STUDY PROTOCOL

A Randomized, Placebo Controlled, Clinical Efficacy Trial of Mexiletine for Myotonic Dystrophy Type-1 (DM1).

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RESEARCH PLAN

A. SPECIFIC AIMS:

To evaluate the efficacy, tolerability, and safety of mexiletine in DM1 we will perform a six month, randomized, double-blind, trial of mexiletine (150 mg three times daily, n=20) vs. placebo (n=20) in ambulatory DM1 patients and pursue the Aims listed below.

Primary Aim:

- To determine if mexiletine (150 mg three times daily) improves six minute walk distances after 3 and 6 months of treatment.

Secondary Aims:

- To monitor the safety and tolerability of 6 months of mexiletine therapy.
- To determine if mexiletine decreases myotonia (measured by relaxation time following maximum voluntary isometric contraction of the finger flexor muscles, eg. maximum hand grip)
- To assess if 6 months of mexiletine improves grip strength, timed function tests (6 minute walk, time to arise from a chair and walk 30 feet, vital capacity), muscle mass (Dual Energy X-ray Absorptiometry (DEXA) scans), swallowing time (100 ml of water), hand dexterity (Purdue Peg Board Test) and patient reported pain and gastrointestinal function.
- To determine if mexiletine decreases the degree of cardiac conduction irregularities as measured by serial 24-hour Holter monitoring.
- To assess if 6 months of mexiletine improves the health-related quality-of-life of patients as measured by a novel disease-specific DM1 quality-of-life instrument and generic quality-of-life instruments.

APPROPRIATENESS FOR ORPHAN PRODUCT DEVELOPMENT GRANT PROGRAM:

This study is being considered for funding by the FDA Orphan Product Development Grant Program. It is appropriate for this program for the following reasons:

1) Myotonic dystrophy type-1 is an orphan disease. The prevalence of DM1 is approximately one out of every 10,000 people worldwide.[1] Based on this estimate, there are fewer than 100,000 cases of DM1 in the United States. Additional reports confirm the rarity of this disease noting prevalence of DM1 ranging from 2.4/100,000 in Northern Ireland, 5.5/100,000 in West Germany, and 4.9/100,000 in Switzerland. [2-4]

2) Mexiletine is available on the market for the treatment of cardiac arrhythmias, but it is not currently approved for the treatment of myotonia or myotonic dystrophy.

3) This study will provide data on the long term (6 months) safety and efficacy of mexiletine in: a) improving the distance participants are able to walk in six minutes; b) reducing myotonia; c) improving muscle strength; d) increasing lean muscle mass; e) decreasing musculoskeletal pain; f) improving gastrointestinal function and swallowing); g) improving functional abilities; h) decreasing cardiac arrhythmias; and, i) improving disease-specific health related quality-of-life as measured by a novel multi-domain instrument.

If the safety and long term effectiveness of mexiletine is demonstrated, we anticipate that these results may lead to the approval of mexiletine as an orphan therapy for DM1.

EVIDENCE FOR SUFFICIENT AVAILABILITY OF STUDY DRUG:

Mexiletine is available by prescription for its approved indication as a ventricular antiarrhythmic. For the active treatment group in this trial we will purchase commercially available mexiletine from Cardinal Drugs. The exact generic brand we purchase depends upon the availability and price at the time of purchase. Once purchased all future doses of mexiletine will be prepared using the same manufacturer's product. Since mexiletine is a commercially available product we are confident that an adequate supply of mexiletine will be available from Cardinal Drug to complete the study.

EVIDENCE FOR SUFFICIENT NUMBER OF ELIGIBLE PATIENTS:

Recruitment for this trial of mexiletine will utilize multiple sources. These include: a) The University of Rochester Muscular Dystrophy Association (MDA) Clinic; b) The University of Rochester Medical Center (URMC) Neuromuscular Disease Center; c) direct referral from our local and national neuromuscular colleagues; d) the URMC NIH funded Wellstone Muscular Dystrophy Cooperative Research Center (MDCRC) project entitled, "Pathogenesis and Progression of Myotonic Dystrophy"; e) by direct advertisement on the MDA and NIH clinical trial websites; and, f) by using the NIH sponsored National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members.

We currently provide care to many hundreds of DM1 patients through our MDA Clinic and the URMC Neuromuscular Disease Center. We have established a steady referral base from western New York State, the Albany area, the southern tier region (northern Pennsylvania and southern New York State), as well as from physicians from other states who are familiar with our research and experience in the clinical management of DM1 patients. In addition to this ready source of patients we have an active waiting list of DM1 patients who wish to participate in our recently funded Wellstone Center project mentioned above, entitled, "Pathogenesis and Progression of Myotonic Dystrophy". This is a multiyear study designed to record the progression of disease in 80 ambulatory DM1 patients all of whom satisfy the inclusion and exclusion criteria for the study described in this application. In an effort to increase the diversity of the patients

recruited for the current proposed trial of mexiletine, we will directly advertise and recruit through several widely accessed national sites, most notably those provided through the NIH and MDA. Lastly, we will recruit patients through the National Registry of Myotonic Dystrophy and Facioscapulohumeral Muscular Dystrophy Patients and Family Members. This registry currently has over 580 active DM1 patients and is headquartered at the University of Rochester.

B. BACKGROUND AND SIGNIFICANCE:

Myotonic Dystrophy type-1 (DM1) is the most common adult muscular dystrophy[1] and is caused by an unstable, trinucleotide repeat expansion on chromosome19q13.3.[1] DM1 is a multisystem, autosomal dominant disorder and affects skeletal, cardiac and smooth muscle, the eyes, heart, brain, skin, reproductive organs, and gastrointestinal function of patients.[5-8] Unfortunately, the pathomechanism of, and effective treatment for, muscle weakness and wasting remain unknown. One of the other cardinal features of muscle dysfunction in DM1 is myotonia, a delay in relaxation following muscle contraction. This myotonia occurs in both skeletal and smooth muscle. Recent studies indicate that the myotonia in DM1 results primarily from a decreased production of functional chloride channel protein. [9-12] This marked deficiency in channel protein is due to abnormal splicing of chloride channel pre-mRNA, caused by sequestration of the nuclear regulatory protein, muscleblind, by the abnormally expanded mutant DM1mRNA that accumulates in the myonuclei. [13-17] Myotonia may contribute to muscle pain, difficulty with ambulation, trouble swallowing, gastrointestinal complaints, and possibly to the skeletal muscle weakness and wasting that afflicts DM1 patients. To date there is no cure or approved therapeutic agent for DM1. Care focuses on symptomatic management, use of assistive devices for ambulation and breathing, and monitoring of cardiac conduction with the use of pacemaker treatment as needed. [1]

Mexiletine hydrochloride is a promising therapy for myotonic dystrophy. Mexiletine has been used for over 35 years by cardiologists as a treatment for cardiac arrhythmias. [18] In addition to being an effective antiarrhythmic, mexiletine has reduced myotonia in patients with non-dystrophic myotonia and with DM1 (n=9). [19] Previous case reports and our more recent FDA funded 7 week, double-blind, randomized, placebo controlled, crossover trial at the University of Rochester have strongly supported the use of mexiletine as an effective antimyotonia drug in DM1. [20-22] During the University of Rochester study, two standard antimyotonic dosages were tested, 150 mg TID and 200 mg TID. This study demonstrated that these dosages were able to significantly reduce the amount of clinical myotonia while being safe both safe and well tolerated. [22] In addition, the 150 mg TID dose produced a statistically significant improvement in hand strength. [22] A copy of our recent manuscript reporting results of this FDA funded 7 week trial is provided in Appendix A. Despite the promising results of this study, a long-term, placebo controled, randomized clinical trial to definitely establish the antimyotonic efficacy and safety of mexiletine has not yet been performed.

The treatment trial described in this orphan product development grant and research protocol has the potential to: a) establish mexiletine as a safe, effective antimyotonia

therapy capable of improving ambulation in DM1; b) identify other therapeutic benefits of long-term mexiletine treatment in DM1; and, c) improve the overall quality of life and clinical care for these patients. The schematic shown in Appendix B and at the start of the Methods summarizes the major elements of the trial. These elements include recruitment, randomization, specific outcome measures and potential benefits that may occur to improve the care of patients with DM1.

Potentially Treatable Symptoms of DM1:

Patients with DM1 often develop progressive distal muscle weakness in the legs, forearms, and hands which invariably leads to functional disability. [23,24] Along with the weakness of leg muscles, myotonic muscle stiffness (myotonia), especially in the ankle stabilizing muscles, contributes to gait instability and falls. In a 2009 qualitative study of relevant issues in DM1, "difficulty with ambulation" was the most frequently mentioned life-altering symptom by DM1 patients.[24a] It is possible that a reduction in myotonia will have a profound effect on patient ambulation. Lower extremity myotonia often impairs muscle contraction speed and stability and is a potentially treatable aspect of gait impairment. Although prior therapies have failed to improve muscle weakness and wasting in DM1, there have been several small investigations that have suggested a beneficial effect from various treatments that ameliorate myotonia. [19,22,25-33] Of these, a short course (7 weeks) of mexiletine has been shown to have a statistically significant benefit on reducing DM1 myotonia.[22]

Antimyotonia therapy with mexiletine may also exert a beneficial effect on cardiorespiratory and gastrointestinal function. Isolated reports have suggested that untreated myotonia in DM1 may contribute to tachypnea, dyspnea, fecal incontinence, and chronic pain. [29-31,34] It is possible that a therapy that minimizes myotonia over a period of months or longer may also reduce the severity of these symptoms. [29,31]

Tongue and pharyngeal muscle myotonia hamper swallowing and may lead to aspiration of saliva, atelectasis of the lung, and pneumonia. Such myotonia along with pharyngeal weakness may aggravate or precipitate obstructive sleep apnea. It has been hypothesized that mexiletine may effectively reduce myotonia in tongue and pharyngeal muscles. If true, mexiletine may also reduce the pulmonary complications that occur in DM1 patients. To evaluate these potential effects of myotonia in DM1 we have included serial assessments of swallowing and pulmonary function as secondary endpoint measures in this clinical trial.

Musculoskeletal pain is another common complaint in patients with DM1. It occurs in up to 64% of all patients. [35] Generalized muscle pain is thought to be a directly related to the myotonic stiffness in limb and axial muscles of patients with DM1. In 2008, Jensen and colleagues systematically studied the nature and scope of chronic pain in patients with DM1 and facioscapulohumeral dystrophy. [35] As part of this study they identified six patients who took mexiletine for chronic pain. On average, these six patients experienced a relief of 3.91 (0 = no relief and 10 = complete relief). These data are consistent with the hypothesis that antimyotonia therapy with mexiletine ameliorates

musculoskeletal pain. The report by Jensen and colleagues also agrees with our anecdotal observations in the DM1 patients that we follow in our Neuromuscular Disease Center Clinic who receive antimyotonia therapy with mexiletine and report better control of their musculoskeletal pain. To evaluate the benefit of mexiletine in the control of musculoskeletal pain we have included serial measurements of patient reported pain (modified Chronic Pain Scale, Brief Pain Inventory, and pain subdomain of our DM1-specific health-related quality-of-life instrument) in this trial.

Cardiac arrhythmias are a frequent occurrence in myotonic dystrophy. It has been estimated that up to 1/3 of DM1 patients may eventually die from the effects of a cardiac arrhythmia.[35a] The exact mechanisms by which myotonic dystrophy exerts an effect on cardiac muscle and interferes with cardiac conduction remains unknown; however, it is possible that mexiletine (a class IB antiarrhythmic medication) may exert some positive cardiac effects on this population. Modern ECG Holter monitoring is a comprehensive tool for investigating factors that might contribute to the mechanism of sudden cardiac death (SCD) in myotonic dystrophy. SCD may occur as a result of a complex interplay of numerous factors among which myocardial ischemia is the most common underlying condition.[35b, 35c] Events leading to a fatal event can be precipitated or influenced by abnormalities or transient changes in the autonomic control of the cardiovascular system as well as transient or progressive disruption of cardiovascular homeostasis. Holter recording will allow us to evaluate heart rate variability [HRV] parameters reflecting the status of the autonomic nervous system controlling the heart and will help to illustrate the relationship between parasympathetic and sympathetic components of this system. Heart rate turbulence complements HRV analysis by providing insight into the baroreflex sensitivity component of central regulation of the cardiovascular system.

The association between decreased variability of RR intervals recorded in 24-hour Holter monitoring and increased mortality was demonstrated in numerous studies.[35d,35e,35f,35g,35h] They indicate that depressed HRV is associated with all-cause and cardiac mortality. A study of 127 patients from the CHF-STAT trial showed that the standard deviation of NN-intervals (SDNN) <65 ms was significantly associated with all-cause mortality and showed a borderline significance for predicting SCD.[35e] Also, in the UK-Heart study a significant association was made between low SDNN and all-cause mortality and mortality from progressive heart failure.[35f]

For our mexiletine study we have added the use of serial 24-hour Holter assessments to better assess the effects mexiletine has on myotonic dystrophy cardiac conduction patterns. All patients will receive three studies; one at baseline, one at three months, and one at the completion of the study. We have consulted our colleagues in cardiology in making this addition to the protocol. They have indicated that based upon their experience there is no reason to include invasive monitoring techniques, such as, cardiac pacing in the ongoing assessment and monitoring of the study participants. They feel that such invasive testing has its own risks, is uncomfortable for patients, and is not indicated given our past findings of the safety of mexiletine in our 7, week double-blind crossover studies of 150 mg and 200 mg dosages given three times daily.[22] Our colleagues have wondered if there may have been therapeutic anti-arrhythmic benefit

from treatment with Mexiletine. For that reason we have included that question in our secondary aims for this proposal.

