6MWT (distance walked in 6 minutes), the North Star Ambulatory Assessment total score, TSQM subscales (effectiveness, side effects, convenience), fat-free mass (DXA), and quality of life (the generic PedsQL and its neuromuscular disease-specific module) will involve the use of a repeated-measures analysis of covariance model (i.e., the so-called "mixed model repeated-measures", or MMRM, analysis strategy (Molenberghs et al. 2004)) with treatment group as the factor of interest, country as a stratification factor, and the baseline value of the outcome variable and initial weight band as covariates. The model will also include terms for visit (categorical), the interaction between treatment group and visit, and the interaction between the baseline value of the outcome variable and visit. The covariance matrix for the within-subject observations will be modeled using an unstructured pattern. This model will be used to determine 98.3% confidence intervals for the pair-wise group differences in adjusted mean response, averaged over all post-baseline visits. The confidence coefficient of 98.3% incorporates a Bonferroni adjustment for the three pair-wise comparisons among the three treatment groups. Confidence intervals for group differences in adjusted mean response at each visit can also be obtained using this model. Outcomes averaged over all post-baseline visits and at the final visit will be of primary interest. These analyses will also be performed for the individual components of the primary outcome variable (log-transformed time to stand from lying, FVC, and global satisfaction with treatment (TSQM)).

Other continuous outcome variables derived from the NSAA (percentage of follow-up time able to perform milestones such as hopping, jumping, and lifting the head from a supine position) will be similarly analyzed using an analysis of covariance model that includes treatment group, country, and initial weight band as independent variables.

If clinically important differences are found among the three groups at baseline, particularly with regard to important variables such as age, the primary analyses will be repeated after statistically adjusting for these differences. These analyses, however, will be considered to be secondary.

The interaction between treatment group and country will be investigated by including the appropriate interaction term in the repeated measures analysis of covariance model and testing for its significance. Also, interactions between treatment group and important baseline variables such as age, ethnicity, time to stand from lying (log-transformed), FVC and initial weight band will be examined separately in a similar fashion. Since the power to detect potentially meaningful interactions will be limited, the magnitudes of mean responses to treatment in the relevant subgroups will be examined. The observation of clinically important subgroup differences in mean treatment response (e.g., age 4-5 vs. age 6-7) will serve as hypothesis generation for possible future studies designed to specifically address the issue of differential therapeutic response.

9.2.2 Treatment of missing data for secondary outcome variables

The principal analyses for the continuous secondary outcome variables for efficacy will be performed according to the intention-to-treat principle and will include all randomized subjects. The repeated measures analysis of covariance model to be used for these analyses uses maximum likelihood to estimate the parameters of interest (treatment effects) using available data from all subjects and is a valid strategy under the MAR assumption (Molenberghs et al. 2004). Analyses based on multiple imputation, similar to those described for the primary outcome variable (but without the multivariate adaptation), may also be performed.

Because assumptions such as MAR are untestable with the observed data, sensitivity analyses will be performed that make various assumptions about the missing data mechanism. Flexible multiple imputation strategies in the context of pattern-mixture models are well suited for this purpose (Carpenter et al., 2013; O'Kelly and Ratitch, 2014). It is hoped that the overall conclusions regarding the relative efficacy of the regimens will not depend greatly on the analysis or imputation strategy used, particularly if subject dropout is minimized.

9.2.3 Exploratory analyses accounting for protocol deviations and noncompliance

Exploratory analyses will also be performed that, for example, may group subjects according to treatment actually received (whether or not this was the randomly assigned treatment). So-called "per-protocol" analyses will also be performed that include only subjects who complete the trial without any major protocol violations (e.g., < 80% compliance with study medication). The identification of subjects to be included in these analyses will be determined before the blind is broken (i.e., before data analysis). Of course, such analyses may lead to biased estimates of the actual treatment group differences, but they may provide an indication of the sensitivity of the analyses to treatment modification and noncompliance. Methods for bias reduction in this setting, such as those based on propensity score stratification (D'Agostino 1998) or inverse probability weighting (Lunceford and Davidian 2004), can be employed. Other analyses may be performed that censor a subject's data after the subject has withdrawn from study medication (if he agrees to continued follow-up) or who concurrently participate in clinical trials of other treatments. Other methods for causal inference that account for subjects switching treatment regimens can be explored (Xie and Heitjan 2004) should this occur with sufficiently high frequency. It should be realized, however, that this trial will only be able to purely address the issue of the comparison of the three different *initial* treatment strategies with respect to three-year outcome. In this sense it is a very pragmatic trial.

9.2.4 Analysis of times to disease milestones

Times from randomization to various disease milestones will be considered as secondary outcome variables for efficacy. These include time to loss of ambulation, time to loss of the ability to stand from lying, time to loss of the ability to rise from a chair, and time to loss of the ability to get up and down one step. Event times will be censored at the last follow-up time for subjects who do not reach the endpoint (milestone). These outcomes will be primarily analyzed using a Cox proportional hazards model that will include treatment group as the factor of interest, country as a stratification factor, and age and initial weight band as covariates. Confidence intervals for the adjusted hazard ratios representing pair-wise treatment group comparisons will be computed using this model. The underlying assumptions of this model will be checked using appropriate numerical and graphical

methods (Hosmer and Lemeshow 1999). Kaplan-Meier curves will be used to describe the cumulative probabilities of reaching the endpoint over time in the three treatment groups. Other aspects of the analysis of the primary outcome variable (e.g., further adjustment for baseline factors, examination of interactions) will be considered here as well.

9.3 Analysis of tolerability and safety outcomes

9.3.1 Tolerability outcomes

Tolerability outcomes will include ability to complete the trial on the originally assigned dosage (for weight) of study medication (the most important secondary outcome variable), ability to complete the trial without switching drug regimens (i.e., discontinuing study medication), and ability to complete the trial. The proportions of subjects with these outcomes will be compared among the treatment groups in a pair-wise fashion using Fisher's exact tests. Time until a dosage modification is required will also be compared among the treatment groups using the methods described above for analyzing times to disease milestones. The frequency of, and reasons for, dosage modifications, study drug discontinuations, and subject withdrawal will be thoroughly summarized by treatment group.

