

# **Protocol for Phase 2 Historically Controlled Trial of Corticosteroids in Young Boys with DMD**

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## Purpose of this Trial

The purpose of this trial is to determine if weekend oral corticosteroids improve development in infants and young boys with Duchenne Muscular Dystrophy (DMD). We will compare the development of infants and young boys with DMD who are treated with prednisolone (10 mg/kg/week given in equal doses over two days) to the development of untreated DMD infants and young boys who have just completed one-year follow-up using the same measures. Gross motor development, fine motor development, speech, language and social skills will be assessed at baseline, and after six months and twelve months treatment.

## Introduction/Background/Rationale

Duchenne Muscular Dystrophy is an X-linked, genetic disorder. The clinical picture consists of progressive proximal muscular weakness, which leads to loss of ambulation with subsequent loss of hand and arm function and respiratory and cardiac failure.

The early careful natural history studies of boys with DMD relied on manual muscle testing using medical research council (MRC) testing and functional outcomes<sup>1-3</sup>. These outcomes have been extended to include quantitative measurements, which allow better inter-rater reliability for ambulatory boys and are currently used in multicenter trials<sup>4-8</sup>. Additional functional measures including activity monitoring are very useful for ambulatory boys<sup>9</sup>.

However, few trials have used younger boys who are unable to be tested using traditional MRC or quantitative testing. Prior studies demonstrate effectively the “honeymoon” period in DMD when absolute function and strength may improve<sup>1, 10</sup>. However, the improvement does not equal that seen in normal children, as they remain weak compared to their peers. A pilot study of baseline motor function in 33 young boys with DMD (mean age 3.4 years) shows markedly different gross motor skills from age-matched controls using the Hammersmith Motor Ability Score<sup>11</sup>. The same study showed the locomotor quotient of the Griffiths’ scales demonstrated deterioration in young boys with DMD<sup>11</sup>. This latter measurement showed a highly significant negative correlation with age. The Bayley infant motor scale (used from birth through 42 months), has been validated in dozens of studies of children with motor delay in the first years of life<sup>12-20</sup>. Furthermore, it has an advantage in that clinical evaluators (CEs) can be trained in its use.

The MDA funded DMD center network recently completed baseline assessment of 24 infants using the Bayley-III, the HFMSE, and the North Star Ambulatory Score to assess infants from age 3 months through 2.9 years. One year follow up studies of 20 of these children are complete. Once ambulatory, boys were also able to complete the early motor skills of the North Star Ambulatory Assessment (NSAA) which has been validated in older boys with DMD.

Here we propose to use the Bayley-III and the North Star Ambulatory as outcome measures in a phase 2 historically controlled trial in infants who are age 3 months through 30 months at enrollment in a multicenter trial using the 5 DMD-MDA funded sites.

**Imaging of muscle in DMD.** Imaging of muscle as a marker of disease progression in

DMD has been considered for some time. Marden et al demonstrated that high resolution MRI could distinguish boys less than age 10 who were still ambulatory<sup>21</sup>. Recently, Dr. Craig Zaidman, a child neurologist at Washington University has studied ultrasound as a marker of disease in boys with DMD<sup>22</sup>. Calculated muscle backscatter (cMB), an ultrasonic measure muscle damage increases with age, even during the “honeymoon period” before age 8 years when absolute strength continues to increase. Additional data obtained from untreated infants with DMD demonstrates that the linear increase in backscatter extends into the first year of life. This suggests that ultrasound may be an excellent, non-invasive marker of this disease. This will form a secondary outcome for this study.

**Mental development of young DMD boys.** Cyrulnik et al demonstrated that cognitive delay is clearly recognized by parents<sup>23</sup>. Hinton et al have also characterized verbal and memory skills in older boys with DMD<sup>24</sup>. The earliest study of mental development in young boys with DMD (6 boys who were a subset of Brooke et al’s original study) was accomplished using the Denver developmental assessment<sup>1 25</sup>. However, because the Denver assessment does not provide a quotient it is not possible to quantify the delays. Detailed work in mental development of young boys with DMD has been reported by Smith et al using the Griffith’s Mental Development Scales (GMDS)<sup>26</sup>. However, this scale is not available in the United States and requires administration by a psychologist.