Clinical Experience of Using Mexiletine for Myotonia:

Despite the need for additional controlled studies, clinicians have been extensively utilizing mexiletine as a therapeutic agent in certain neuromuscular disorders. In the routine care of patients with different forms of non-dystrophic as well as those with dystrophic myotonic disorders followed in our Neuromuscular Disease Center Clinic we have frequently chosen mexiletine as the treatment of choice to control myotonia. We use mexiletine to treat patients with rare sodium channel diseases, such as, paramyotonia congenita and myotonia fluctuans, and in chloride channel diseases, such as, autosomal dominant Thomsens disease and autosomal recessive generalized myotonia. The total number of patients with these disorders under our care receiving mexiletine exceeds thirty, and all have tolerated this medication with only mild or no side effects. Most have experienced significant lessening of myotonic stiffness and have been able to resume sports activities, work in a cold environment, and handle stressful situations without an exacerbation of their myotonia. We have used mexiletine to treat these patients with non-dystrophic myotonic disorders for over fifteen years, and we have noticed no loss of efficacy and no unexpected complications of therapy.

More recently, over the past seven years, we have initiated mexiletine treatment in selected patients with DM1 to control some of their skeletal and smooth muscle complications which have been exacerbated by their myotonia. The inability to open their hands, locking of the jaw, gastrointestinal hypomotility (sometimes requiring hospitalization), and severe muscle pain – especially in the upper back, posterior shoulder, and neck regions – are complaints in our DM1 patients that we and our patients attribute to myotonia. We have found that mexiletine is extremely helpful in the treatment of these complaints, and our DM1 patients with these problems have responded with benefit to our prescribed treatment with mexiletine. Eight patients have received mexiletine for periods varying from ten weeks to three years to treat these complaints. One of the most severely affected patients is a woman with congenital DM1 who had a history of episodic locking of her jaw for periods of 24-48 hours and who on other occasions had intermittent bouts of pseudo-obstruction of the intestine requiring several hospitalizations. Since the initiation of mexiletine this patient has had a marked reduction in her problems with poor gastrointestinal motility, reduced her abdominal complaints, had no episodes of jaw locking, and has improved her hand dexterity.

Four other DM1 clinic patients have received mexiletine to assist in the treatment of disabling pain. These patients have all had amelioration of their discomfort and have also had an associated, remarkable decrease in their grip and percussion myotonia.

Despite this encouraging anecdotal evidence, a systematic placebo controlled trial is essential to further determine the true benefit of mexiletine for DM1 patients.

The University of Rochester's Experience in Therapeutic Trials in DM1:

In the recent past we have used the methods described in this proposal to evaluate ambulation, myotonia, and muscle function in patients with DM1. We have found that patients are comfortable with these procedures and that the measurements are reliable in assessing the efficacy of treatment with testosterone, recombinant human growth hormone, insulin-like growth factor 1, as well as mexiletine. [25,32,36] In other studies we have found that the measurements of grip myotonia using our methodology helps to quantitate and to describe a particular type of variable myotonia in a specific type of sodium channel myotonia, myotonia fluctuans. [37,38] Our methods for measuring whole body muscle strength and function have proven useful in several types of adult muscular dystrophy. Recent studies in our Center have shown that maximum voluntary isometric contraction force is reliable, and is useful in evaluating the response of patients with facioscapulohumeral muscular dystrophy to treatment. [39-41] Furthermore, our primary outcome measure, the six minute walk, has been shown to be reliable, feasible, and relevant to the DM1 population.[41a, 36]

Through our previous studies (including the FDA funded trial of mexiletine, past NIH funded investigations of metabolic alterations in DM1, previous MDA funded pilot study of DHEA in DM1 and recently completed NIH – MDA funded trial of IPLEX insulin-like growth factor-1 (IGF-1) complexed with IGF-1 binding protein 3 for DM1) we have demonstrated that we have the necessary equipment, the expertise, and practical day to day experience with the methods proposed to accomplish our study aims.

C. PRELIMINARY STUDIES:

Previous Mexiletine Trials and Reports:

In 2007 our University of Rochester Neuromuscular Disease Center group gave oral presentations of results from the FDA funded, short-term, seven week, double-blind, randomized, crossover trial of DM1 patients and in 2010 published the full report. [22] [Appendix A] In this study, two sequential, randomized, double-blind, placebo-controlled, crossover investigations of mexiletine (mexiletine 150mg three times daily vs. placebo; mexiletine 200mg three times daily vs. placebo TID) were carried out. Each study involved 20 moderately affected patients with DM1. The inclusion and exclusion criteria for that study are identical to those in the study proposed in this FDA grant and research protocol. Patients were randomized to receive seven weeks of treatment followed by seven weeks of placebo; or, seven weeks of placebo followed by seven weeks of treatment. A four to six week washout period separated the active treatment and placebo arms of the trials. Both dosages of mexiletine (150 mg and 200 mg) were well tolerated, safe, and effective in reducing isometric grip relaxation time ($p<.05$) following seven weeks of treatment. Side effects were minimal for both doses, and there was no worsening of first-degree heart block or bundle branch block in any patient with these conduction disturbances. Although both dosages significantly improved myotonia, there was not an additional benefit to the higher 200 mg three times daily dose over the 150 mg three times daily dose, suggesting a plateau effect. Furthermore, the lower dose produced a statistically significant increase in peak grip

force not demonstrated at the higher dosage. [Appendix A]. The data obtained from this study was utilized to select the 150 mg TID dose for our study. Although limited in duration, our prior seven week trials of mexiletine have demonstrated the short term safety, tolerability, and potential benefit of antimyotonia therapy with mexiletine in DM1. Prior to this University of Rochester crossover trial of mexiletine, there had been several small case reports suggesting a beneficial effect of mexiletine and other antimyotonia medications for different myotonic conditions. Although these studies also reported encouraging results, all had significant limitations regarding their time frame, clinical design, and selected study populations.

To our knowledge the first report of mexiletine use for muscle myotonia was in 1983. At that time, a French group gave mexiletine (400 mg/day) to a patient with myotonia congenita (a non-dystrophic myotonic disorder) with reports of marked improvement measured by ergometric bicycle testing.[20] The patient had previously failed a trial of other antimyotonia drugs including carbamazepine and diphenylhydantoin. Other reports have described dramatic clinical and electromyographic improvement in mexiletine treated infants with myotonia congenita and electrical myotonia.[21] Mexiletine has also been previously tested in other rare myotonic disorders, such as, the hereditary sodium and chloride channel non-dystrophic myotonic disorders. [42,43] Kwiecinski and colleagues reported a beneficial effect of mexiletine in reducing myotonia in nine DM1 patients, nine patients with autosomal dominant Thomsens disease, and 12 patients with recessive generalized myotonia. [19] During this treatment trial the efficacy of phenytoin, disopyramide, mexiletine, and tocainide was compared to placebo. These researchers concluded that mexiletine and tocainide displayed the most potent antimyotonia activity and that mexiletine was safe at both 400mg and 600mg per day dosages. [19] These same investigators indicated that despite similar beneficial effects of tocainide on myotonia in DM1 patients. the tendency of tocainide to cause bone marrow suppression has precluded its acceptability for the long term treatment of myotonia and made mexiletine the therapeutic agent of choice. [19,44,45]

A recent Cochrane review concluded that none of the 'currently published' treatment trials for myotonia reported as of 2006, were of high enough quality to conclude that any available drug for the treatment of myotonia is effective and safe. [46] For example, although the 1992 report by Kwiecinski and colleagues[19] provides an important step forward in recognizing the antimyotonic properties of mexiletine, it had some significant deficiencies: short duration (4 weeks), a heterogeneous patient group with 3 different forms of chloride channel myotonia, a single blind study design, an inscrutable randomization process in which different numbers of patients were assigned to different study drugs, and incompletely validated methods to measure myotonia. Ultimately, these types of study limitations, not their observed results, have limited the widespread acceptance of mexiletine as a treatment for patients with DM1.

In addition to reducing myotonia in muscles that control grip and stability of the ankles , mexiletine may have important beneficial effects on whole body musculature (both skeletal and smooth muscle) in DM1 patients. Mexiletine has been reported to have reversed fecal incontinence in one patient and tocainide (a lidocaine-like drug similar to

mexiletine) has been shown to eliminate both dyspnea and tachypnea in a DM1 patient with a history of severe dyspnea requiring hospitalization. [29,31] Although anecdotal, such benefits may be secondary to the antimyotonic effect that lidocaine-like drugs have on skeletal and smooth muscle. A long-term trial of mexiletine, such as the one described in this protocol, is needed to establish not only safety and efficacy in reducing myotonia in specific limb muscles but also to determine if mexiletine can ameliorate whole body symptoms. As part of our clinical trial, we will measure not only clinical myotonia, but also potentially related, additional outcome measures, such as, strength, gastrointestinal function, pulmonary function, swallowing function, muscle mass, timed testing of ambulation, hand dexterity, and quality-of-life.

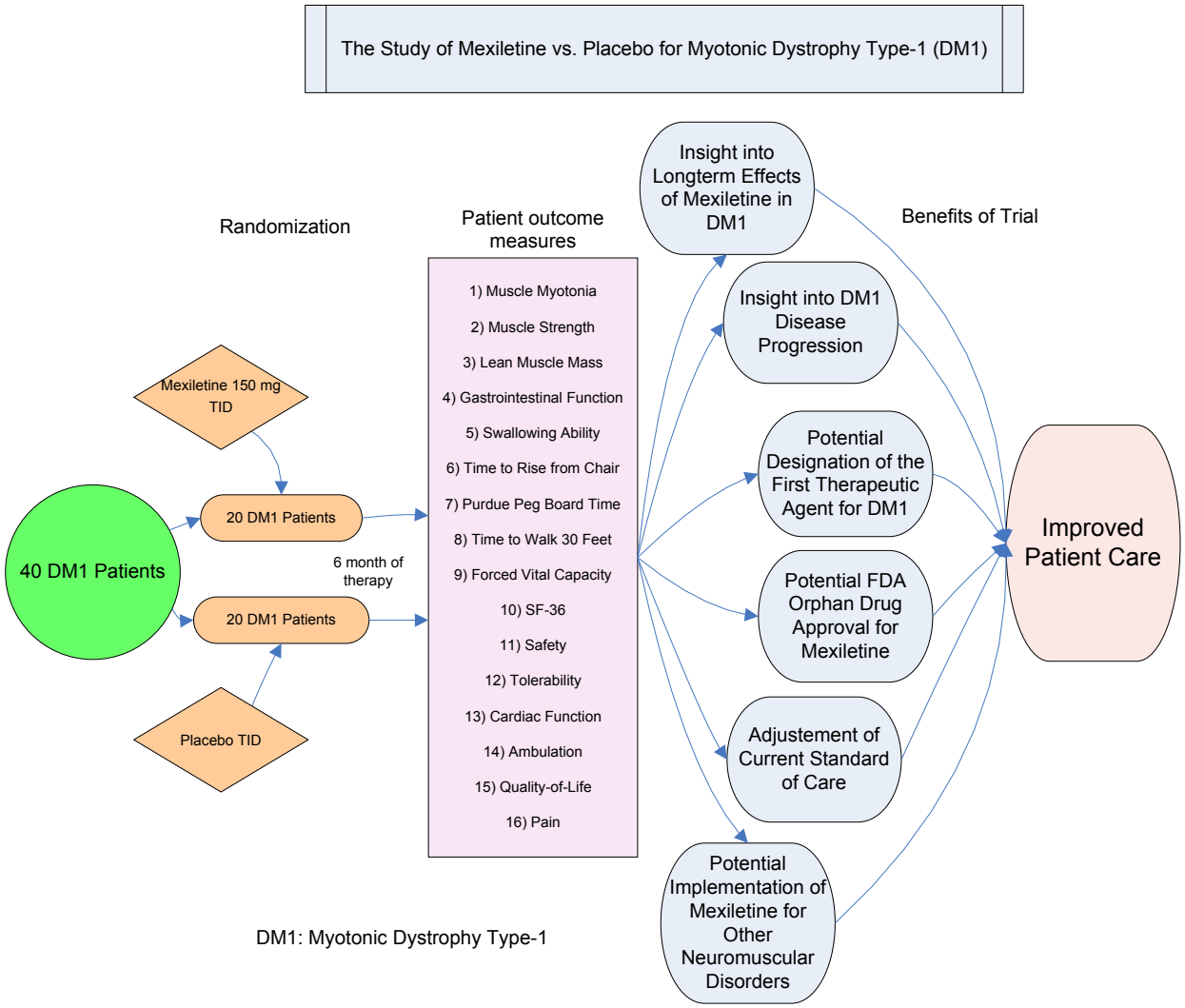
Our research design in this FDA grant and research protocol has built upon the encouraging results of previous treatment trials. As a part of our research plan we will: a) extend the duration of treatment with mexiletine; b) use the most effective, tolerated dose of mexiletine (150 mg three times daily); c) perform a traditional placebo controlled trial of treatment; and d) evaluate multiple outcome measures, focusing on those with highest relevance to patients with DM1.