9.3.2 Adverse events

Adverse events will be tabulated by treatment group, severity, and perceived relationship to study drug. For each adverse event, pair-wise comparisons among the treatment groups will be performed regarding the occurrence of at least one event using Fisher's exact tests. The comparisons will be repeated excluding all mild adverse events. Similar analyses will be performed after grouping adverse events by body system using MedDRA coding. Individual adverse events will be listed. Particular attention will be paid in the analyses to significant behavioral changes, fractures, cataracts, Cushingoid appearance, GI symptoms, glycosuria, hypertension, immunosuppression, slow growth (height restriction), skin changes (e.g., excessive hair growth, acne, atrophy, easy bruising), (excessive) weight gain and abnormal echocardiography results, especially those requiring treatment. Adverse events that are classified as "serious" or lead to a dosage modification or withdrawal of study drug will also be carefully scrutinized.

9.3.3 Continuous safety outcomes

Continuous safety outcomes such as height, weight, body mass index, vital signs, DXA outcomes, bone age, vertebral height, markers of bone formation and resorption, echocardiography outcomes, behavioral ratings and laboratory test results will be analyzed descriptively. Results (actual values and changes from baseline) will be summarized by visit using descriptive statistics. Formal analyses may be performed using methods similar to those described above for the secondary efficacy outcomes (repeated measures analysis of covariance).

9.4 Miscellaneous analyses and outcomes

9.4.1 Measures of compliance with study medication

Compliance with study medication will be summarized by treatment group and visit. It will be quantified as the percentage of doses of study medication that were apparently taken (based on the number of pills distributed compared to the number returned at each study visit) out of the number of doses expected. Relevant circumstances such as dosage modifications will be taken into account in the calculation of the expected number of doses.

9.4.2 Blindedness Assessment

The association between guessed treatment from the blindedness assessment and actual treatment will be assessed using a chi-square test. Results will also be summarized by confidence in the guess and primary/secondary reasons for the guess.

9.4.3 Concomitant Medications

A listing of concomitant medications will be provided for each subject. Concomitant medication use will be summarized by treatment group according to the percentages of subjects using particular medications (or classes of medications).

Exploratory analyses may be performed that tabulate certain adverse events (e.g., those that are unusual/unexpected or serious) by treatment group and use of particular concomitant medications.

9.5 Sample size considerations

As described in Section 9.1 above, the primary outcome variable will be three-dimensional and will consist of time to stand from lying (log-transformed) averaged over all post-baseline visits during the three-year follow-up period, forced vital capacity (FVC) averaged over all post-baseline visits, and (3) subject/parent global satisfaction with treatment, as measured by the TSQM, averaged over all post-baseline visits. The primary statistical analysis will be a global test of the null hypothesis that the corticosteroid regimens do not differ with regard to any of the three outcomes against the alternative that they differ (in the same direction) with regard to at least one of the outcomes. O'Brien's OLS statistic will be used to carry out this test. The analyses will involve three separate pair-wise comparisons among the three treatment regimens; each will be performed using a Bonferroni-corrected two-tailed significance level of 0.017.

Existing data from the trials comparing 0.75 mg/kg/day prednisone vs. placebo suggest that the effects of prednisone on the time to stand from lying and FVC outcomes are of a magnitude of one standard deviation unit (difference between the treatment group means divided by the standard deviation of the outcome, adjusted for baseline values) (Mendell, Moxley et al. 1989; Griggs, Moxley et al. 1991; Manzur, Kuntzer et al. 2004). A difference in mean response between two corticosteroid regimens of 0.50 standard deviation units (i.e., half of the effect of 0.75 mg/kg/day of prednisone vs. placebo) will be considered to be the group difference that is of minimal clinical significance on these two outcomes (corresponding to approximately 1 second on time to stand from lying and 0.08 liters on FVC for a single time point). For example, if the intermittent regimen provides at least 60% of the benefit of daily prednisone on these two outcomes, the difference between the regimens will not be judged to be clinically important.

For global satisfaction with treatment on the TSQM, data on 378 subjects (mean age 50.5 years, range 18 to 88 years) using oral medications for a variety of illnesses (migraine, arthritis, high blood pressure, high cholesterol, and depression) suggest that the group difference of minimal clinical significance may be slightly less than 0.50 standard deviation units (Atkinson, Sinah et al. 2004). Subjects who described the seriousness of their illness as "Moderate" and those who described it as "Severe" differed by approximately 0.40 standard deviation units on this scale. Also, subjects who appraised their health as "Excellent" or "Very Good" and those who appraised their health as "Good" or "Fair" differed by approximately 0.50 standard deviation units on this scale. These data are limited in that they were not obtained in children or parents of children with Duchenne muscular dystrophy, but they do provide some idea of what group differences in mean response may be considered to be clinically important.

We performed a pilot study of the TSQM in 37 boys with Duchenne muscular dystrophy (DMD) between the ages of 4 and 12 years who were taking corticosteroids, 6 at the University of Rochester, 7 at the University of Kansas, 6 at Children's Hospital of Western Ontario (Canada), and 18 at the University of Newcastle (UK) (Herr et al. 2008). We collected data on the age and ambulatory status of the subjects, allowing us to examine the relationships between the TSQM subscale scores and these characteristics (Table 9.1). Although the small sample sizes limit our ability to detect significant differences among the groups determined by age or ambulatory status, the expected patterns of responses are apparent: lower mean Effectiveness and Global Satisfaction scores among those > 7 years old ($p < 0.05$) and among those unable to walk outside the home; lower Side Effects scores among those > 10 years old and among those unable to walk outside the home.