The most validated, commonly used scales of language and cognition in all infants and children through age six years are the Bayley scales of infant development (Bayley-III) (valid through 42 months)<sup>27</sup> and the Stanford Binet Intelligence Scale 5<sup>th</sup> ed. (ages 3 years and up)<sup>28</sup>. Both provide measurable quotients. The Bayley-III has been used studies of children at risk for both motor and mental delays including premature infants, children with hypoxic ischemic injuries, children with Downs syndrome and children with immune deficiency<sup>12-20</sup>. We also recently completed evaluation of 24 infants and young boys with DMD using the Bayley-III<sup>29</sup>.

**Treatment of children with DMD with twice weekly oral prednisolone (10mg/kg/week) is safe and effective in improving strength in both boys with DMD and the mdx mouse model.** There is preclinical data demonstrating that weekly oral prednisolone improves strength and prolongs life of the mdx mouse<sup>30, 31</sup>. A pilot study by Connolly et al demonstrated a favorable side effect profile with no increased risk of obesity and maintenance of linear growth with improved strength and function compared to historical control boys with DMD who were not treated<sup>5</sup>. The follow-up study, a randomized, blinded, controlled study of daily versus high dose weekly corticosteroids showed both were equally efficacious in improving strength and function in ambulatory boys with DMD<sup>32</sup>. Here we propose to use the weekly regimen in young infants who would not tolerate the cumulative effects of daily corticosteroids.

## Study objectives and Design

**Objective 1. Establish gross motor development as a valid outcome measure in young boys with DMD at the 5 MDA-DMD centers.** Preliminary data show that average gross motor function infants and young boys with DMD declined over six and 12 months compared to age matched peers when assessed using Bayley-III Scales of Infant Development (Bayley-III). Fine motor, cognitive, and language skills did not decline.

**Aim1a. Continue Validation of Bayley-III as an outcome measure in infants with DMD.** We will train/retrain Clinical Evaluators (CE's) from the 5 MDA-DMD centers in this assessment tool.

**Aim1b. Continue validation of the North Star Ambulatory Assessment (NSAA) in the youngest ambulatory boys with DMD.** We will train/retrain CE's from the 5 MDA-DMD centers in this assessment tool.

**Aim 1c. Establish age of independent walking as a valid outcome in infants with DMD.** The precise age of walking for young boys with DMD has not been established in a prospective fashion. For those children already walking we will ask for the age at independent walking defined as 10 independent steps. For those who are not yet walking, we will prospectively capture this information in this study.

**Objective 2. Determine if twice-weekly high dose oral prednisolone improves gross motor development in infants and young boys with DMD.** We will perform a phase 2 historically controlled trial of oral twice-weekly prednisolone (5mg/kg/dose on two consecutive days) in infants and young boys with DMD. Here we propose to study the effect of this therapy in a multicenter trial of boys with DMD who are less than 30 months old at the baseline visit. Each boy will be followed for one year.

**Aim2a. Determine if treatment improves gross motor function in infants with DMD over a 6-12-month period as measured by the Bayley-III.** The Bayley-III infant score is the primary motor clinical endpoint of this therapeutic trial. Secondary outcomes include fine motor function, speech and language, and social function.

**Aim 2b. Determine if treatment improves the Adaptive Behavior Subtest of the Bayley-III (ABS) as scored by the infants' primary caregiver.** In the study of untreated boys, the primary caregiver noted clear deficits, predominantly related to areas relevant to gross motor function. The ABS

**Aim 2c. Determine if treatment improves performance on the NSAA for those boys who are ambulatory.**

**Aim 2d.** Determine if treatment with weekly corticosteroids is tolerated and is safe in boys with DMD who are less than 30 months of age.