The opportunity is now at hand to perform a carefully controlled, double blind, long-term, randomized treatment trial of mexiletine vs. placebo in DM1. There is currently clinical equipoise in the medical community regarding which therapeutic agents (if any) should be used in the DM1 population. This study will determine the efficacy, tolerability, and safety of 6 months of treatment with mexiletine (vs. placebo) in DM1. It is our belief that this study will finally break the medical community's equipoise and potentially establish mexiletine as an orphan drug for DM1.

D. RESEARCH DESIGN AND METHODS:

TRIAL DESIGN:

SCHEMATIC SUMMARY OF MEXILETINE TREATMENT IN DM1



This FDA Orphan Product Development Project proposes a double-blind, randomized, placebo-controlled, six month clinical trial of the efficacy and safety of mexiletine (150 mg three times daily) for the treatment of moderately affected ambulatory patients with DM1. Twenty patients will be randomized to receive treatment while another 20 patients will receive placebo. Patients will be randomized in a 1:1 ratio to receive either mexiletine (150 mg three times daily) or placebo. The primary outcome measure will be the assessment of ambulation by six minute walk time. Secondary outcome measures will include: a) grip myotonia as determined by relaxation time following maximum voluntary isometric contraction of the finger flexor muscles; b) muscle strength; c) change in lean muscle mass; d) pain measurement using the Brief Pain Inventory and a

modified Chronic Pain Scale; e) Gastrointestinal function measured by two gastrointestinal questionnaires; f) The ability to swallow as measured by a timed swallowing test with water; g) physical function as measured by the time to rise form a chair, Purdue Peg Board Score, time to walk 30 feet, six minute walk, and SF-36; and, h) pulmonary function (measured by serial determinations of forced vital capacity); i) change in Holter monitor data from baseline; and j) patient relevance as measured by a novel disease-specific health-related quality-of-life instrument designed specifically as an clinical outcome measure for the DM1 population.

During the trial of treatment with mexiletine, all patients will receive careful safety monitoring, including serial EKGs, laboratory testing, three in-person evaluations on the University of Rochester NIH funded Clinical Translational Sciences Institute sponsored Clinical Research Center, and phone calls to assess for any side effects or problems with the study medications, to encourage adherence to the treatment regimen, and to grade musculoskeletal pain. Below is a more detailed description of the study design and the outcome measures.

Rationale for Design:

A randomized, double-blind, placebo-controlled approach was selected based on its efficacy, simplicity, widespread acceptance, and power to compare the efficacy of mexiletine vs. placebo in our study population.

Study Population:

Our decision to select patients with DM1 for our investigation has occurred for several reasons. DM1 is an orphan disease and is appropriate for the Orphan Product Development Grant Program. Published estimates of the prevalence of DM1 in European-American populations range, for example, from 2.4 per 100,000 in Northern Ireland to 5.5 per 100,000 in West Germany. [2,4] A study from Switzerland, that carefully attempted to obtain complete ascertainment of all cases, has reported a prevalence of 4.9 per 100,000. [3] A general estimate of the prevalence of DM1 in populations Americans is approximately 10 per 100,000 and indicates a total prevalence of less than 100,000 patients with DM in the United States. [1]

In addition, DM1 has clinical and laboratory features that permit careful assessment of symptoms. Patients often have easily identified clinical signs of myotonia, and, as mentioned previously, myotonia may play an important contributory role in their symptoms. For example, myotonia may have an additive effect with weakness to decrease dexterity in performing certain movements with the hands (e.g., compromising employment opportunities). Myotonia may contribute to muscle spasm and pain in the posterior neck and low back (e.g., further compromising employment opportunities). [34] It may hamper swallowing and breathing (e.g., increasing the risk of life threatening illness), and it may worsen already compromised gastrointestinal motility. [23,24,29,30] Myotonia may also exaggerate difficulties with agility, balance, and ambulation caused by progressive weakness (increase the risk of falls and associated injuries).

Demonstration that an effective antimyotonia treatment improves one or more of these clinical problems will provide an opportunity to improve the quality of care of these patients and extend their productive life span.

One of the benefits of studying DM1 patients is that the diagnosis can be definitively established. DM1 is an autosomal dominantly inherited disease and it results from an unstable trinucleotide repeat, $[CTG]_n$, expansion in the DM gene on chromosome 19.[5-7] The gene defect is well characterized and a specific diagnostic test using leukocyte DNA analysis is available to identify the abnormal enlargement of the $[CTG]_n$ repeat and to identify affected individuals.[47] The availability of a standard diagnostic test for DM1 assures us that all the patients in our study population have a family history DM1.

There will be 40 subjects with myotonic dystrophy between 18-80 years of age enrolled for this clinical trial. Up to 60 patients will be screened for this trial until accrual of 40 patients is met. Every effort will be made to insure that the study population reflects the makeup of the general population, including women and minorities, from which it is drawn.

For over 30 years in our Neuromuscular Disease Center we have provided care to a large population of DM1 patients, and over the past 25 years we have carried out clinical investigations to clarify the pathomechanism of the muscle wasting that occurs in these patients. We have also performed multiple therapeutic trials in subgroups of these DM1 patients.[25-32] At present we have a funded NIH study to investigate the disease progression of DM1. This study has provided us with access to many patients from our local area and from other regions of the United States. It is possible that these patients may also wish to participate in our therapeutic trial. We also have access to over 580 DM1 patients through the National Registry of Myotonic Dystrophy Patients. We anticipate having no significant difficulty in recruiting the required number of patients for this trial.

Patient Selection:

Myotonic dystrophy type-1 patients of both genders will be recruited for this study. All NIH guidelines regarding gender and minority inclusion will be followed. Issues regarding human subjects are discussed in the section identified as Human Subjects.

All patients must fulfill the following **inclusion criteria** to participate in the study:
1) Age 18 years or older and less than or equal to 80 years old.
2) Have a diagnosis of myotonic dystrophy type 1 and a 1st degree family member with a positive DNA test for myotonic dystrophy type 1
3) Have delayed relaxation of grip of one second or more following a maximum voluntary isometric contraction using our standard Jamar grip ergometer**.**
4) Have sufficient finger flexor strength to grasp the handle of the ergometer used to measure myotonia.
5) Have sufficient strength to swallow.

6) Be able to walk independently 30 feet and to walk continuously for more than six minutes (cane, walker, orthoses allowed) at a distance over 100 meters.
7) Have a reliable method of birth control (if a female subject of child bearing potential).
8) Able to swallow an appropriately sized capsule.

Patients with one or more of the following criteria will be **excluded from participation** in the study:
1) Known allergy to mexiletine.
2) Treatment with mexiletine within past 8 weeks.
3) Second or third degree heart block, atrial flutter, atrial fibrillation, ventricular arrhythmias, or is receiving medication for treatment of a cardiac arrhythmia.
4) Receiving another antimyotonia drug.
5) Liver or kidney disease requiring ongoing treatment.
6) Have a seizure disorder.
7) Are pregnant or lactating.
8) Had severe depression within 3 months of randomization or a history of suicide ideation. Physicians review current medications and clinical assessments of primary care physicians and coordinate participation in the study with them. If the primary care doctor is not comfortable including assessments of cognitive or emotional state (i.e. severe depression) we will not include them in the study until they satisfy all of the inclusion criteria. We always share laboratory data and significant findings with the primary care doctor and any other care providers with permission of the subject.
9) History of non-compliance with other therapies.
10)Have any one of the following medical conditions: uncontrolled diabetes mellitus, congestive heart failure, symptomatic cardiomyopathy, symptomatic coronary artery disease, cancer other than skin cancer less than five years previously, multiple sclerosis, or other serious medical illness.
11)Have any of the following conditions on routine blood screening: WBC <3000, platelets <100,000, hematocrit <30%, symptomatic liver disease, BUN >30mg%.
12)Drug or alcohol abuse within 3 months of enrollment.
13)Coexistence of another neuromuscular disease.
14)Is unable to give informed consent.
15) Severe arthritis or other medical condition (besides DM1) that would significantly impact ambulation.

Study Time Line and Procedures:

Patients will receive three in-person evaluations during this study. An outline of the testing that will take place during these visits is provided in **Schedule 1 (attached)**.

Baseline Screening:

A baseline evaluation will determine the eligibility of each recruited individual to participate in the study. At this visit consent will be obtained, and measurements of height, weight, blood pressure, pulse, urinalysis, and electrocardiogram will be performed. A blood specimen will be drawn for: complete blood count and differential

cell count, serum sodium, chloride, potassium, bicarbonate, calcium, phosphorus, total protein, glucose, blood urea nitrogen, prothrombin time, partial thromboplastin time, creatinine, thyroid stimulating hormone, T3, T4, gamma glutamyl transferase, aspartate aminotransferase, and lactic dehydrogenase. A pregnancy test will be given to women of childbearing potential.

Patients will be required to have had a 24 hour Holter monitor study performed within 2 months, or prior to their initial screening visit. The Holter monitoring assessment will occur through collaboration with our study cardiologist, Dr. [REDACTED], who is reviewing the resting electrocardiograms and 24 hour Holter monitoring results on each of the study participants. Patients will come to the University of Rochester Medical Center > 36 hours before their scheduled Clinical Research Center [CRC] visit for out-patient electrode placement and attachment of the Holter recording equipment. The Holter equipment and electrode removal will occur at the time of admission of the participant to the CRC. Rapid review of the tracing will occur to allow a determination of their eligibility after all the initial baseline screening is performed to assure that the patient satisfies the inclusion and exclusion criteria for participation in the trial of mexiletine. The out of town participants will stay in a hotel close to the University of Rochester Medical Center during the period before their CRC admission. The application of the Holter monitor will occur as noted above as an out-patient procedure that will be coordinated through our cardiology group, including Drs. [REDACTED] and [REDACTED] (cardiologists), [REDACTED] (ECG Core Lab Manager) and [REDACTED] (Technician).

Past medical history will be collected by the study coordinator and a physical exam will be completed by one of the investigators. If an individual patient meets the inclusion criteria and has none of the exclusion criteria, that patient will be enrolled and their inpatient evaluation continued. If recruited individuals do not meet the inclusion criteria or have one or more exclusion criteria, they will not be eligible to participate and will not continue in the study.

Screening Evaluations:

- Review of the study procedures/consent review: Upon arrival at the CRC, the information in the screening consent form will be reviewed with the patient in detail. The patient will be provided with an opportunity to ask any additional questions prior to starting the study procedures scheduled for the day.

- Standard blood testing. Up to 4 tablespoons of blood will be taken from a vein in the participants arm. This blood will be used for routine laboratory testing listed above and in the schedule. A pregnancy test will also be performed for women of childbearing potential.

- A urine sample will be collected a urinalysis will be performed. Height, weight, and vital signs will be recorded.

- A standard 12 lead electrocardiogram (ECG) test will be performed.

- A study doctor will perform a physical examination and medical history. Medical records will be reviewed.

- A 6-minute walk test (6MWT) will be performed under the supervision of a trained physical therapist. Blood pressure, heart rate, breathing rate, and oxygen saturation will be recorded before and after this test.

- A swallowing evaluation will be conducted to determine the ability of the patient to swallow pills with water.

- Myotonia testing. For this testing we will have the patient grasp a handle that is connected to a computer. The patient will squeeze the handle as strongly as they can for 3 seconds and then relax. The time required for the patient's hand to relax will be recorded by the computer and be used to measure the patient's hand myotonia. To find out if repeated muscle contractions shorten the time required for grip to relax (warm-up effect) a similar test will be performed. With the right hand patients will grasp onto the handle. They will squeeze the handle as strongly as they can for 3 seconds and then relax for 10 seconds. They will repeat this five times. This series of grip exercises will be repeated for a total of 3 sets. Each set will be separated by a 10 minute rest period.

- Placement of a 12-lead 24-hour Holter monitor test. The patient will come to the University of Rochester Clinical Research Center (CRC) and a technician from the Cardiology Group working on this project will work with the CRC nursing staff to set up the Holter monitor. Patients will not require this testing if they have had a Holter monitor within 2 months. This testing can be done before or after the above screening procedures and after the screening consent form has been reviewed and signed.