Table 9.1 Results of the TSQM Pilot Study in 37 Boys with DMD

	Age Group			Ambulatory Status	
Scale	**4-6 (n = 9)**	**7-9 (n = 11)**	**10-12 (n = 17)**	**Able (n = 29)**	**Home/Unable (n = 8)**
Effectiveness	79.0 (16.1)	58.6 (22.7)	61.4 (26.2)	68.8 (20.4)	50.7 (31.5)
Side Effects	85.9 (18.2)	83.5 (17.1)	71.2 (29.3)	82.6 (19.4)	68.8 (31.9)
Convenience	88.9 (15.7)	90.6 (11.4)	88.0 (16.6)	89.6 (13.9)	87.3 (17.5)
Global Satisfaction	82.5 (18.2)	67.1 (18.5)	63.9 (26.7)	73.2 (18.7)	54.1 (35.2)

Data from this study indicate that the mean global satisfaction with treatment differed by 0.65-0.80 standard deviation units between boys age 4-6 and those age 7-12. In this context, an effect size of 0.40 standard deviation units does not appear to be unacceptably large.

The power of the test based on O'Brien's OLS statistic also depends on the correlations among the three outcomes. Data on 51 subjects between the ages of 5 and 7 from the CIDD natural history cohort suggest that the correlation between the average time to stand from lying (log-transformed) and the average FVC over a three-year follow-up period is very small and possibly even slightly negative. Correlations between these outcomes and the TSQM global satisfaction rating, while expected to be mildly-to-moderately positive, were of unknown magnitude at the onset of the trial. For this reason, an interim sample size re-estimation was performed in July 2015 using all available longitudinal data, blind to treatment group assignment. The results revealed that the three components of the primary outcome variable (log-transformed time to stand from lying, forced vital capacity, and subject/parent global satisfaction with treatment) were at best weakly correlated ($0 < r < 0.25$).

Table 9.2 provides the power (estimated using Monte-Carlo simulation, with each estimate based on 50,000 replications) required to detect the specified treatment effects (differences between two groups, expressed in standard deviation units) under various assumptions regarding the correlations among the three outcomes, using O'Brien's OLS test and a two-tailed significance level of 0.017. A sample size of 67 subjects per group is assumed. This table indicates that a total sample size of 201 subjects (67 per group) will provide at least 80% and often greater than 90% power to detect treatment effects of at least 0.45 standard deviation units on at least two of the three components and as little as 0.25 standard deviation units on the third component of the primary outcome variable. The power becomes unacceptably low only in the case where there is no group difference in treatment satisfaction. To account for an anticipated 10% subject withdrawal rate, 225 subjects (75 per group) will be enrolled in the trial.

Table 9.2 Power calculations

Effect Sizes			Correlations			
Δ_T	Δ_F	Δ_S	ρ_{TF}	ρ_{TS}	ρ_{FS}	Power
0.45	0.45	0	0	0	0	72%
0.45	0.45	0	0	0.10	0.10	66%
0.45	0.45	0	0	0.15	0.15	63%
0.45	0.45	0	0	0.25	0.25	58%
0.45	0.45	0.25	0	0	0	92%
0.45	0.45	0.25	0	0.10	0.10	88%
0.45	0.45	0.25	0	0.15	0.15	86%
0.45	0.45	0.25	0	0.25	0.25	82%
0.45	0.45	0.45	0	0	0	98%
0.45	0.45	0.45	0	0.10	0.10	96%
0.45	0.45	0.45	0	0.15	0.15	96%
0.45	0.45	0.45	0	0.25	0.25	93%
0.50	0.50	0	0	0	0	83%
0.50	0.50	0	0	0.10	0.10	77%
0.50	0.50	0	0	0.15	0.15	74%
0.50	0.50	0	0	0.25	0.25	69%
0.50	0.50	0.25	0	0	0	96%
0.50	0.50	0.25	0	0.10	0.10	93%
0.50	0.50	0.25	0	0.15	0.15	92%
0.50	0.50	0.25	0	0.25	0.25	88%

Δ_T = Effect size for log(time to rise from the floor); Δ_F = Effect size for FVC; Δ_S = Effect size for global satisfaction with treatment. All values are expressed in standard deviation units.

ρ_{TF} = Correlation between log(time to rise from the floor) and FVC; ρ_{TS} = Correlation between log(time to rise from the floor) and global satisfaction with treatment; ρ_{TF} = Correlation between FVC and global satisfaction with treatment.

A secondary hypothesis concerns potential differences between daily deflazacort and daily prednisone with respect to adverse events, with intolerability (dosage reduction) and weight gain being the events of primary interest. Data from the long-term trials of prednisone (Fenichel et al. 1991) suggest that nearly 50% of subjects may require a lower dosage of daily prednisone than 0.65 mg/kg during the three-year follow-up period. The data from this study also indicate that subjects in the daily prednisone group will have an average weight gain of approximately 25% per year (standard deviation = 12%). The sample size of 225 subjects (75 per group) will provide 80% power to detect a group difference of 22% (50% in the daily prednisone group vs. 28% in the daily deflazacort group) regarding the percentage of subjects taking a reduced dosage at the end of the three-year follow-up period, using a chi-square test and a 5% significance level. It will also provide > 80% power to detect a group difference of 6% (25% in the daily prednisone group vs. 19% in the daily deflazacort group) in mean annual weight gain during the three-year follow-up period, using a t-test and a 5% significance level (two-tailed).

9.6 Data and safety monitoring

9.6.1 General guidelines

The monitoring of data quality and subject safety in this trial will follow the NINDS Guidelines for Data and Safety Monitoring in Clinical Trials. The NINDS will appoint an independent Data and Safety Monitoring Board (DSMB) that will be responsible for periodic review of the data related to adverse events throughout the trial. The MSG-CC and the MSG Biostatistics Center will prepare data and make them available for review by the DSMB, including information on all serious adverse events, other adverse events, laboratory test results, recruitment and retention, data completeness and data quality. The DSMB will act independently to review the foregoing data.

9.6.2 Interim analyses for safety

Interim analyses of safety data will be performed periodically throughout the trial. While the safety of subjects will be the primary concern of the DSMB, it is difficult to formulate precise stopping guidelines that would cover all of the possible situations that might arise. Adverse events, particularly serious adverse events such as deaths and any that are unexpected will need to be carefully considered by the DSMB in terms of treatment group imbalances. The adverse events associated with daily corticosteroid use in DMD have been reasonably well characterized in previous studies and include behavioral changes, fractures, cataracts, Cushingoid appearance, GI symptoms, glycosuria, hypertension, immunosuppression (e.g., infections), slow growth (height restriction), skin changes (e.g., excessive hair growth, acne, atrophy, easy bruising), and abnormal weight gain. Detailed procedures are in place to clinically manage these anticipated adverse events (see Sections 5.3.2 and 7.4). The DSMB will be provided with estimated incidences of these adverse events based on data from previous clinical trials of daily prednisone to use as benchmarks at the outset of the trial since there will be no placebo group in this trial.