**Objective 3. Determine if ultrasound of biceps and quadriceps using calibrated backscatter improves in infants and young boys with DMD who are treated with oral high dose weekly corticosteroids.** Preliminary data of ultrasound imaging in infants and young boys with DMD demonstrate progressive structural damage as measured by calibrated backscatter. The ultrasound studies will be limited to the infants and boys who will enroll at the primary site (Washington University) where Dr. Craig Zaidman has the equipment and expertise to accomplish this aim.

**Objective 4. Determine if caregiver burden changes with treatment of infants and young boys with DMD.** Preliminary data from questionnaires suggests the caregiver

burden for the primary caregiver of untreated infant and young boys with DMD is minimal. Assessment of this with in this trial will allow us to discern if this changes with a therapeutic trial.

## **Subject selection criteria**

### **Inclusion Criteria**

Clinical Diagnosis of Duchenne Muscular Dystrophy. This must be confirmed in one of two ways

1. Appropriate degree of weakness for age, creatine kinase >20X the upper limit of normal, and genetic mutation known to be causative for DMD.
2. Appropriate degree of weakness for age, creatine kinase >20X the upper limit of normal and genetic or biopsy confirmation of Duchenne muscular dystrophy in a primary relative (e.g. brother or maternal uncle)
3. De-identified, genetic studies will be reviewed by collaborator Kevin Flanigan prior to enrollment of subjects.
4. Age at entry: one month through 30 months

### **Exclusion Criteria**

Glucocorticoid treatment

**Recruitment of infants and young boys:** We will enroll children from age 1 month through age 30 months. Follow-up examinations will be performed 6-month and 12 months after the baseline visit. The specific goal would be to determine whether the average change in Bayley-III scores differ from the scores of the boys who are untreated. A total of 25 children will be needed and we expect to follow them every 6 months for one year. Based on the recruitment in the study of untreated infants we expect to recruit these children over 15-24 months. We are allowing for a potential drop out of 5 infants.

### **Statistical considerations and Power Calculations for current study.**

Follow-up of twenty untreated infants and young boys with DMD showed that the average negative change in the Bayley III gross motor scaled score over six months was -0.4. If the effect size of therapy is an increase of 1.5 points on this scaled score, then 19 infants would be required for 95% confidence to detect a difference. If the effect size of corticosteroids is +2.0 points only 11 infants would be required. We have chosen to enroll 24 infants, with the expectation that 4 might be lost to follow up or drop out of the study. While we have calculated the effect size for six months, additional data in a small subset suggest there is further decline over 12 month (total average decline of 1.0 point in 12 boys. The six month and 12 month follow-up of the cohort will be analyzed and reported to the MDA.

## **Study Procedures and Visits**

The fundamental goal of this work is to determine if two reliable developmental assessments (Bayley-III and NSAA) in young boys with DMD will detect a change in gross motor function in infants and young boys treated with twice weekly oral prednisolone. We will follow children for one year and they will be ages 1 month through 30 months at enrollment.

**There will be a total of six visits, Baseline, and at 1, 3, 6, 9, and 12 months.**

**Baseline evaluation and visits at 6 and 12 months will include:**

**a) History to include age of walking defined as 10 independent steps**

**b) Every 6 months Vital signs** including height, weight, heart rate, blood pressure

Height will be assessed in two ways

1. Measurement of supine length if child is not able to stand

2. Standing height if child is able to stand

**c) Every 6 months the following will be performed**

### **1. Bayley-III Scales of Infant Development.**

This test consists of a standardized assessment of cognitive, language, and motor using small toys, blocks and books. For infants there is a special set of activities to assess the muscle function called Bayley-III infant motor scale which has both a fine motor and gross motor component. This assesses the degree of body control, large muscle coordination, finer skills of the hands and fingers, dynamic movements. This will be done through observations and questions. The Bayley-III infant mental scales will test language and cognition.