Potential Enrollment: All screening information will be reviewed by the PI to determine subject eligibility. If a patient satisfies all the inclusion and exclusion criteria, the patient will be invited to participate in the research study and a consent form for the treatment trial (attached) will be reviewed with them. If the patient decides to participate in the clinical trial the patient will undergo the following:

I. <u>Continuation of the Screening/Baseline Visit at the University of Rochester Clinical Research Center (CRC)</u>. This visit will take two days. During this visit a series of evaluations will be carried out to determine how the patient is affected by myotonic dystrophy. An additional aspect of the Screening/Baseline Visit is that the patient will be started and monitored on the study drug (either mexiletine or placebo).

II. Follow-up visits to the CRC 3 months and 6 months after the Screening/Baseline Visit. During these visits many of the same evaluations from the Screening/Baseline Visit will be repeated to determine how the patient's condition has changed over time.

III. Telephone evaluations. The patient will receive a telephone call about every two weeks while they are enrolled in the study, except for the weeks when they come to the CRC for a study visit. The study coordinator will telephone the patient to check on any side effects that may occur and make sure that the study medication is being taken as directed. The coordinator will also ask each patient about their pain level during these phone calls.

A schedule of procedures and assessments for this project is outlined in **schedule 1** (Appendix C).

Description of study procedures:

The Screening/Baseline Visit of the study will take place over two consecutive days on the CRC. On Day 1 the patient will be admitted to the Clinical Research Center (CRC) for an overnight stay.

Screening/Baseline Visit Day 1 - The activities during the first day will take all day (about 4 hours in the morning and 3 hours in the afternoon). These activities include the screening evaluations listed above as well as the procedures outlined below.

- Review of the study procedures/consent review: Upon arrival at the CRC, the information in the treatment consent form will be reviewed with the patient in detail. The patient will be provided with an opportunity to ask any additional questions they may have prior to starting the study procedures scheduled for the day.
- An assessment of the patient's ability to swallow. A swallowing evaluation will be conducted to determine the time it takes for the patient to swallow water.
- The patient's muscle strength will be tested in several ways by a physical therapist using hand grading and a myometer. The patient's force vital capacity will be checked. The patient will be timed as they get up from a chair and walk 30 feet and perform a Purdue Peg Board test and Jebsen-Taylor Hand function tests. The patient will be asked to pinch a piece of equipment with their fingers to measure their pinch strength.
- Each patient will be given a standard lunch on the CRC.
- They will be asked to complete a series of questionnaires to find out how myotonic dystrophy impacts upon the patient's life and daily activities. These include the following questionnaires: Upper Extremity Functional Index, myotonia visual analog scale, Medical Outcome Short Form Health Survey (SF 36), Epworth Sleepiness Scale, an Individualized Neuromuscular Quality of Life

Questionnaire (INQoL), two gastrointestinal function questionnaires, a chronic pain scale and brief pain inventories, and a DM1 specific Health related quality of life questionnaire (MDHI). Additionally, patients will be asked to complete an assessment of the usability and relevance of some of these questionnaires (i.e., SF-36, INQoL, and MDHI).

- Each patient will receive a standard dinner on the CRC.
- After all of the baseline assessments are completed, each patient will receive the first dose of study medication (mexiletine or placebo) with dinner. The patient will stay overnight on the CRC.

Screening/Baseline Visit Day 2 - The activities during the second day will take approximately 4.5 hours to complete. The procedures described for Day 2 will begin on the Clinical Research Center (CRC) in the morning at 7:30AM.

- Each patient will be given a second dose of study medication with their breakfast.

The amount of muscle tissue, fat tissue, and bone in the body will be measured using dual energy X-ray absorptiometry (DEXA). The DEXA machine will scan over the patient's body while they lie still for about 15 minutes. The DEXA scan involves radiation exposure which is less than one day's worth of exposure to natural background radiation.

- Video-recording of Hand Opening Time. The dominant wrist and hand are placed on a bedside table with the forearm fully supinated. The participant is asked to open the hand after making a tight fist for 3-5 seconds. A digital video recording is made of the hand opening. The video field of view only includes the participant's forearm and hand. The time required for hand opening, which often ranges from 3 to 20 seconds in individuals with DM1, is determined by blinded review of the video recording. The procedure is carried out three times over 30 minutes.
- Each patient will be given a third dose of study medication with their lunch.
- Up to 4 tablespoons of blood will be taken from a vein in the patient's arm. This blood will be used for routine laboratory testing listed in the schedule. The level of mexiletine in the blood will also be measured.
- An electrocardiogram will be performed and reviewed by a physician in real-time.
- The study coordinator will give each patient bottles containing a three month supply of study medication. Each patient will also be given a diary to record the amount of medication taken each day and any side effects that they may experience. The coordinator will go over instructions for taking the study medication and completing the medication diaries. At the 3 and 6 months follow-up visits patients will be asked to return the study medication bottles, any unused study medication, and completed diaries.

Itinerary of Follow-up Visits: (Month 3 and Month 6)

The evaluations of patients at their Month 3 and Month 6 Visits will be similar to those performed at their Screening/Baseline Visit with the exception that a DEXA scan will only be performed at Screening/Baseline and at Month 6. Holter monitoring will occur within the week immediately before the CRC admissions at Month 3 and Month 6, and the procedure for placement of the Holter recording equipment and electrode placement will use the same standard procedure described above and routinely used by our cardiology consultant group at the University of Rochester Medical Center.

On the Month 3 and Month 6 follow-up visits, the patient will complete the following study procedures following an overnight fast. The patient will be supplied with a standard breakfast after the blood draw.

- An electrocardiogram will be performed.
- The patient will have up to 4 tablespoons of blood drawn, and if the patient is a female of childbearing potential, a pregnancy test will be done. A urine sample will be collected to test kidney function.
- A study doctor will perform a history and physical examination; height, weight and vitals will be recorded.
- A study doctor and study coordinator will discuss any side effects that the patient may have experienced and any recent changes in medications.
- An assessment of the 6-minute walk test (6MWT) will be performed.
- A swallowing evaluation will be conducted.
- Myotonia, functional, and strength testing will be performed (as described above).
- A standard lunch will be given on the CRC.
- A DEXA study will be performed (six month only).
- Questionnaires will be completed (Upper Extremity Functional Index, myotonia visual analog scale, Medical Outcome Short Form Health Survey (SF 36), Epworth Sleepiness Scale, an Individualized Neuromuscular Quality of Life Questionnaire (INQoL), two gastrointestinal function questionnaires, chronic pain scale and brief pain inventories, and a DM1 specific Health related quality of life questionnaire (MDHI). Additionally, patients will be asked to complete an assessment of the usability and relevance of some of these questionnaires (i.e., SF-36, INQoL, and MDHI).
- The study coordinator will collect medication bottles, unused medication and the patient's diary. At the month 3 visit, the patient will be provided with a new supply of study medication and a patient diary.
- The patient will receive a standard dinner on the CRC.

  Once all of these activities are completed, the visit will be finished and the patient will be discharged from the CRC.

Diet:

During inpatient evaluations on the Clinical Research Center of the University of Rochester Medical Center (CRC) each participant will receive a constant diet that is designed in advance with the CRC dietitian. The meals provided on Study Day 1 will be the identical to the meals provided on Study Day 2. Each meal will be given at the same time (8AM, 12:30PM, and 6:00PM) on both Study Days 1 and 2. During both study days participants will only consume the research diet provided and will not perform vigorous physical exertion other than that required for the muscle strength testing in the research protocol. This dietary control helps to avoid changes in hormonal regulation of potassium balance that might exert a significant influence on the degree of myotonia in study participants.

Randomization:

After eligibility has been confirmed and the treatment consent has been reviewed and signed, the patient will be randomized to one of two treatments (placebo or mexiletine) according to the randomization plan developed by the biostatistics programmer at the University of Rochester, under the supervision of the biostatistician (Dr. [REDACTED]). The randomization will include blocking to insure balance among the two treatment sequences after a certain number of patients have been enrolled. Only Dr. [REDACTED] and the biostatistics programmer will be aware of the block size used.

After the randomization plan has been generated by the biostatistics programmer, it will be sent to the pharmacy at the University of Rochester Medical Center where drug packaging and labeling will take place. All drug will be labeled with a patient ID number. Only the biostatistics programmer and the pharmacist will have access to the treatment assignments, i.e., the link between the patient ID number and treatment. The biostatistician (Dr. [REDACTED]) will remain blinded to treatment assignment.

Drug will be assigned sequentially. No patient will be dispensed study drug until after all baseline assessments have been completed. The study coordinator will be required to check all baseline forms for completeness and verify eligibility criteria before calling the pharmacy to officially randomize a patient. Enrollment will be documented on a case report form.

The biostatistics programmer will also provide the study coordinator with a set of sealed emergency disclosure envelopes which will allow the investigator to become quickly unblinded to the patient's treatment assignment in case of a medical emergency. It is anticipated that such disclosure will not be necessary in this study.

Study Drug, Dosage, and Compliance:

<u>Study Medication:</u>
Mexiletine is available by prescription for its approved indication as a ventricular antiarrhythmic. In support of this research protocol the Investigational Drug Service (IDS) will supply both active and placebo products in a blinded fashion.

For the active treatment group commercially available mexiletine will be purchased from Cardinal Drugs and charged to the research grant. The exact generic brand to be purchased is to be determined and will be based off of availability and price at the time of purchase. Once purchased all future active doses will be prepared using the same manufacturer's product.

To blind the active product the IDS will over-encapsulate the commercial product by placing each capsule inside a larger empty opaque capsule. The placebo product will consist of a placebo capsule (size 3 capsule containing 240mg of lactose powder USP) placed inside the same type of larger opaque capsule.

Rationale for dosage:
Mexiletine has an established pharmacokinetics and side effect profile and it is already approved as an alternative treatment for symptomatic ventricular arrhythmias.[48-53] Previous research has established that serum concentrations of mexiletine exceeding 1.5 to 2 mcg/ml are associated with an increased risk of toxic side effects and a standard assay of the serum level of mexiletine is available.[48-53] This information provides assurance that the present study design has utilized an appropriate dosage, an appropriate approach to monitoring of potential adverse events related to the treatment, and has appropriate precautions to monitor the patients. The availability of a serum assay for mexiletine is another advantage in this investigation because the measurements of serum levels of mexiletine included in the protocol will help to determine if the concentrations achieved are in the therapeutic range, if there is any correlation between the serum level and its antimyotonia efficacy, and if the patients are taking the medication. The fact that much higher doses of mexiletine have been used to treat pain in patients with diabetic neuropathy without producing serious toxicity gives additional assurance that mexiletine in the dose set forth in this proposal (mexiletine 150 mg three times daily) is not only appropriate, based upon previous research in DM1 patients, but is also well within the safe therapeutic range for this medication.[19,22,54,55] We also have considerable anecdotal experience in using mexiletine to control myotonia in patients with various myotonic diseases, and feel that the dosage of mexiletine in this protocol will be well tolerated by most DM1 patients. Lastly, the mexiletine dose of 150 mg three times daily in this protocol was selected over a higher dose of 200 mg three times daily based upon data from our FDA funded 7 week, double-blind, crossover trials of mexiletine that demonstrated that this lower dose of mexiletine had a slightly greater clinical efficacy in increasing hand grip peak force while demonstrating a similar effect in reducing myotonia.[22]

Compliance:
Participants will be asked to return the study medication bottle at each follow-up visit [Month 3 and Month 6]. In addition, study subjects will be supplied with compliance diaries to record their compliance with taking the study medication. In addition, the study coordinator will contact each participant at about 2 week intervals during the trial to assess side effects and pain, and will encourage each study subject to adhere to the treatment regimen.

Withdrawal/ Discontinuation/ Dosage Reduction:

Patients will have the option of withdrawing from the study at any time. Patients may also be withdrawn because of an inability to comply with study procedures (e.g., because of significant surgery or medical illness). If a patient experiences intolerable adverse events, the dosage may be reduced by one level (e.g. from three times a day dosing to twice a day dosing). Patients who experience intolerable adverse events requiring withdrawal of study medication or who require treatment with exclusionary medications will continue to be followed according to the protocol, if the patient is willing. Primary statistical analyses will be performed according to the intention-to-treat principle and will utilize all patient data collected.

All patient withdrawals, dosage reductions, treatment discontinuations, and treatment with exclusionary medications will be carefully documented on case report forms.

In case of a medical emergency, the principal investigator will contact the pharmacy and become unblinded to the patient's treatment assignment.

Coordination of Patient Care Following the Completion of the Study Protocol:

At the completion of the study all patients will be tapered off the study drug/placebo over a one week period. We will provide each patient's primary care physician and/or neurologist a detailed summary of the patient's current health status and will coordinate with them any questions regarding management of their patient including the potential use of mexiletine therapy.

Study Testing Procedures:

<u>Evaluation of safety and tolerability:</u>
Adverse side effects will be monitored during each CRC visit (Baseline, Month 3, Month 6) and during telephone calls at about 2 week intervals during the intervening weeks of the trial. The adverse effects of mexiletine observed most commonly include: dizziness, lightheadedness, nervousness, nausea, vomiting, or upset stomach, diarrhea, constipation, trembling, shaking of hands, blurred vision, tiredness, or weakness. More serious side effects, which are less common include: irregular heart beat, chest pain, shortness of breath, trouble breathing, skin rash, severe itching, or hives.