9.6.3 Interim analyses for efficacy and futility

This is a trial designed to compare three corticosteroid regimens commonly being used to treat boys with DMD throughout the world. One of the important issues that the proposed trial and its possible extension can eventually resolve is the long-term consequences of starting boys on a particular corticosteroid regimen relative to the competing regimens. Even if, say, daily corticosteroids were found to be superior to intermittent corticosteroids in terms of the primary outcome variable in an interim analysis, it would not be desirable to stop or modify the trial on the basis of this (relatively) short-term outcome. The rationale for intermittent corticosteroid regimens is that they are thought to reduce the side effect burden in the short-term and, importantly, in the long-term. Therefore, it is important to maintain all subjects on their randomly assigned regimens for as long as possible in order to address issues related to the long-term consequences of treatment. We propose to conduct two interim analyses, after 33% and 66% of the subjects have completed 3 years of follow-up. The analysis of the primary outcome variable will be performed using an overall significance level of 0.001 (instead of 0.05), a conservative Haybittle-Peto-type strategy. We propose to have no interim analyses for the purpose of early identification of futility.

The DSMB will periodically review data regarding the rate of subject accrual over time. If the NINDS, in consultation with the DSMB, determines that the accrual rate falls substantially below that which is necessary for the timely completion of the trial, the trial may be halted for futility. The trial may also be halted for futility if other indicators of trial performance (e.g., subject retention, data quality) suggest that this is appropriate. In particular, if a substantial number of subjects (> 20%) in a treatment group discontinue their assigned treatment regimen, it would be prudent for the DSMB to consider halting enrolment in that arm and modifying the trial to change the regimen of all subjects in that treatment group.

10 STUDY COMMITTEES

10.1 Study Steering Committee

A study steering committee (SSC – FOR-DMD) will be responsible for protocol development, review of any study amendment, and coordination of study conduct and interpretation of study results. The SSC comprises the principal investigators, the chief medical coordinator, the biostatistician, the project managers and several experts in DMD. Other specialists may be invited to participate as members of the SSC at any time if additional expertise is desired.

10.2 Data and Safety Monitoring Board

A data and safety monitoring board (DSMB), operating autonomously from the SSC and the site investigators, will be responsible for providing independent recommendations to the NINDS about risk-benefit of the study and any modification required during the course of the study. The DSMB will be appointed by the NIH and its members must not be actively involved in study design, conduct or daily management of this study and must not have financial, propriety, professional, or other interests that may affect impartial, independent decision-making.

Specialists may be invited to participate as non-voting members at any time if additional expertise is desired. The DSMB will formally interact with the SSC through the sharing of minutes.

The DSMB will be responsible for:

- Examining accumulated safety, efficacy, and other relevant data at pre-specified points during the course of the study in order to make recommendations concerning continuation, termination, or modification of the studies
- Reviewing major study design modifications proposed by the SSC prior to implementation of those modifications
- Reviewing the general progress of the studies as regards such issues as subject accrual, study conduct, and protocol violations
- Providing expert advice to the SSC on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

Based on the results of its deliberations, the DSMB can recommend continuation of the studies unchanged, study interruption, study termination, modification of the studies, or alteration in the DSMB monitoring plan.

11 DATA COLLECTION, STUDY RECORDS, SITE MONITORING, AND ADVERSE EXPERIENCE REPORTING

11.1 STUDY RECORDS

11.1.1 RECORD TO BE KEPT

This trial will use electronic remote data capture (eRDC). However, the impracticalities of real-time data entry in busy clinics are recognized. Therefore, data from evaluations (see Section 6 above) will be initially captured on paper work-sheets (essentially paper mock-ups of the electronic data capture screens) for subsequent entry to the eRDC system.

Data capture, recording and entry will be the responsibility of site staff (site investigator, site coordinator, clinical evaluator); details of which members of site staff are responsible for specific activities will be recorded in the site delegation log.

11.1.2 Data to be collected for each subject

The following information will be collected and retained for each study subject. A study file will be created and maintained for each subject, will all relevant documentation filed in date order.

- Documentary evidence of diagnosis of DMD.

  The original (top copy) of the signed informed consent form (and assent from child if appropriate), as well as originals of any subsequent re-consent forms that might be required.
- Contact details form, to include name, address, shipping address and telephone number of child and parent(s)/guardian (if parents live separately, contact details for both parents to be sought), and name, address and telephone number of an alternative contact (e.g., grandparent) to be used in the event of apparent loss to follow-up.
- Completed worksheets and questionnaires for all evaluations and all visits (see Section 6 above and Manual of Operations).
- Copies of laboratory reports, findings on DXA scans, spine and wrist X-rays, echocardiograph, ECG.
- Copies of correspondence to and from other health professionals involved in the child's care (e.g. family physician) where that correspondence has a possible bearing on the child's participation in this trial (e.g. copy of letter to family physician indicating that the child is participating in this trial).
- Copies of correspondence to and from the clinical trials supplies company (e.g., initial fax to confirm contact details for shipping of drug supply, subsequent faxes advising on drug dosage following review at follow-up visits).
- Copies of correspondence (including notes of telephone calls) with the family in connection with the child's participation in this trial.
- Copies of correspondence (including notes of telephone calls) with the NCTU in connection with the child's participation in this trial.

- Copies of correspondence (including notes of telephone calls) with the MSG-CC in connection with the child's participation in this trial.

A record of the fact that the child is participating in a clinical trial will be recorded in his general medical records, and a copy of the signed informed consent form will be provided to the appropriate clinic be kept in those records.

11.1.3 Site master file

In addition to the subject-specific Study Files, each site will also maintain a Site Master File, containing the following documents and materials.