### **2. North Star Ambulatory assessment North Star Ambulatory Assessment**

**(NSAA).** The NSAA<sup>33, 34</sup> assesses functional activities including standing, getting up from the floor, negotiating steps, hopping, and running. The assessment is based on a 3 point rating scale of 2= ability to perform the test normally, 1= Modified method or assistance to perform test, 0=unable to perform the test. Thus, total score can range from 0 (completely non-ambulant) to 34 (no impairment on these assessments).

### **3. Ultrasound of the muscle (this measure will be followed only on infants recruited from the Washington University Site)**

This will be done by keeping the ultrasound probe on biceps and quadriceps to see the image of the muscle for structural changes. As the muscle changes the ultrasound will reflect the changes.

**4. Behavior:** The Adaptive Behavior Assessment Scale (ABAS) is a well-validated measure of adaptive behavior and will be tested every 6 months.

**5. Caregiver Burden:** This will be tested by filling out the Caregiver stress questionnaire.

## 6. Complete Physical Examination and Neurological examination

The Visits at 1, 3, and 9 months will be safety visits which can be performed locally or on site. If laboratory studies are performed locally, phone visit will occur.

**Table 1. Schedule of Events**

Study Period (+/-7 days)	Month 0	Month 1*	Month 3*	Month 6	Month 9*	Month 12
Informed consent	X					
Vital signs, Height, Weight, Occipital Frontal Circumference BMI (kg/m <sup>2</sup> )	X			X		X
Medical History	X	X	X	X	X	X
Medication review	X	X	X	X	X	X
Con Medication review	X	X	X	X	X	X
Medical Events		X	X	X	X	X
Adverse Events		X	X	X	X	X
Physical examination	X			X		X
Neurological Examination	X			X		X
Ultrasound for WU infants only	X			X		X
North Star Ambulatory Assessment	X			X		X
Bayley-III Scales of Infant development	X			X		X
Adaptive Behavior Assessment Scale	X			X		X
Care giver Burden assessment	X					X
CBC/Diff	X	X	X	X	X	X
CPK	X	X	X	X	X	X
Sodium	X	X	X	X	X	X
Potassium	X	X	X	X	X	X
Chloride	X	X	X	X	X	X
CO <sub>2</sub>	X	X	X	X	X	X
BUN	X	X	X	X	X	X
Fasting Serum Glucose	X	X	X	X	X	X

\*\*Phone call or on site assessments will take place at visits 1, 3, and 9 months.

## **Criteria for dose reduction:**

Prednisolone dose will be reduced for

- 1) An increase in Body mass index (BMI) (kg/m<sup>2</sup>) greater than 10% over 6 months
- 2) A fasting blood sugar greater than 100mg/dl after dietary modification
- 3) An increase in diastolic blood pressure greater than 10mm Hg over upper limit of normal for age
- 4) An increase in systolic blood pressure greater than 15mm Hg since the last visit
- 5) Otherwise, non-manageable side effects including irritability or difficulty sleeping.

## **Data Management Repository**

The informatics component of the proposed specific aims will provide a centralized data management repository. The system will provide a secure web-based application designed to harmonize data from the all-participating institutions. The functionality of the system will include data entry, data integration, data validation and quality control, searching, reporting, and exporting. The system will have three core components to include administration, institution, and investigator data requests. The administration component will allow a defined member of the MDA DMD CRC Network access to data generated from their sites and data from the network at large, upon validation that data request forms are from participating institutions. The approval process will be defined in the Manual of Operations. Once approved, the data set is generated and released to that approved investigator. **The data that will be submitted to the central data management repository will include the following information.**

### **1) Demographics**

- ID#
- Date of Birth
- Date of study visit
- DMD Gene Mutation
- Age (derived from DOB, Date of study)
- Height/Length in centimeters
- Weight in kilograms
- Body Mass Index
- Occipital Frontal Circumference in centimeters

### **2) Assessments**

- a) Bayley-III scales of Infant Development
- b) North Star Ambulatory Assessment
- c) Adaptive Behavior Assessment Scale (ABAS)
- d) Caregiver Burden

### **3) History including Dietary history recorded**

### **4) Medical events recorded**

### **5) Adverse events recorded**

### **6) Concomitant medications recorded**

**Time expected to complete these visits** will vary somewhat depending on the subjects' own strength and function. The predicted time to complete all procedures and questionnaires is 2-3 hours.