If there are more serious side effects, the principal investigator will be notified. The principal investigator will contact the patient and determine if it is necessary to have the patient reduce the dosage of treatment agent of to stop it. The principal investigator will also determine if an urgent evaluation of the patient is necessary. These medical plans and any related change in care will be coordinated with the primary care physician of the patient. If necessary, the code will be broken to determine if the patient is receiving placebo or mexiletine treatment.

Additional details regarding the evaluation of the safety and tolerability of this medication are provided in the human subjects section of this application.

Description of Efficacy Measures:

As described in the section on Rationale for the Study, the effects of myotonia on patient function can be profound. Mexiletine has the potential to ameliorate many symptoms attributed to myotonia (**FIGURE 1**). Below is a description of the outcome measures we will utilize to help determine the effect of mexiletine on patient health.

PRIMARY MEASURE OF EFFICACY:

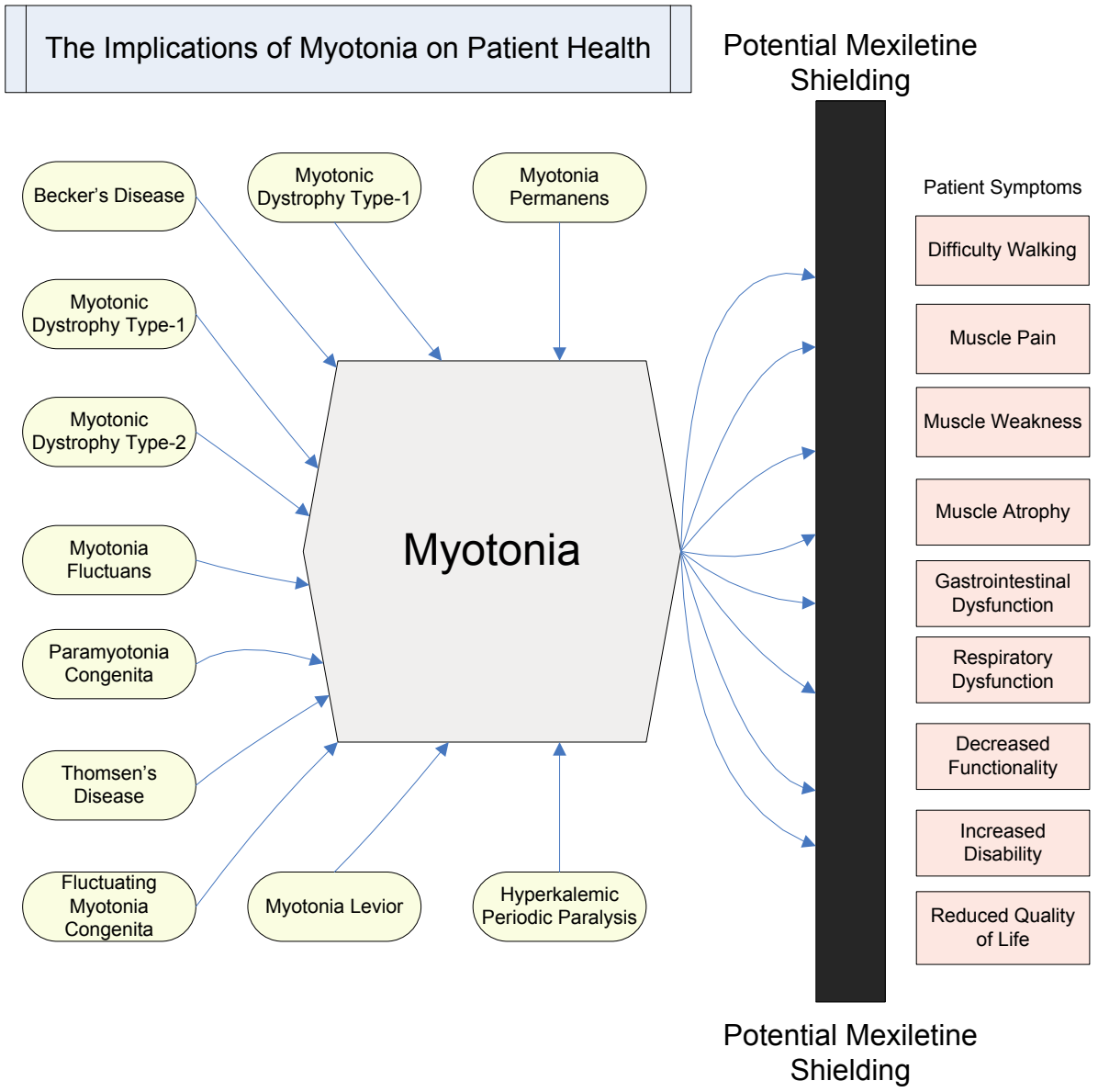
6 Minute Walk - Evaluation of Gait & Endurance:

The primary outcome measure for this study will be the distance patients can walk during a 6 minute period (6-minute walk test). Ambulation has been identified as one of the most important and relevant symptoms in DM1. [36] The six minute walk has been shown to be a reliable and feasible mechanism for testing DM1 patient ambulation and endurance.[41a] Our Neuromuscular Disease Center has extensive experience safely utilizing this measure and has used this measure in clinical trials. All patients will be timed and monitored under the close supervision by a clinical evaluator during the implementation of this clinical test.

Protocol For 6 - Minute Walk Test (6MWT)

The 6MWT will be used to assess changes in mobility, strength and endurance in the DM1 patients participating in this long term trial of mexiletine versus placebo. The guidelines published by The American Thoracic Society[42b] will be used for administering this test. The object of the test is for the subject to walk as far as possible in 6 minutes. The subject will rate their baseline dyspnea and overall fatigue using the Borg scale before and after the test. Blood pressure, respiratory rate, heart rate and oxygen saturation will be measured before and after the test. The clinical evaluator supervising and monitoring this procedure will record the use of any braces, canes or assistive devices. The 6WMT will be performed in a long, straight, hard surfaced corridor in our CRC that is about 20 meters. Once the participant reaches the end of the corridor they will pivot, continue back along the corridor, and continue back and forth until 6 minutes is over. The subject may slow down, stop or rest as necessary. The distance walked during 6 minutes at screening will help determine a subject's eligibility. Throughout the study, the same corridor of the CRC will be used for all of the 6MWTs.
[42b]

FIGURE 1:


The Implications of Myotonia on Patient Health
Potential Mexiletine Shielding
Becker's Disease
Myotonic Dystrophy Type-1
Myotonia Permanens
Myotonic Dystrophy Type-1
Myotonic Dystrophy Type-2
Myotonia Fluctuans
Paramyotonia Congenita
Thomsen's Disease
Fluctuating Myotonia Congenita
Myotonia Levior
Hyperkalemic Periodic Paralysis
Myotonia
Patient Symptoms
Difficulty Walking
Muscle Pain
Muscle Weakness
Muscle Atrophy
Gastrointestinal Dysfunction
Respiratory Dysfunction
Decreased Functionality
Increased Disability
Reduced Quality of Life
Potential Mexiletine Shielding

SECONDARY MEASURES OF EFFICACY:

Evaluation of Myotonia:

Two procedures will be used to obtain serial measurements of myotonia in each participant. They are: 1) The measurement of maximum isometric voluntary contraction force and relaxation time; and, 2) Video-recording of Hand Opening Time. Given its overall reliability and sensitivity, data from the maximum isometric voluntary contraction and relaxation time measurement will be utilized as the primary outcome measurement. Details regarding these procedures for determining myotonia are provided below.

1. Maximum Isometric Voluntary Contraction Force and Relaxation Time Measurement of Myotonia:

Maximum isometric contraction force of the long finger flexors and the subsequent relaxation time (myotonia) will be measured using a highly reliable technique we have utilized for a number of years.[38,56,57] The testing will use the right arm. Patients will be seated while the right arm is flexed to 90^{o} at the elbow and the forearm neutral. With the palm up the 2nd, 3rd, 4th, and 5th fingers are flexed in their distal portions to hold to the grip handle. The hand is strapped securely to prevent movement during contraction and during relaxation. This configuration of hand and force transducer has eliminated the variability in measuring isometric grip myotonia that we had previous observed using a hand dynamometer without maintaining the hand and fingers in fixed position.[58] The output from the transducer is played out on an oscilloscope for the patient to watch and recorded on diskette for computerized analysis of the relaxation time.

To determine the grip myotonia in resting forearm muscle, each participant will squeeze with a maximum grip for three seconds then relax until force returns to baseline. The time required for relaxation following this initial maximum isometric contraction will be used to calculate the degree of myotonia. To determine if repeated muscle contractions shorten the time required for full muscle relaxation, e.g., warm-up, a series of three maximum voluntary contractions (MVC) will be made each for three seconds duration with each of these contractions followed by a ten second period of rest. Following the final contraction, the time required for the force to return to baseline will be used to measure the effect of warm-up on myotonia. The measurement of warm-up will be made by comparing relaxation time for the initial maximum isometric voluntary contraction to the relaxation time following the final contraction in the series of five contractions used to evaluate warm up exercise.

Myotonia will be assessed by the time required for the force to fall from 90% of maximum voluntary contraction force to 5%, a measurement we have found most reliable to assess myotonia.[22,38,57] The change in this time with treatment will serve as the primary outcome for this clinical trial. Each participant will perform three sets of hand grip exercises using our standard grip myotonia measurement protocol.[56,57] Each set will be separated by a 10 minute rest period. During this rest period the opposite hand will undergo brief myotonia testing using the repetitive stimulation protocol described below.

2.Video-recording of Hand Opening Time. The dominant wrist and hand are placed on a bedside table with the forearm fully supinated. The participant is asked to open the hand after making a tight fist for 3-5 seconds. A digital video recording is made of the hand opening. The video field of view only includes the participant's forearm and hand. The time required for hand opening, which often ranges from 3 to 20 seconds in individuals with DM1, is determined by blinded review of the video recording. The procedure is carried out three times over 30 minutes.

Evaluation of Muscle Strength:
Muscle strength will serve as a secondary outcome measure. Evaluation of muscle weakness will be carried out by blinded clinical evaluators and will include quantitative myometry, and manual muscle testing (MMT). These tests will occur at the baseline evaluation, at three months, and at the completion of the trial of mexiletine (six months). A brief description of the muscle strength testing is provided below.

1. Quantitative Myometry (QMT):
Maximum Voluntary Isometric Contraction Testing (MVICT) of the limb muscles will be performed using the Quantitative Muscle Assessment (QMA) system designed by Computer Source, Atlanta, GA. This system uses an adjustable cuff to attach the patient's arm or leg to an inelastic strap that is connected to a force transducer with a load of 0.5 to 1,000 Newtons. The clinical evaluator is a trained physical therapist with previous experience in clinical trials. Photographs and written instructions illustrating patient position, strap placement, examiner fixation, and common substitutions will be used by the evaluators to ensure standardization of testing. Each muscle will be tested twice while the patient is encouraged by the evaluator to exert maximal effort. The maximum force generated by the patient will be recorded for each trial, and the maximum over the two trials will be used as the final measurement for each muscle. Measurements resulting from this method of testing have been shown to be reliable and valid in several neuromuscular diseases.[39,61] Seven muscle groups will be tested bilaterally (shoulder abductors, biceps, triceps, quadriceps, hamstrings, ankle flexors and hand grip) for a total of twelve muscle groups. These particular muscles were chosen because they show excellent test-retest reliability in neuromuscular patients and normal volunteers and they reflect the distribution of muscle involvement in myotonic dystrophy. If myotonia exerts a deleterious effect on muscle strength, we anticipate that the above QMA assessment will have the greatest sensitivity to detect this influence. The QMA assessment will serve as our primary measure of strength for our analysis of the effect of mexiletine on muscle strength.

2. Manual Muscle Testing:
Manual muscle testing will be performed on each of 26 muscle groups (shoulder abductors, elbow flexors, wrist flexors, wrist extensors, hip flexors, knee extensors, hip extensors, knee flexors, hip abductors, elbow extensors, ankle dorsiflexors, and plantar flexors on the right and left plus neck extensor and neck flexors). The muscles will be tested in various positions including sitting, supine, prone, and side-lying and each graded on a modification of the Medical Research Council (MRC) scale of 0-5.

Measurements resulting from this method of testing have been shown to be reliable and valid in many neuromuscular diseases, as well as being sensitive to detect the beneficial effects of treatment in clinical trials of neuromuscular disease. [62,63]

The Measurement of Lean Muscle Mass:

Lean muscle mass (LMM) will be measured via Dual Energy X-Ray Absorptiometry (DEXA). DEXA uses a very small amount of x-ray energy (0.5 to 1.0 mREM vs. 20-30 mREM for a chest x-ray) to measure body composition and it is an easily performed safe method. Lean muscle mass is composed predominantly of muscle. The other contributors to lean muscle mass are relatively constant, and as a result the DEXA technique provides a reliable estimate of true muscle mass. DEXA measured lean muscle mass in neuromuscular patients is highly correlated with urinary creatinine excretion (Ucr). Measurement of Ucr excretion has until now been the standard method for estimation of muscle mass. However, valid measurement of UCr requires subjects to be on a meat free diet and to carefully collect urine for 72 hrs. Even under carefully supervised conditions, the day to day variability in Ucr excretion is much greater. In the present investigations DEXA provides a more practical approach and has been utilized previously in multiple myotonic dystrophy clinical trials as an outcome measure. [22,36] Moreover, each scan requires only 20-30 minutes to perform. DEXA will be performed at baseline and after six months of therapy.