- Investigator site information (names and brief CVs for all personnel at site engaged in the trial, with indication of their role and evidence of their suitability by training and experience for that role, including training in Human Subject Research; delegation & authorized signature log).
- Sub-contract with site and any relevant financial agreements
- Site initiation letter
- Copies of general communications with NCTU and MSG-CC (e.g., newsletters, records of PI meetings, records of general correspondence (including notes of telephone calls) regarding trial conduct).
- Signed protocol and protocol amendments (if any)
- Copy of Investigators Brochure / Summary of Product Characteristics
- Central approvals (regulatory and central / national REC/IRB communications) where applicable, including progress & safety reporting to the appropriate bodies
- Local approvals (local REC/IRB communications and any other locally required permissions, including progress & safety reporting to the appropriate bodies).
- Master copy of subject information sheet(s) and consent form(s) (country- or site-specific translated and otherwise adapted versions).
- A note stating the location of all source documents.
- Laboratory documentation (e.g., local laboratory ranges, current accreditation/certification)
- Insurance statement (where required)
- Screening log
- Reports of monitoring visits

11.2 Maintaining confidentiality of medical records

At randomization, unique non-informative identification numbers will be assigned by the site principal investigator to study subjects. The subject identification number will be the principal means of identifying study subjects. The subject identification number will be used on all documents relating to that subject, in eRDC and as the link between all study data files. Recording 'strong' identifiers (in particular, name and/or address) on study documents should be the exception rather than the norm. Such details will however be needed on informed consent forms, subject contact forms, correspondence with other health professionals and correspondence with the clinical trials supply company. Strong identifiers may also appear on

original laboratory reports and findings on DXA scans, spine and wrist X-rays, echocardiograph, ECG; such identifiers should be removed and replaced by the subject identification number on any copies of reports etc. submitted for central monitoring, review and/or analysis. They will not, however, be entered into the central database.

Source documents are the original documents where that source data was recorded; this could be the subjects' medical file/records, laboratory reports, dispensing logs or the trial worksheets. Paper copies of all source documents should be stored under double lock (locked filing cabinet or cupboard, in a locked room) in individual subject Study Files at each site; only authorized study personnel (as indicated in the site delegation log) should have access to these records. Particular care should be exercised to ensure the confidentiality of any documents (e.g., consent forms, subject contact forms, correspondence with the clinical trials supply company) containing both identifying subject information (in particular, name and address) and the link to the subject identification number. Source documents shall be maintained at site as per local policy and/or national/local legislative requirement for data retention for clinical trials.

In conformance with HIPAA regulations, no records or other documents containing 'strong' identifiers (e.g., name, address) should be released off-site unless it is so stated in the consent form. Records and forms (e.g. worksheets, questionnaire) that are pseudo-anonymized (e.g., display subject identification number and initials, but not strong identifiers) may be released to authorized members of the NCTU and/or MSG-CC to facilitate central monitoring and data checks. The consent/subject information sheet will make it clear that this level of data release will be allowed. All staff at NCTU and MSG-CC who may see pseudo-anonymized data or (in the case of the site monitor) fully identifiable data will be bound by explicit written codes of confidentiality.

No names or other personal identifiers except for initials and date of death will be collected in the central database. Gender, date of birth, race and ethnicity will be collected solely for the purpose of mandated reporting and statistical analysis.

All data files and other research documents (e.g., copies of pseudo-anonymized worksheets or correspondence with a site regarding a specific study subject) at the NCTU and at MSG-CC will be kept under double lock and will be accessible only to authorized study personnel. Communication by fax will use a secure fax machine in a room not accessible to unauthorized individuals. No individual identifiers (other than subject identification number) will be displayed on data listings for internal use. All data listings will be shredded before recycling. No individual identifiers will ever be included in any published data listing, nor will any individual subject be identified in any publications from this study.

Electronic data collected throughout the course of this study will be retained indefinitely. Data for an enrolled subject will be removed from the system and destroyed only at the written request of the subject (or his parent/guardian). Computerized data will be stored in Oracle databases residing on University of Rochester computer systems. Several layers of security will protect the database from unauthorized access. The University of Rochester's Information Systems Department (ISD) and the Heart Research Follow up Program provide network level security, including password maintenance, firewall and antivirus protection, intruder tracking, regular backups, and disaster recovery. The MSG-CC employs additional password protection for access to folders containing confidential research data. User IDs and initial passwords will be assigned by the MSG-CC and transmitted to the users via secure email. NIH guidelines regarding the length, content, and frequency of changing of passwords will be followed.

If a FOR-DMD subject elects to participate in another Duchenne MD clinical trial that allows for concurrent participation in FOR-DMD, some data, including (but not limited to) FOR-DMD subject ID, mutation information, and FOR-DMD treatment regimen will need to be shared with staff/data managers affiliated with the other trial. At no time prior to completion of the FOR-DMD Month 36 visit will the unblinded FOR-DMD treatment regimen be shared with the

subject/family or study personnel from either trial for the purpose of allowing concurrent participation in another trial. Prior to completion of the Month 36 visit, a subject/family will be unblinded to FOR-DMD treatment regimen only in case of a medical emergency that warrants knowledge of the treatment regimen. If a subject elects to participate in both FOR-DMD and another clinical trial, concurrently, the subject will be asked to sign a separate consent form for this purpose, giving permission for the FOR-DMD Team to share that subject's data (i.e., treatment regimen) with the other trial.

11.3 DATA MANAGEMENT AND QUALITY ASSURANCE

11.3.1 Division of responsibilities

11.3.1.1 Site responsibility

Site investigators, clinical evaluators and coordinators will be responsible for collecting data from the study subject, and from evaluations performed on the subject during the course of the trial. They will keep all source documents, worksheets and questionnaires related to each subject in a subject-specific Study File which will be kept in a secure area, accessible only to authorized study personnel. The study coordinators will be responsible for entering all data for a given subject visit into the online data management system within 5 working days of the conclusion of the visit. Where the online system indicates data entry problems the site coordinator will be responsible for investigating, and if necessary correcting, the flagged items. The site coordinator will also be responsible for resolving queries identified by the central data management group (MSG-CC) in a timely fashion (within one week of notification of the query).