## **Data Management**

A centralized data management repository will be used for this study. The system will provide a secure web-based application designed to harmonize data from all participating institutions. The functionality of the system will include data entry, data integration, data validation and quality control, searching, reporting, and exporting. The system will have three core components to include components to include administration, institution, and investigator data requests. The administration component will allow a defined member of the MDA DMD CRC Network access to data generated from their sites and data from the network at large, upon validation that data request forms are from participating institutions. The approval process will be defined in the Manual of Operations. Once approved, the data set is generated and released to that approved investigator.

## **Procedures for maintaining confidentiality**

Institutions participating in the DMD Clinical Outcomes Project including Washington University in Saint Louis, Nationwide Children's Hospital in Columbus Ohio, University Texas Southwestern, Nemours Children's Hospital, Orlando Florida, and University of California Davis will collect the necessary data as defined in the Manual of Operations. Patients and the supporting data will be de-identified at each given site using a defined identifier schema satisfying HIPAA requirements prior to submitting study data to the informatics Core. As each case is being completed the participating institution will securely submit to the data center the case report forms utilizing a secure file transfer protocol (SFTP) incorporating technology providing encrypted channels, preventing passwords and sensitive information from being transmitted via the Internet.

## **Adverse events reporting:**

Adverse events in this trial to validate outcomes will be reviewed within 24 hours by the PI at each site who will be responsible for reporting such events and communicating those events to the primary PI, **Dr. Anne Connolly (314-362-6981 Work) or 314-581-9948 (Cell phone).**

## **Assessment of Risks**

### **Risks of oral weekly Prednisolone**

Likely: Mild irritability or sleep disturbance on the days prednisolone is taken. Some children may experience increased hunger on the days prednisolone is taken

Less Likely: Corticosteroid use may decrease the immune response. With intermittent use proposed in this study, this risk is less common. Some children may develop stomach pain or discomfort. Some children may develop excessive weight gain

Rare: Rarely, children may develop intestinal bleeding. Rarely, children may develop adrenal suppression. While this is common in children taking daily corticosteroids it is rare with the weekend dosing regimen. This will be tested for with safety laboratory tests at baseline, 1, 3, 6, 9, and 12 months.

### **Risks of Muscle Testing.**

Likely: Muscle fatigue.

Less likely: None Known.

Rare: None Known.

### **Risks of Language and Cognitive Assessments:**

Likely: Some children may feel uncomfortable with the evaluator.

Less Likely: None Known.

Rare: None Known.

### **Risk of Ultrasound of muscle:**

Likely: Irritation or rash at the probe site.

Less Likely: None Known.

Rare: None Known.

### **Risk of Blood Draws:**

Likely: Bruising at site

Less likely: Fainting

Rare: Local infection

Patients may experience all or some of the risks listed above. There may also be unknown risks. The PI will be responsible for any questions subjects have about these risks.

## **Assessment of Benefits**

There is abundant evidence in older children that oral corticosteroids improve strength and function. There is also emerging evidence that those treated early with corticosteroids may have benefits many years later with prolonged walking. The direct benefit may be improvement in motor development. There may also be an improvement in behavior as this was also seen in the randomized trial of daily versus weekly corticosteroids. It is hoped that the knowledge gained from this study will help us know if this group of infants can be reliable subjects in other clinical trials.

## **Decision to discontinue treatment**

If the family decides to discontinue corticosteroid therapy they will be given the option to continue to be followed using the same clinical outcomes described above.

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