Pain Measurement:

During our study we will serially measure pain intensity and duration using a modified Chronic Pain Scale and a Brief Pain Inventory. The Chronic Pain Scale is a 10 point rating scale with 0 symbolizing “no pain” and 10 representing pain “as bad as could be”. This scale will be modified for clinical trial use by adjusting its timescale to represent symptoms over the prior week as opposed to the prior six months. Documentation of the patient reported score of their musculoskeletal pain from 0 to 10 will be made by the study coordinator at two week intervals during her regular telephone calls to each patient to assess safety, side effects and any other problems the patient reports.

The Brief Pain Inventory is a 9 item scale designed to measure the interference pain has with patient daily activities. These scales were selected based on their validity, simplicity, ability to detect change in pain with treatment, patient relevance, reliability, test-retest scores, and their previous use in pain studies of the myotonic dystrophy population.[35,64-66] These scales will be given to patients at baseline, 3, and 6 months to measure patient assessed pain while on mexiletine or placebo.

The Measurement of Gastrointestinal Function:

Gastrointestinal function will be measured using the Irritable Bowel Syndrome Impact Scale (IBS-IS), and the Gastrointestinal Symptom Rating Scale modified for use in patients with IBS (GSRS-IBS). Both of these scales have been previously tested and utilized to monitor and track myotonic dystrophy gastrointestinal symptoms during a

treatment trial. [36] The GSRS-IBS is a 13 question scale (point range 1-7 for each question) which measures pain, bloating constipation, diarrhea and satiety symptoms over the preceding 7 days. The questionnaire has been validated against current health-related quality of life questionnaires. The Irritable Bowel Syndrome Impact Scale (IBS-IS) is a 26 question scale (point range 1-7 for each question) which measures modalities in fatigue, daily activities, sleep, emotions, and eating habits. It was developed specifically for use in clinical trials and validated against the GSRS-IBS, SF-36, Visceral Sensitivity Index, and hospital anxiety and depression scale. Both of these questionnaires can be completed in less than 10 minutes. These scales were selected based on their question content and the significant symptomatic overlap between myotonic dystrophy gastrointestinal symptoms and irritable bowel syndrome. These scales will be given to patients at baseline, 3 months, and at 6 months.

The Measurement of Swallowing Function:

In order to test patient dysphagia and myotonia of the tongue and pharyngeal muscles we have included a timed testing of swallowing. This test was previously piloted in our FDA funded initial 7 week, double-blind crossover trials of mexiletine and found to be an effective, safe, and well tolerated procedure to evaluate dysphagia. [22] The swallowing testing will occur immediately before eating breakfast during all three in–person evaluations (baseline, 3 & 6 month CRC visits). Each participant will drink 100ml of water as fast as they can without choking. The time will be kept with a stopwatch and will begin with the first swallow and conclude with completion of the final swallow. As part of the screening visit, a patient will also be asked to demonstrate their ability to swallow a placebo pill with water. At the conclusion of this study the change in swallowing times will be compared across treatment groups.

Measurement of Cardiac Conduction Defects:

The data obtained from Holter recordings will provide 24 hour circadian data in addition to basic autonomic electrocardiographic tone parameters at baseline and at Month 3 and Month 6 on therapy with mexiletine (and placebo) in the DM1 patients participating in this research protocol. DM1 has a tendency for lower blood pressure and alters peripheral vasomotor control that may affect heart rate adaptation to positional changes. Information from the dairy used in the Holter monitoring protocol may provide important clinical management information about potential benefits that mexiletine may exert on cardiovascular function as well as on skeletal muscle relaxation. Potential correction or modulation of the chloride channel dysfunction that occurs in DM1 by mexiletine may alter/improve peripheral vasomotor control and parasympathetic tone in the study participants. Ventricular arrhythmia data including ventricular ectopy counts, nonsustained ventricular tachycardia number of events and duration over a circadian time period of one day may provide greater insight into any proarrhythmic or antiarrhythmic effects of mexiletine therapy in this disease. While the current study design is not powered to answer questions about the possible beneficial effect of mexiletine on the heart in DM1, the findings on Holter monitoring may encourage subsequent investigations to explore such a possibility.

Serial 24-hour Holter monitors will be utilized during this study to determine if there are any effects of mexiletine on cardiac conduction patterns. Each study will be analyzed by a cardiologist with specific training in the interpretation of the findings on Holter monitoring. Measured variables include: 1) heart rate variability; 2) number of premature ventricular contractions during a 24 hour period; 3) QTc intervals; 4) average heart rate; 5) presence or absence of atrial arrhythmias; 6) presence or absence of non-sustained ventricular arrhythmias; 7) duration of non-sustained ventricular tachycardia (if present); and, 8) presence or absence of AV block progression. If any significant abnormalities are observed by the cardiologist reviewing the results of the Holter monitoring, the independent medical monitor and PI of the study will be notified immediately. In addition to the important analysis of Holter findings during the CRC admissions of each study participant, at the completion of our study biostatistical analyses will be performed on the Holter monitoring data to compare baseline to Month 3 and Month 6 findings in each individual receiving mexiletine and placebo to search for trends in our findings that suggest a beneficial or non-beneficial effect of mexiletine compared to the variations that occur in similar patients with DM1 receiving placebo.

We will utilize the below ECG data collection and review template (see Figure 2) that will be used in the data collection and analysis for the study and will be available to the members of the DSMB for their review. Our staff will enter the appropriate information on each participant's electrophysiology and this information will be charted longitudinally throughout the study. This format for the analysis of ECG data has been used by investigators in other studies. It provides both a numerical/statistical and graphical representation of trends in various ECG and Holter variables in a timeline. Abrupt changes as well as potential clinically significant trends in the ECG parameters of an individual participant will be detected. Abnormal values will be highlighted for the DSMB for rapid initial review.

Figure 2 A sample template for the basic electrocardiographic data to be collected. This data will also be graphically represented for each subject.

Cardiac DSMB Considerations in Mexiletine Treatment of Myotonic Dystrophy Type-1			
	Baseline	3 Months	6 months
	n; m±sd or freq.	n; m±sd or freq.	n; m±sd or freq.
12-lead ECG			
Heart rate bpm			
R-R interval sec.			
PR interval sec.			
QRS duration sec.			
QT interval sec.			
QTc interval sec.			
T-wave amplitude in Lead II mm			
2nd degree block y/n			
3rd degree block y/n			
Other ECG abn y/n			
24-hour Holter			
VPB frequency #/hr			
VPB pairing y/n			
VPB triplets y/n			
VPBc≥4 but <10 in a row y/n			
Ventricular tachyardia >10 in a row y/n			
rate bpm			
2nd degree block y/n			
3rd degree block y/n			
Sinus pause/arrest >3 sec y/n			
Symptoms/Signs			
Syncope y/n			
Chest pain y/n			
Palpitations y/n			
Possible adverse Mexiletine effects y/n			

Our DSMB will be organized to help monitor these data and will include a cardiologist (Dr. [REDACTED]), a biostatistician (Dr. [REDACTED]), and a neurologist (Dr. [REDACTED]) with DSMB experience. None of the members of the DSMB have active collaborations with the investigators on this grant and none are members of the specific subspecialty units of which the investigators are faculty members.

The criteria for DSMB intervention will consist of three levels:

Level One- Abnormality noted. Possible normal variation. Clinically non-significant.

Level Two- Abnormality noted. Potential clinical significance. Requires further review and decision by DSMB.

Level Three- Critical Value. Clinically significant and immediate intervention required.

Any Level Three occurrence will warrant a temporary stoppage of study medication use for an individual patient until an expedited DSMB determination can be made.

Figure 3 below lists possible observable cardiac findings via ECG or Holter monitoring and each event's required DSMB action.

Figure 3: Required DSMB interventions for possible cardiac events.

Data Category	Variable	DSMB Intervention Level
ECG	1 degree AV block	1
ECG	2nd Type 1	2
ECG	2nd type 2	3
ECG	3rd degree AV block	3
ECG	Sinus tachycardia	1
ECG	Sinus bradycardia	2
ECG	New Bundle branch block	2
ECG	QRS widening>50%	3
ECG	QTc>500msec	3
Holter Monitoring	PVC frequency Increase	2
Holter Monitoring	Nonsustained VT Increase	2
Holter Monitoring	Sustained VT	3
Clinical Symptom	Syncope/unresponsiveness	3

Functional Testing:

In addition to the six minute walk, three timed functional tests have been selected for serial testing. The tests include: placement of pegs in a Purdue peg board for 30 seconds with dominant hand (number placed), the time to walk 30 feet, and time required to "rise up from a chair." These tests reflect specific functional impairments that occur in patients with DM1, specifically: hand weakness (especially finger flexors) and gait impairment due to quadriceps stiffness and weakness and cardiorespiratory functional limitations due to myotonic stiffness and weakness. In addition to these tests, forced vital capacity and serial SF-36 evaluations will be performed at all inpatient visits. Forced vital capacity directly reflects respiratory function while the SF-36 is a widely studied, 36 question, generic health survey index designed to measure functional health and well-being.

DM1-Specific Patient Reported Health-Related Quality-of-Life:

There is an increasing need to demonstrate that potential new treatments being evaluated in therapeutic trials have relevance to patients. To meet this need, over the last two years we have been developing a disease-specific patient reported outcome instrument to measure health related quality-of-life of DM1 patients for use during therapeutic trials. To date, this research has led to the identification, transcription, and coding of over 1100 DM1 patient quotes regarding the highest-impact, most relevant

issues and symptoms for DM1 patients. Under the guidance of the NIH funded PROMIS (Patient-Reported Outcomes Measurement Information System) and Neuro-QoI networks we will soon have a DM1-specific patient reported instrument capable of measuring health-related quality-of-life for this population. This instrument/questionnaire will directly represent the issues of highest importance to patients with DM1; as identified and validated by several hundred DM1 patients. The completion and development of this instrument was carefully planned to abide by the FDA's recommendations for PRO instrument use during clinical trials.[Patrick et al, 2007] Using a patient validated question set this instrument has the capability to measure patient-relevant DM1-specific quality-of-life. In addition, this instrument will be able to measure and tract subdomains of DM1-specific quality-of-life. These subdomains include 1) ambulation; 2) problems with hands or arms; 3) inability to do activities; 4) fatigue; 5) pain, 6) gastrointestinal issues; 7) impaired sleep; 8) emotional issues; 9) cognitive issues; 10) decreased satisfaction in social situations; 11) decreased performance in social situation; 12) myotonia; 13) breathing difficulties; 14) choking issues; and 15) issues related to medicine side effects. A draft version of this instrument is included in the application.

Independent Medical Monitor:

Dr. [REDACTED], Professor of Neurology at the University of Rochester Medical Center and an international authority on therapeutic trials in neuromuscular disorders, will serve as the independent medical monitor for this study. Dr. [REDACTED] will coordinate his assessments of the laboratory data with the Data Safety Monitoring Board (Dr. [REDACTED] will not serve as a board member of the Data Safety Monitoring Board) overseeing this study and will serve as resource member to that group. The independent medical monitor and the statistical programmer will be unblinded and will review laboratory data and side effects. The independent medical monitor will work closely with the statistical programmer to identify any potential deleterious effects of mexiletine in our patients. Concerns will be discussed as appropriate with the principal investigator. When necessary the blind will be broken and appropriate medical treatment carried out. Because of previous experience in the use of mexiletine, we do not anticipate any major adverse events that will require discontinuation of the study. Additional information regarding the safety monitoring of this study is provided in the Human Subjects Protection portion of this application.

Data Management:

Study forms, logs, databases, data entry screens, data audit trails, and secure daily computer backups have been developed. The study coordinator will send all forms on a weekly basis to the data manager, who will supervise data entry and verification. Forms relating to adverse events, dosage changes, randomization, terminations, will be faxed to the data manager. Data from DEXA and MVICT measurements will be sent electronically. The manager will track receipt of data and identify missing data. Immediately thereafter this data will be electronically transferred to the statistical programmer. The study coordinator will notify the principal investigator and IRB and follow FDA stipulated guidelines to report any serious adverse events within 24 hours.

All paper copies will be kept in locked cabinets. Additional information regarding the data monitoring of this study is provided in the Human Subjects Protection portion of this application. Some patients may simultaneously participate in the University of Rochester Pathogenesis and Progression in Myotonic Dystrophy Study (RSRB 24971, CRC 1259). In such cases data sharing may take place to minimize redundancy in functional or laboratory testing.