11.3.1.2 MSG-CC (Statistical/Data Management Center) responsibilities

Data Management staff at the MSG-CC will be responsible for data collection, processing, management and query processes, and the timely delivery of an accurate and complete database to the MSG Biostatistics Center. The study will use electronic web-based data entry using the clinical data-management system produced by eResearch Technologies (EXPeRT). The EXPeRT system is currently licensed to the Heart Research Follow-up Program. The MSG-CC will use the system deployed on Heart Research servers. MSG-CC will partner with Heart Research for actual system and database development.

MSG-CC personnel will train site coordinators in the use of the system, provide user IDs and passwords to all authorized users, and monitor data security and integrity. The MSG-CC will also develop online data checking and validation tools to identify potential errors at the time of data entry, as well as batch programs for querying suspect data after data entry. They will provide a user guide (paper and online) to all users and will maintain a 'help desk' for answering questions and resolving user problems via phone and email. The MSG-CC will create programs to report on data completeness and quality, to meet DSMB requirements, and any other blinded reports deemed necessary for the successful implementation of the trial. At the conclusion of the study the MSG-CC will clean and lock all study databases, and provide a final copy of all data to the study biostatistician for analysis. Unblinded data reports will be produced by the un-blinded biostatistics programmer.

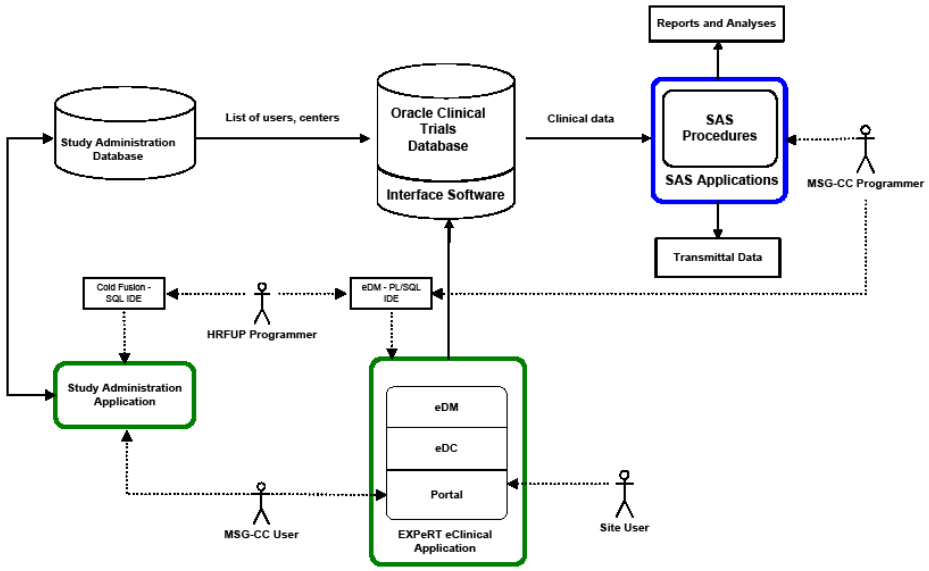
11.3.2 Data flow and management

The EXPeRT system supports the collection and management of clinical data through several integrated subsystems that use a common relational database to consistently store the clinical data. A web-enabled portal provides access to the system services. The system is configured to have data entered electronically at the investigational sites, with at-source real-time data editing and correction. The underlying foundation of the system provides the

capability to define data editing rules for ensuring the quality and consistency of the clinical data, a query management process to track data discrepancies and their resolutions, and source monitoring and verification of the clinical data.

The EXPeRT System provides audit trail, security mechanisms, and electronic signature capabilities that meet FDA 21 CFR Part 11 requirements regarding electronic records and electronic signatures. The Heart Research Follow-up Program's use of this system meets FDA requirements for the validation of off-the-shelf software. An implemented quality system of documented policies and procedures governs the use of the EXPeRT System by the Heart Research Follow-up Program at the University of Rochester. The major components of the data management environment that will support the collection, processing, and reporting of data collected for this study are presented in Fig. 11. The diagram identifies the individual applications, databases storing the data, and points of user interface with the various applications. The Coordination Data Center (CDC) has a full complement of staff that effectively manages various clinical studies and clinical trials with this electronic data management system. This database permits data expansion, easy updating, and rapid retrieval; it has simplified report-generating routines and audit trail component.

Figure 10.1 Major components of the EXPeRT-based electronic clinical data management system.



eDM is the electronic data management; eDE is the electronic data entry; and eRC is the electronic research community, the portal through which the eDE is accessed.

11.3.3 Quality control

All submitted data will be subject to an extensive computer edit-checking process for completeness, internal consistency, identification of numerical values outside specified rational limits, invalid codes, subject identification errors, and date errors.

The CDC uses a tape backup routine consisting of full nightly, weekly, and monthly backups, with tapes moved to an off-site location on a quarterly basis to cover a physical disaster at the CDC. All servers and major computers are housed in a temperature-controlled room. The computers are provided with an uninterruptible conditioned power supply to maintain smooth current, with battery power to facilitate a safe shutdown in the event of a complete power

failure. All subject information stored on the computerized database will be identifiable only by a unique subject identification number. The computerized database will be provided with "password" security so that only authorized persons will have access to the information within the database.

11.3.4 Staff Training

Site staff will be trained on the data entry system at the beginning of the project. If turnover occurs at the site, new staff will be trained as needed. On-line user manuals and help screens are available at all times. Call in 'help desk' support will be available on a schedule that will allow all sites a minimum 3 hour a day call in window.

11.3.5 Quality assurance

To assure the quality of the trial conduct and data, the NCTU and MSG will monitor the progress of the study on a day to day basis and provide support to sites. Elements of progress assessment monitoring and quality assurance will include tracking recruitment rates, compliance with visit schedules, timeliness and completeness of electronic data entry, compliance with adverse event reporting etc. The large number and geographical dispersion of sites in this trial necessitate a mixture of central and site monitoring to check for regulatory compliance and data entry accuracy. All monitoring findings will be reported and followed up with the appropriate persons in a timely manner.

11.4 MONITORING

11.4.1 Central monitoring

Copies of all documentation essential for site initiation (e.g., notification of national/local regulatory and ethical approval and any other permissions required, copies of CVs for all site staff, completed delegation and signature log) will be reviewed and stored at the University of Rochester prior to site authorization/initiation. (For less experienced sites, a site initiation visit may be conducted by the Site Monitor)

11.4.2 Site monitoring

In compliance with GCP guidelines and sound clinical research principles, a monitoring plan will be developed. The monitor will visit each site when the first subject has been on study drug for 3 months, annually thereafter and at close out. While at the site, the monitor will:

- Review on-site resources (personnel, space, equipment, milieu);
- Discuss the study protocol and visit schedule with staff to ensure familiarity;
- Review maintenance of study records;
- Review the informed consent forms executed by participating research subjects, and the process by which consent was obtained;
- Review submitted study data to ensure consistency with source documentation, and to ensure study data have been collected in an accurate, complete and timely manner, consistent with the protocol and GCP's;
- Review site REC/IRB approvals and regulatory documentation (e.g. Clinical Trial Authorizations) to ensure all such regulatory and ethical documents are correct and up to date;
- Assist the sites with resolution of electronic data clarifications (queries);
- Ensure that all serious adverse events have been properly and promptly reported;

- Ensure that laboratory results conform to study standards and that investigations required to be transmitted centrally are compatible;
- Collect copies of de-identified DXA scans (N/A in Germany) and EKG/Echo reports to transport to the Project Manager (either in UK or in Rochester, as appropriate).

Reports of these visits will be provided to the NCTU (charged with seeing protocol compliance) and the University of Rochester (study sponsor). Each site will receive a report on the visits to that site, with indications of required actions (if any). The Project Managers in will periodically review the site monitoring reports for their area of oversight (EU or US/CAN) with the lead project investigators (Dr. Bushby or Dr. Griggs) or the Chief Medical Coordinator..

12 HUMAN SUBJECTS

12.1 Compliance with Ethical and Regulatory Guidelines

The site investigator will be responsible for assuring that the clinical study is performed in accordance with GCP guidance documents and all other regulations and guidance pertaining to the conduct of clinical trials in the participating countries (US: GCP guidance; all EU countries: EU Clinical Trials Directive (2004) and its enactment into legislation in each participating EU country, and the Declaration of Helsinki (revised version of Edinburgh, Scotland, 2000); UK: Research Governance Framework for Health and Social Care (2nd edition)); Canada GCP guidance; Italy: Decreto legislativo 24 giugno 2003, n. 211 http://oss-sper-clin.agenziafarmaco.it/normativa/dlgs_211_24-6-03_Dir_UE_sper.pdf; Germany: In accordance with the provisions of the AMG and the GCP regulations, the Federal Data Protection Act or the applicable /Land/ Data Protection Act, the requirements of Good Clinical Practice (GCP) and in compliance with the Declaration of Helsinki, as amended.

12.2 Institutional Review Board (IRB) Review and Informed Consent

Informed consent will be obtained from the parents/guardians (with legal authority to consent on behalf of the child) of the boys and an assent process appropriate to the age of each boy will be carried out. The consent and assent will be obtained by the research coordinator and site investigator prior to initiation of any evaluations.

As part of the assent process, the boy will be told that when he comes for his regular doctor's visit that the doctor would like to write some of the information down to use in a big science project to see which way of taking his medicine helps the most and causes the least amount of gaining weight, feeling upset, or having weaker bones. He will be asked if he has any questions and if he would like to be part of the study.

The site investigator will explain the nature of the study and the risks of participation in the study to each parent and subject at an initial office visit in an unhurried discussion. A copy of the informed consent form and assent form will be given to the parents and subject to read. The site investigator will again explain thoroughly the experimental nature of the study and the risks of participation in the study to each family, prior to the boy entering the study and beginning the screening evaluations. If the subject and parents/guardians still wish to

participate in the study, the parent/guardian will sign and date the informed consent form along with the site investigator. The child will sign the assent form or give verbal assent. The original copy of the signed and dated consent and assent forms will be retained by the site investigator and one copy will be provided to the family.

The protocol and model informed consent and assent documents will be reviewed by the NCTU's and the University of Rochester's Ethics Committee/IRB prior to distribution to each investigative site for IRB submission. Copies of the written approval and approved informed consent document will be provided to the NCTU and University of Rochester prior to enrolment of subjects.

12.3 Subject Confidentiality

The measurements and observations that will be recorded will take place during the routine out-patient visits that boys with DMD receive as standard of care. The data will be recorded in the patient medical chart but will then also be captured on the research forms. The information will be kept confidential and entered in the secure electronic database. All medical records and study data will be kept confidential. A confidential and unique subject identification number will be used to identify each subject's research case report forms and all communications, in accordance with the Health Insurance Portability and Accountability Act. No names or other personal identifiers except for initials and date of death will be collected in the central database. Gender, date of birth, race and ethnicity will be collected solely for the purpose of mandated reporting and statistical analysis. Only site personnel and the clinical trials supplies company will have access to subject identities. The site monitor will see this information during site visits. All records will be kept in locked drawers. Information will not be released without written permission of the subject, except as necessary for monitoring by IRB, the FDA, the NINDS, the OHRP, and similar European regulatory bodies.

Medical information to be obtained from the subjects will include demographics, medical history, the results of physical examination, and concomitant medication usage. Subjects will provide blood and urine specimens; they will have wrist and lateral spine x-rays, DXA's, EEG's, and ECHO cardiograms; they will have tests of forced vital capacity and muscle function. Each boy and a parent/guardian will be asked to fill out questionnaires about Quality of Life. The parent/guardian will fill out a questionnaire about satisfaction with the treatment and the PARSIII, Iowa Connors – Parent, SDQ and Revised Rutter scales to assess the boy's behavioral changes.

All study records will be maintained for 10 years after the end on the study or 2 years post marketing or 2 years after shipment and delivery of the drug for investigational use is discontinued and FDA has been so notified, whichever is longer.