Statistical Analyses:

The primary outcome variable in this clinical trial will be the change from baseline to Month 6 in the mean distance walked during the six minute walk test. Using historical six minute walk test data in the DM1 population, we will have 80% power to detect a group mean change of 183 feet in distance walked over six minutes. The primary statistical analysis will involve fitting a repeated measures analysis of covariance model with treatment group as the factor of interest and the baseline value of the outcome variable as a covariate. The model will also include terms for month (categorical) and the interaction between treatment group and month. An unstructured covariance pattern will be used for model fitting. This model will be used to determine a 95% confidence interval for the adjusted mexiletine – placebo difference in mean response (treatment effect) at Month 6. Confidence intervals for treatment effects at Month 3, as well as averaged over Months 3 and 6, can also be obtained using this model; these will be considered to be secondary analyses.

If clinically important differences are found between the groups at baseline, particularly with regard to important variables such as age, gender, and years since symptom onset, the primary analyses will be repeated after statistically adjusting for these differences. These sensitivity analyses will be considered to be secondary, however.

The underlying assumptions of the analysis of covariance model will be thoroughly checked (e.g., normality, linearity), including analyses of residuals. Remedial measures (e.g., transformations, use of nonparametric methods) will be taken if serious violations of these assumptions are detected.

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 taking study medication, we will continue to follow and evaluate that subject if he/she is willing. If a subject drops out, attempts will be made to bring the subject in for a final evaluation. Compliance with trial procedures, dropouts/dropins, and reasons for subject withdrawal will be carefully tracked throughout the study. The repeated measures analysis of covariance model above uses maximum likelihood to estimate the parameters of interest (treatment effects) using available data from all subjects. A key assumption underlying this analysis is that the missing data are “missing at random” (MAR), i.e., the probability that 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. [67]

An alternative approach that will be used to deal with missing data in this setting, as a secondary (confirmatory) analysis, is multiple imputation. This will be applied using a regression-based imputation model.[68] For subjects with complete data up to a particular visit, a multiple regression model will be fit that includes the outcome at that visit as the dependent variable and outcomes at previous visits and treatment group 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) and treatment group of the subject.[68] 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 confidence interval and p-value).[68,69] This strategy is appropriate for data sets that have a monotone missing pattern. If the data set does not precisely have this pattern, the monotone data augmentation method using Markov-Chain Monte-Carlo[70,71] will be used to impute the small amount of missing data that is required to make the missing data pattern monotone before applying the multiple imputation algorithm described above. This approach to imputation should be superior to other strategies such as carrying forward the last available observation, which often yields unrealistic imputed values. Also, the use of multiple imputation 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.[67, 69]

Analysis of the Secondary Outcome Variables for Efficacy:

The secondary outcome variables for efficacy include: relaxation following maximum voluntary isometric contraction of the long finger flexors, repetitive stimulation relaxation time, rapid hand contraction and extension time, composite MVICT score derived by averaging the standardized (normalized) scores across the 10 individual muscles[40], grip strength derived by averaging the strength scores over the left and right hands, average MMT score derived by averaging the individual MMT scores across the 26 individual muscles[40], DEXA lean body mass, Modified Chronic Pain Scale scores, Brief Pain Inventory scores, holter monitor findings, IBS-IS scores, GSRS-IBS score, swallowing times, Purdue pegboard score, time to rise from a chair, time to walk 30 feet, Holter monitor data, SF-36 scores, and disease-specific health-related quality-of-life scores. These variables will be analyzed as described above for the primary outcome variable using repeated measures analysis of covariance, with the baseline value of the outcome variable used as a covariate. Again, depending on the nature of the outcome variable, data transformation or the use of nonparametric statistical methods may be required for analysis.

Analysis of Safety Outcomes and Subject Disposition:

Adverse events will be tabulated by treatment group, severity, and perceived relationship to study drug. For each adverse event (AE), the treatment groups will be compared regarding the occurrence of at least one event using Fisher's exact tests. The comparisons will be repeated excluding all mild symptoms. Particular attention will be paid to AEs known to be associated with mexiletine in previous studies. Individual AEs will be listed, with particular attention paid to serious AEs. Laboratory test abnormalities will be similarly analyzed, whether or not they are judged to be clinically significant (classified as AEs).

Continuous measures of safety (vital signs, EKG results, laboratory test results) will be analyzed descriptively. Formal analyses may be performed using methods similar to those described above for the primary outcome variable (repeated measures analysis of covariance).

The frequency of and reasons for subject withdrawal, dosage reduction, and premature withdrawal of study drug will be summarized by treatment group. The compliance data (amount of unused drug returned, compliance diaries) will be summarized by treatment group and visit, as will dosage level of study drug. Guessed treatment from the blindness questionnaire will be tabulated by actual treatment separately for subjects and the investigator. Chi-square tests will be used to determine whether or not the proportion of subjects who guess that the subject received mexiletine treatment differ among the actual treatment groups. The investigator's guesses will be similarly analyzed. Additional information regarding adverse event assessment and processing is provided in the Human Subjects Protection portion of this application.

Sample Size Considerations:

The primary outcome variable in this clinical trial will be the change from baseline to Month 6 in the mean distance walked during the six minute walk test. Using historical six minute walk test data in the DM1 population, we will have 80% power to detect a group mean change of 183 feet in distance walked over six minutes. This is based on a sample size of 18 per group (increased to 20 to account for the possibility of a 10% withdrawal rate), and a standard deviation of 190 feet. A two-sample T-Test Power Analysis is provided in Appendix A.

An important secondary outcome variable is the change from baseline to Month 6 in the time for relaxation of grip force following maximum voluntary isometric contraction of the long finger flexors.
This will be operationally defined as the time required to go from 90% of MVC to 5% of MVC averaged over three trials. In our randomized cross-over trials of mexiletine 150 mg three times daily and 200 mg three times daily, relaxation time from 90% to 5% of MVC was found to be the most sensitive measure of myotonia in terms of detecting a benefit of mexiletine. In the 18 subjects who completed the trial of 200 mg TID, the mean (± standard deviation) change (mexiletine – placebo) in this outcome was -1.34 ± 1.42 seconds. These data suggest that a sample size of 20 subjects per group will

provide 82% power to detect a group difference in mean response of -1.3 seconds in the proposed trial, using a t-test and a significance level of 5% (two-tailed).

Another important secondary outcome variable is the change from baseline to Month 6 in grip strength, averaged over the left and right hands. In our pilot randomized trial of troglitazone, grip strength data were available from 17 of the 20 randomized subjects at baseline and Month 8. The mean change averaged over both hands was -0.93 kg (reflecting mean changes of -1.32 kg in the left hand and -0.53 kg in the right hand) and the standard deviation of the changes was approximately 2.5 kg. Similar results were obtained at the Month 4 visit. These data suggest that a sample size of 20 subjects per group will provide 80% power to detect a group difference in mean response of 2.3 kg in the proposed trial, using a t-test and a significance level of 5% (two-tailed).

The sample size will be increased as necessary to achieve a final group of 20 DM1 patients in both the mexiletine and placebo treatment groups. We anticipate that there may be a 10% rate of subject withdrawal based upon our recently completed FDA funded, 7 week, double-blind crossover trial of mexiletine in DM1 [Appendix A].

E. HUMAN SUBJECTS

Monitoring and Human Subjects Protection

Risks to Human Subjects

1. Human Subject Involvement:
Ambulatory moderately affected DM1 patients between the ages of eighteen and eighty will be evaluated during this clinical trial. The inclusion/ exclusion criteria are listed in the patient selection section above.

Nonambulatory patients have been excluded because in our experience the majority of non-ambulatory patients have advanced weakness in the arms and legs, especially in the flexors of the fingers and the intrinsic hand muscles. Such severe weakness will prevent this group of patients from participating in the assessment of myotonia (grip myotonia testing, repeated rapid contraction and extension of the fingers). These patients are also unable to perform 6 minute walk testing which is the primary end point used to assess efficacy of treatment for this study.

2. Sources of Research Material:
The sources of our research material are the data collected from the history and physical examination of each patient, and from the results of 6 minute walk testing, myotonia testing, muscle testing, blood and urine specimen analyses. The material is solely for research purposes. Patients will be asked to give permission for investigators to examine existing medical records and to determine their eligibility.

All data forms will contain the initials of each study subject and their assigned study number.

3. Potential Risks:
The risk category of this study is greater than minimal.

Mexiletine is approved by the FDA as an alternative treatment for symptomatic ventricular arrhythmias. The dosage selected for use in this study is in the low therapeutic range. Toxic side effects of mexiletine occur with greater frequency at higher dosages required to control arrhythmias and neuropathic pain. [52-55] These dosages are typically two to three times higher than the dosages used in the present study. Patients taking these higher dosages of mexiletine (600-3200 mg/day) have a significantly increased incidence of upper gastrointestinal distress, 41%, lightheadedness and tremor, 12.5%.[72] These symptoms are dose related, generally not serious, and disappear after dose reduction or discontinuation of treatment. No patient in our study will receive a dose of mexiletine greater than 450 mg a day.

A recent study which included 9 patients with DM1 has demonstrated that the relatively low dosage of mexiletine proposed for use in the present study is effective and has greater efficacy than other commonly used antimyotonia drugs, such as, dilantin, disopyramide, and tocainide. [19] In addition, there were no severe side effects, worsening of heart block, or worsening of bundle branch block in our previous mexiletine crossover study of DM1 patients evaluating two low to moderate dosages [150 mg three times daily and 200 mg three times daily]. [22]

We anticipate that treatment with mexiletine will reduce or eliminate myotonia in our patients, and that they will experience few if any side effects at the dosage we have proposed.

There is a small risk of bruising from blood draws and muscle soreness from the quantitative myometry (QMT), manual muscle testing (MMT), maximum voluntary isometric contraction testing, and functional tests. Dual energy x-ray absorptiometry (DEXA) uses 0.5-1.0 mREM which is only a fraction of that used in a routine chest x-ray (20-30mREM) and is considered to pose to significant risk. There is minimal risk of transient discomfort from direct irritation to the nerve associated with the electrical stimulation during the repetitive stimulation test (measuring duration of myotonia).

Questionnaires, although we believe their content is benign, may produce mild emotional stress.

<u>Adequacy of Protection Against Risks</u>

1. Recruitment and Consent Procedures:
Patients will be recruited from the University of Rochester Neuromuscular Disease Center and from the list of patients who have received permission from their regular physicians to participate in our ongoing research studies of DM1. Both sexes will be recruited, as will members of all minorities. Interested potential subjects will be contacted by phone by the study coordinator and questioned about their health status.

Interested potential subjects who report no history of medical or psychiatric disease and a previous diagnosis of DM1 will be asked to come to the Clinical Research Center (CRC) for a screening visit. Women will be recruited only if they are using adequate birth control measures, or are postmenopausal, or have had a tubal ligation, or have had a hysterectomy.

When possible, subjects will be provided with a copy of the consent form for their review prior to the screening visit. Informed consent will be obtained by the principal investigator or study coordinator after details of the study and its requirements have been presented, and there has been an opportunity for the subject to ask questions. Consent will be obtained only after complete information has been provided to the participant about the purpose of the study, the procedures, risks, benefits, contact persons, compensation, and care for injury, and voluntary participation. The subject study personnel obtaining consent will sign the IRB approved consent form. The subject will receive a copy of the consent form after it has been signed. The original will be retained in the files of the investigator.

2. Procedures for Protecting Against or Minimizing Risks:
All subjects will be monitored closely by the CRC nursing staff and investigators during the procedures to prevent and minimize any potential risks or discomfort. The nursing staff and study personnel will receive in-service training regarding these procedures. Each participant will be asked to report any continuing discomfort caused by any of the performed procedures.

If a woman is pregnant, she will not continue in the study.

Safety data receive appropriate review by our DSMB and independent medical monitor and will be given to the data manager who will keep the records in a locked file cabinet and maintain their confidentiality. In all databases and reports, subjects will be identified by an ID number.

In addition to the assessments during each evaluation on the CRC adverse events will be monitored during telephone calls at about 2 week intervals. The laboratory studies will provide additional means to detect any evidence of major organ toxicity.

Patients will be withdrawn from the study if intolerable side effects or severe adverse events, as determined by the PI, are identified. Patients who cannot tolerate the medication or procedures, have surgery or other illnesses which affect the evaluations will have the drug discontinued. Patients may withdraw at any time. All withdrawals will be reported to the statistical center, DSMB, and safety monitor within 24 hours. Occurrence of a serious adverse event must be reported to the IRB and principal investigator, DSMB, and independent medical monitor within 24 hours.

<u>Costs and Reimbursement</u>

1. Costs to subjects
   There are no costs to the subjects for participating in this study.

2. Honorarium
   Subjects will receive an honorarium of $150 after completing the baseline, 3 month and 6 month follow-up visits (for a total of $450). A limited amount of travel money is also available.

Data and Safety Monitoring Plan

1. Reporting of adverse events

The study will comply with Food and Drug Administration (FDA) regulations requiring expedited reporting of any adverse events (AE) that are serious, unexpected and associated with the use of a study drug. All serious adverse events will be reported within 24 hours to the IRB, DSMB, Independent Medical Monitor, and FDA.