12.4 Study Modification/Discontinuation

The study may be modified or discontinued at any time by the IRB, the NINDS, the OHRP, the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

13 PUBLICATION OF RESEARCH FINDINGS

The members of the FOR-DMD SSC will be responsible for ensuring that this protocol is listed at the clinicaltrials.gov website and that information at the website relating to study design and conduct is appropriately updated during the course of the study.

Results from the trial, whether positive or negative, will be submitted for publication.

All articles utilizing data on subjects recruited in the study must acknowledge support from the NIH.

The FOR DMD Steering Committee will serve as the Publication Committee for review of the proposed content and authorship of all papers based on study data. This review should occur before data are released for preparation of abstracts or papers. A Publication Policy Committee has been established to develop a policy on the authorship of papers reporting study data.

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APPENDIX A. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Association General Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Association General Assembly, Tokyo, Japan, October 1975 35th World Medical Association General Assembly, Venice, Italy, October 1983 41st World Medical Association General Assembly, Hong Kong, September 1989 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other subjects in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

11. The subjects must be volunteers and informed subjects in the research project.

12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the site investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the site investigator must obtain that assent in addition to the consent of the legally authorized representative.

17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the site investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

19. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

20. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

21. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

22. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

23. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

PROTOCOL ADDENDUM

FOR-DMD Flow Sheet for Data

Subject data collected at site where subject was recruited/randomized

(Data is raw at this point and the FOR-DMD staff performing the procedure are entering the raw data onto a data collection form as it is gathered)

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Data entered into EXPeRT (online data management system) by site where subject had visit

(DATA MAY BE SEEN BY STUDY COORDINATOR, PI, PHYSICAL THERAPIST, DATA ENTRY PERSON – ESSENTIALLY ALL OF FOR-DMD STAFF AT THE SITE – MAY ALSO BE REVIEWED (IF REQUESTED) BY SITE'S LOCAL ETHICS OR R&D COMMITTEE; ALSO WILL BE SEEN BY SITE MONITOR FOR GIVEN COUNTRY

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↓

All data entered in EXPeRT has only a SUBJECT ID attached, however one form also shows date of birth (SUBJECT ID is a combination of country letters and number, and sequential numbers – i.e., USA01R02, where USA is country, 01 is Rochester site, R means subjects was randomized, and 02 is the sequential order of subjects randomized at site) – this (and Date of Birth) is the only identifier entered in the online data system at this stage

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Data entered in EXPeRT (only has subject ID/DOB) may be reviewed by the following:

University of Rochester FOR-DMD Data Management Team

University of Rochester Biostatistician(s)

University of Rochester Project Manager and Lead Principal Investigator

University of Newcastle FOR-DMD Management Team, including Project Manager and PI

NIH/NINDS staff associated with FOR-DMD review/approval

Data Safety Monitoring Board (assigned by NIH/NINDS)

Medical Monitor for FOR-DMD trial

FDA (for IND)

Competent authorities in other countries (MHRA in UK, BfARm in Germany, Health Canada, AIFA in Italy)

To meet regulations or for reasons related to this research, the study investigator may share a copy of the consent form and records that identify the subject with the following people:

- The University of Rochester
- The Institute for Human Genetics in the United Kingdom

- The study sponsor: National Institutes of Health, which is a part of the Department of Health and Human Services (a federal government department)
- The Newcastle upon Tyne Hospital's NHS Foundation Trust (the institution that contracts with the drug supply company)
- Food and Drug Administration (FDA) (the governmental agency that oversees research of investigational agents in the United States)
- The regulatory agencies that are similar to FDA in the other countries participating in this study
- The Institutional Review Board (IRB) or Research Ethics Committee (IEC) [INSERT APPROPRIATE NAME] (an institutional committee that makes certain that your child's rights are protected)
- The Newcastle Clinical Trials Unit, Institute of Health and Society, Newcastle University (the center that manages the clinical aspects of this study)
- The Muscle Study Group Coordination Center at the University of Rochester (the center that manages the information (data) from the study)
- The Department of Biostatistics at the University of Rochester (the center that will be analyzing the data and will prepare tables, graphs and figures for publication purposes)
- Catalent (the company that is supplying the study drugs)
- "Instituto Auxologico Italiano IRCCS, in Milan Italy (the center that will be analyzing the DEXA scans and bone measurements using blood and urine samples)
- MRC Neuromuscular Center BioBank in Newcastle upon Tyne, UK for use in future approved research projects (Optional)
- Data Safety Monitoring Board (DSMB) (the committee that follows the study data several times during any given year for any safety concerns as well as how quickly the study is enrolling)
- Medical Monitor (the doctor who monitors the day to day safety of people who are in the study)
- The research investigators at the OTHER clinical centers that are participating in the study.

Data flow and management

The EXPeRT system supports the collection and management of clinical data through several integrated subsystems that use a common relational database to consistently store the clinical data. A web-enabled portal provides access to the system services. The system is configured to have data entered electronically at the investigational sites, with at-source real-time data editing and correction. The underlying foundation of the system provides the capability to define data editing rules for ensuring the quality and consistency of the clinical data, a query management process to track data discrepancies and their resolutions, and source monitoring and verification of the clinical data.

The EXPeRT System provides audit trail, security mechanisms, and electronic signature capabilities that meet FDA 21 CFR Part 11 requirements regarding electronic records and electronic signatures. The Heart Research Follow-up Program's use of this system meets FDA requirements for the validation of off-the-shelf software. An implemented quality system of documented policies and procedures governs the use of the EXPeRT System by the Heart Research Follow-up Program at the University of Rochester. The major components of the data management environment that will support the collection, processing, and reporting of data collected for this study are presented in Fig. 11. The diagram identifies the individual

applications, databases storing the data, and points of user interface with the various applications. The Coordination Data Center (CDC) has a full complement of staff that effectively manages various clinical studies and clinical trials with this electronic data management system. This database permits data expansion, easy updating, and rapid retrieval; it has simplified report-generating routines and audit trail component.

Major components of the EXPeRT-based electronic clinical data management system.