Adverse events must be recorded starting from the time of informed consent until the final study visit. Any medical condition present at the initial visit, which remains unchanged or improves, should not be recorded as an adverse event at subsequent visits. However, if there is **deterioration** of a medical condition that was present at the initial visit, this should be considered a **new** adverse event and reported. All adverse events (AEs), whether or not they are considered related to the study, shall be recorded on the Case Report Forms (CRFs).

Clinically significant changes (abnormalities), in the judgment of the investigator, in physical examination from the baseline exam will be recorded as an adverse event.

The following information must be collected and recorded for each AE:

- AE term (diagnosis)
- Start date of AE
- Stop date of AE
- Severity of AE (mild, moderate, or severe)
- Seriousness of AE (serious or non-serious)
- Action taken regarding study medication (none, study medication dose reduced, study medication interrupted, or study medication stopped);
- Action taken regarding AE (specific treatment instituted, subject hospitalized, etc.)
- AE outcome (resolved, ongoing, death, or lost to follow-up)
- AE causality (none, possible, probable)

Relationship to study drug:

The investigator, using the following explanations, will determine study drug relationship for each adverse event:

None

The event is clearly related to other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Possible

- The event follows a reasonable temporal sequence from the time of drug administration,
- And/or follows a known response pattern to the trial drug, but could have been produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.

Probable

- The event follows a reasonable temporal sequence from the time of drug administration,
- **And** follows a known response pattern to the study drug,
- **And** cannot be reasonably explained by other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject,
- **And** either occurs immediately following trial drug administration, **or** improves on stopping the drug, **or** reappears on repeat exposure, **or** there is a positive reaction at the application site.

Severity of an adverse event is defined as a qualitative assessment of the degree of intensity of an adverse event as is determined by the investigator or reported to him/her by the subject.

The assessment of severity is made irrespective of drug relationship or seriousness of the experience and should be evaluated according to the following scale:

1 = Mild– The adverse event is easily tolerated and does not interfere with daily activity.

2 = Moderate– The adverse event is not easily tolerated and interferes with daily activity.

3 = Severe– The adverse event is incapacitating and the subject is unable to function.

Adverse side effects will be monitored during each CRC visit (baseline, month 3, month 6) and during telephone calls at about 2 week intervals during the intervening weeks of the trial. The adverse effects of mexiletine observed most commonly include: dizziness, lightheadedness, nervousness, nausea, vomiting, or upset stomach, diarrhea,

constipation, trembling, shaking of hands, blurred vision, tiredness, or weakness. More serious side effects, which are less common include: irregular heart beat, chest pain, shortness of breath, trouble breathing, skin rash, severe itching, or hives.

The laboratory studies will provide additional evidence of any major organ toxicity. Patients will also receive a diary to record adverse events as they occur as well as a schedule to remind them to take the study medication.

The following definitions will be utilized:

> **An adverse event** is any untoward medical occurrence in a subject that occurs during the conduct of a clinical study of a pharmaceutical product that does not necessarily have a causal relationship to the study drug. This can, therefore, be any unfavorable 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.
>
> **A serious adverse event** (SAE) is defined as any adverse drug experience occurring at any dose that results in any of the following outcomes:
>
> - Results in death,
> - Is life-threatening (NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.),
> - Results in inpatient hospitalization or prolongation of existing hospitalization,
> - Results in a permanent disability,
> - Results in a congenital anomaly/birth defect,
> - A new malignancy,
> - Overdose, suspected or confirmed.
>
> Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, the event may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

2. Study Conduct

The study will be conducted according to the protocol, Good Clinical Practice (as outlined in the ICH Guidelines and Code of Federal Regulations), and the Declaration of Helsinki. Written informed consent for the study must be obtained from all subjects prior to protocol specific procedures being performed. Subjects must be informed of their right to withdraw from the study at any time.

3. Study Oversight

The principal investigator has primary oversight responsibility for this trial. The PI will meet with the study coordinator, as well as any other necessary members of the research team as needed. The meetings will include reviews of safety data, protocol deviations, adverse events, subject compliance, test article accountability and inventory, logs for screening, enrollment, and subject withdrawal, as well as any other pertinent issues identified by the PI, study coordinator, or other research team member.

4. Data Safety Monitoring Board

Working under the direct guidance of the FDA, a qualified data safety monitoring board (DSMB) has been established. Written procedures for monitoring of the clinical trial to assure the quality of the study and to assure that each person involved in the monitoring process carries out their duties will be set to comply with FDA regulations. These monitoring procedures will be included in a Manual of Operations for the study.

5. Interim Analyses for Safety and Efficacy

Interim analyses of safety data will be performed periodically throughout the project. While the safety of subjects will be the primary concern of the data safety monitoring board (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 hospitalizations, will need to be carefully considered by the DSMB in terms of treatment group imbalances. It is helpful to emphasize that our previous double-blind, randomized crossover trial of 20 DM1 patients treated with 150 mg three times daily of mexiletine for 7 weeks was completed without any significant adverse events; and, that a subsequent second double-blind, randomized crossover trial of 20 DM1 patients treated with 200 mg three times daily of mexiletine for 7 weeks was also completed without any significant adverse events. We do not anticipate encountering any expected side effect that based upon our advanced knowledge of mexiletine will constitute a reason to stop the study or specifically stop a given patient's participation. Severe confounding medical illness or severe trauma are reasons noted previously in this application for discontinuing patient participation. We perform serial laboratory studies throughout the course of the treatment trial. If the DSMB observes trends in all patients that suggest that a given value(s) is rising or falling 2-3 fold outside the normal range and is not known to occur in the usual clinical course of DM1, this finding will prompt a discussion of the need to stop the study. The same actions will occur if a serious medical illness develops in a significant portion of the DM1 patients receiving mexiletine which is not typically observed in the usual clinical course of a DM1 patient.

In addition, we will perform an interim analysis of the primary outcome variable after 50% of the trial participants (20 participants) have completed 6 months of follow-up. We will use an O'Brien-Fleming stopping boundary whereby the interim analysis will be performed using a significance level of 0.003 and the final analysis will be performed

using a significance level of 0.049 (two-tailed). This will ensure that the overall probability of a Type I error is controlled at 0.05.

6. Independent Medical Monitor

The independent Medical Monitor (Dr. [REDACTED]) will be responsible for monitoring the conduct and progress of the study as well as evaluating clinical situations and communicating new safety information to the PI and the FDA. The independent Medical Monitor will review aggregate data (adverse events and safety labs) and ascertain whether adverse events are thought to be occurring more frequently than expected. If they are, they will be reported by memo to the PI and the DSMB. The independent Medical Monitor will review the SAE notification form to determine if the event is unexpected and associated with the use of study medication. The site may be called to provide further information, if necessary. The progress of each SAE will be followed by the independent Medical Monitor until resolution or until an appropriate endpoint is reached (resolution or determination of the event to be chronic and/or stabilized).

7. Adverse Event Monitoring

The PI will review data regarding adverse events and laboratory abnormalities in a blinded fashion. An independent medical monitor will receive and review reports of all adverse events. The independent DSMB can review unblinded data as necessary. In the rare event that an investigator needs immediate knowledge of the subject's treatment assignment for emergent care of the subject, individual treatment assignment envelopes generated by the Biostatistics Center will be available.

8. Data Management

The original Case Report Forms (CRFs) for each visit will be sent to the Neuromuscular Disease Data Center (NMD-CC), with a duplicate copy stored in the subject's research chart. All original and duplicate CRFs will be kept under double lock by the Data Manager at the NMD-CC. Completed CRFs will be entered into a SAS database on the Neurology file server. Access to study subject CRFs and Statistical Analysis Software (SAS) database will be limited to study personnel. For each CRF, custom data entry screens will be developed with error checking built in using SAS/FSP software by the Study Data Manager. SAS/FSP software provides convenient interactive capabilities for data entry, editing, and retrieval.

To minimize data entry errors Screen Control Language (SCL) will be developed to edit individual fields and perform cross-field validation. When SCL detects an invalid data value, entry is suspended. An appropriate error message is displayed, prompting the data entry clerk to resolve the discrepancy before entry can be completed. Batch SAS programs will also check for inconsistencies and incompleteness of data after initial entry. The Data Manager will develop edit check programs, and these programs will generate output that describes data discrepancies found in the database. All CRFs are

reviewed for clarity and completeness. In addition, all output generated by the edit check program will be reviewed by a Data Manager. Data discrepancies identified through edit check programs, manual review of CRFs, or clinical reviews will generate queries which will be e-mailed to the investigator/coordinator on a Data Clarification Form (DCF). The DCF will identify the subject, visit number, CRF number, and the data element flagged for review. The study coordinator will investigate the discrepancy. The DCF must be completed showing what corrections need to be made (or indicating why no changes are necessary) and signed by the site investigator or coordinator, then faxed back to the NMD-CC. Data entry staff at the NMD-CC will enter the response to the DCF into the database and the data manager will verify that they have been entered correctly. The original DCF will be filed by the study coordinator with the corresponding CRF source documents.

All DCFs should be returned to the NMD-C within two weeks after the DCF was sent to the investigator/coordinator. All completed CRFs should be sent to the NMD-CC with two weeks after each study visit. Any CRF or DCF that is not received within the two weeks will generate request to the coordinator with a copy to the investigator.
NMD-CC Data Manager will perform a final quality audit of a random sample of 5 patients at the end of the study. All CRFs from the random sample of patients will be 100% verified against the database. If the error rate is less than or equal to 0.1% (an accuracy rate of at least 99.9%) and the errors encountered are not significant, NMD-CC will correct the errors and finalize the database. If the error rate is greater than 0.1% or if the errors encountered are significant (i.e. an adverse event was not entered), a rework of these sections of the database will be performed, and these sections will be re-audited on another 5 patient random sample.

Upon completion of the study, the cleaned databases are locked and send to the study biostatistician for final analysis.

9. Risk/Benefit Assessment

We believe that the relatively mild side effects and risks of treatment associated with mexiletine in patients with DM1 will be heavily outweighed by the likely improvement in their muscle function resulting from this treatment. If our results lead to a new approved indication for the use of mexiletine as an antimyotonia therapy, this finding will have a wide beneficial effect for all patients with DM1.

Inclusion of Women and Minorities

Myotonic dystrophy (DM-1) has a prevalence rate of approximately 1 per 7,500. We anticipate that our study population will have no gender differences, but there may be a relative predominance of certain ethnic backgrounds. The prevalence rates of DM1 in major ethnic populations have not been established within the United States, but DM1 prevalence rates in Africa are much lower than those in Europe and the United States.[23,24] The demographics of myotonic dystrophy in Monroe County are not known. However, the latest demographics of Monroe County (White 80.8%, Black 14.7%, Hispanic 5.7%, Asian 2.8%, Native American 0.3%) indicate that our area contains

minority populations similar to the national distribution (http://quickfacts.census.gov/qfd/index.html; accessed on 2/2/2009). We have based our recruitment projections to reflect the demographics of Monroe County which closely parallel those of the general U.S. population. We will send information describing this study to the local and national offices of the Muscular Dystrophy Association as well as the NIH. It is our hope that this will increase the diversity of the patients enrolled in our clinical trial. Based on the above information, we expect the ethnic distribution of enrollment to be as indicated in the Table 3.

Targeted/Planned Enrollment

TABLE 3:

Targeted/Planned Enrollment Table

Study Title: A Randomized, Placebo Controlled, Clinical Efficacy Trial of Mexiletine for Myotonic Dystrophy Type-1 (DM1).

Total Planned Enrollment: 60 myotonic dystrophy patients

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	2	2	4
Not Hispanic or Latino	28	28	56
Ethnic Category: Total of All Subjects *	30	30	60
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	4	4	8
White	24	25	49
Racial Categories: Total of All Subjects *	30	30	60

Goldman, A., Ramsay, M., and Jenkins, T. "New founder haplotypes at the myotonic dystrophy locus in Southern Africa". Am.J.Hum.Genet. 56:1373-1378, 1995.

Inclusion of Children

Children have not been included for several reasons. Patients with a history of congenital DM1 have been excluded because they have a different natural history from the adult onset form of this disease.

These patients if they survive the neonatal period often have significant intellectual impairment as well as difficulty with hypotonia and muscle weakness, respiratory and gastrointestinal dysfunction. These symptoms gradually lessen in severity throughout childhood and the patients may slowly regain close to normal muscle function during their early teens. After a few years these patients gradually develop manifestations typical for classical myotonic dystrophy of Steinert. The extent to which residual manifestations of congenital-childhood onset DM1contributes to differences in the clinical course in adult life is unknown and poses difficulty in interpreting the response to treatments compared to individuals who clearly have an onset in adult life. The majority of children with DM have had onset very early in childhood or in infancy and have clinical features associated with congenital DM. Myotonia is often not apparent or prominent in childhood myotonic dystrophy. [23,24] The typical onset for DM1 occurs in the late teens, early twenties, or later in life. Because of the very small number of DM1 children with myotonia, because of differences in the natural history of DM1 with early childhood onset, and because the safety and effectiveness of mexiletine in the paediatric population have not been established, we have excluded children from present investigation.

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