

Study title;

***Combining N-of-1 trials to estimate population clinical effectiveness
of drugs using Bayesian hierarchical modeling;
The case of Mexiletine for patients with Non-Dystrophic Myotonia.***

(June 2011, version 2)

Protocol ID	mexiletine201011
Short title	Mexiletine vs. placebo in NDMs
Version	2
Date	03-06-2011
Coordinating investigator/project leader	<p>Dr. G. Drost (Neurologist/ Clinical neurophysiologist) tel: 024-3613450 E-mail: G.Drost@neuro.umcn.nl</p>
Principal investigators	<p>Dr. G. Drost (Neurologist/ Clinical neurophysiologist)</p> <p>Prof. G.J. van der Wilt (Professor Department of Epidemiology, Biostatistics and HTA) Tel: 024-3610383 E-mail: G.vanderWilt@ebh.umcn.nl</p> <p>MSc. B.C. Stunnenberg (Medical Biologist/ PhD-student Neurology/ HTA) Tel: 024-3615285 E-mail: B.Stunnenberg@neuro.umcn.nl</p>
Sponsor	The Netherlands Organisation for Health Research and Development (ZonMw)
Independent physician(s)	<p>Dr. F.E. de Leeuw (Neurologist/ Clinical epidemiologist) Tel:024-3668374 E-mail: H.deLeeuw@neuro.umcn.nl</p>
Pharmacy	<p>Department of Clinical Pharmacy Postbus 9101 6500 HB Nijmegen. Tel: 024-3617613/ Fax: 024-3668755</p>

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Head of Department: Prof. G.J. van der Wilt (Professor Department of Epidemiology, Biostatistics and HTA)		
Coordinating Investigator/Project leader/Principal Investigator: Dr. G. Drost (Neurologist/ Clinical neurophysiologist)		
Phd student: MSc. B.C. Stunnenberg (Medical Biologist)		

TABLE OF CONTENTS

1. INTRODUCTION AND RATIONALE	8
2. OBJECTIVES	10
3. STUDY DESIGN	12
4. STUDY POPULATION	18
4.1 Population (base)	18
4.2 Inclusion criteria.....	17
4.3 Exclusion criteria	18
4.4 Sample size calculation	19
5. TREATMENT OF SUBJECTS	22
5.1 Investigational product/treatment.....	22
5.2 Use of co-intervention (if applicable)	22
5.3 Escape medication (if applicable).....	22
6. INVESTIGATIONAL MEDICINAL PRODUCT.....	24
6.1 Name and description of investigational medicinal product(s)	24
6.2 Summary of findings from non-clinical studies.....	24
6.3 Summary of findings from clinical studies.....	25
6.4 Summary of known and potential risks and benefits	28
6.5 Description and justification of route of administration and dosage.....	30
6.6 Dosages, dosage modifications and method of administration	30
6.7 Preparation and labelling of Investigational Medicinal Product	30
6.8 Drug accountability.....	30
7. METHODS	31
7.1 Study parameters/endpoints.....	31
7.1.1 Main study parameter/endpoint	31
7.1.2 Secondary study parameters/endpoints (if applicable)	31
7.1.3 Other study parameters (if applicable).....	31
7.2 Randomisation, blinding and treatment allocation	31
7.3 Study procedures	31
7.4 Withdrawal of individual subjects.....	35
7.4.1 Specific criteria for withdrawal (if applicable)	35
7.5 Replacement of individual subjects after withdrawal.....	35
7.6 Follow-up of subjects withdrawn from treatment.....	35
7.7 Premature termination of the study.....	35
8. SAFETY REPORTING	36
8.1 Section 10 WMO event	36

8.2	Adverse and serious adverse events.....	36
8.2.1	Suspected unexpected serious adverse reactions (SUSAR).....	37
8.2.2	Annual safety report.....	38
8.3	Follow-up of adverse events.....	38
8.4	Data Safety Monitoring Board (DSMB).....	38
9.	STATISTICAL ANALYSIS.....	40
9.1	Multivariate analysis.....	40
9.2	Interim analysis (if applicable).....	40
10.	ETHICAL CONSIDERATIONS.....	43
10.1	Regulation statement.....	43
10.2	Recruitment and consent.....	44
10.3	Objection by minors or incapacitated subjects (if applicable).....	47
10.4	Benefits and risks assessment, group relatedness.....	47
10.5	Compensation for injury.....	48
10.6	Incentives (if applicable).....	48
11.	ADMINISTRATIVE ASPECTS AND PUBLICATION.....	49
11.1	Handling and storage of data and documents.....	49
11.2	Amendments.....	49
11.3	Annual progress report.....	50
11.4	End of study report.....	50
11.5	Public disclosure and publication policy.....	50
12.	REFERENCES.....	51

LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
DSMB	Data Safety Monitoring Board
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC	Informed Consent
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
(S)AE	(Serious) Adverse Event
SPC	Summary of Product Characteristics (in Dutch: officiële productinformatie IB1-tekst)
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgegevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen)

SUMMARY

Rationale: A current problem in the context of a coverage decision for the use of mexiletine for NDM patients is the lack of a sufficient evidence base. An innovative trial design could facilitate in establishing such an evidence base in a small group of rather heterogeneous patients. As more than 7000 rare diseases in Europe and the USA suffer from a similar lack of treatment evidence, more experience with this innovative trial design would be very helpful.

Objective: To further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient basis for coverage decisions on drugs for rare diseases. The previously mentioned will be tested in combined N-of-1 trials using mexiletine vs. placebo in patients with non-dystrophic myotonic syndromes (NDMs). The secondary objective of this proposal is to assess whether mexiletine improves myotonia measured (both quantitatively and qualitative) in non-dystrophic myotonia (NDM) patients.

Study design: A double-blind, randomized and placebo-controlled combined N-of-1- trial using a Bayesian statistical approach.

Study population: Non-dystrophic myotonia (NDM) patients, at least 18 years old, with a genetically confirmed diagnosis.

Intervention (if applicable): Each N-of-1 trial consists out of a minimum of one, and a maximum of 4 treatment sets, each comprising a 4-week period of active treatment (Mexiletine) and a 4-week period of treatment with placebo, in random order, with one week for wash-out in between. Within each mexiletine period, treatment dosage of mexiletine will be built up from 200 mg 1 time a day PO on the first day of the first week, to 200 mg 2 times a day on the second day of the first week, to the desired dosage of 200 mg 3 times a day PO on the third day of the first week and throughout the remaining days of the 4-week treatment period. A similar build-up scheme will be used within each placebo period.

Main study parameters/endpoints:

The primary outcome measure for this study is a decrease in the most prominent clinical symptom: stiffness. Stiffness will be quantified by an Interactive Voice Response System (IVR) in which the patient will rate their mean daily IVR participant-assessed severity of stiffness on an ordinal scale (1-9). The secondary outcome measures will include changes in pain, weakness, and fatigue on IVR, Individual Neuromuscular Quality of Life (INQoL), SF-36 (adults), blood plasma levels of mexiletine, clinical myotonia assessments, quantitative handgrip myotonia, biceps force test and needle EMG.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: In the screening phase, ECG and EMG recordings, laboratory values and baseline blood plasma levels of mexiletine will be tested. Medical history and written

consent will also be obtained in this phase. Patients will be asked to visit the department of Neurology between 4-16 visits (depending on number of treatment sets necessary to obtain enough evidence) during the study enrolment. Each visit will approximately cost 2 hours; within each visit two questionnaires (INQoL, SF-36) need to be filled, blood plasma levels of mexiletine will be measured and clinical and electrophysiological myotonia tests need to be performed. Furthermore, an ECG and EMG will be recorded at the end of each treatment or placebo period. In addition, patients will have to call in to an interactive voice response system to report their mean daily IVR participant-assessed severity of stiffness once a week in every first and second week and daily in every third and fourth week of each treatment or placebo period.

This study is best performed in patients with NDM, because of (1) the genetically characterized population of patients with skeletal sodium or chloride channel mutations, (2) the pathophysiological knowledge on the working mechanism of mexiletine on the skeletal sodium channel, and (3) the need for an evidence-base for NDMs.

1. INTRODUCTION AND RATIONALE

Non-dystrophic myotonic syndromes are a heterogeneous group of rare diseases caused by mutations in genes encoding skeletal muscle ion channels. The key symptom is myotonia, a delayed relaxation after voluntary contraction.¹ Despite the general notion that NDMs are benign diseases, symptoms do cause lifetime morbidity and a recent study demonstrated that the symptoms of these patients do greatly impact their self-reported health status.² In our recent Cochrane review, we concluded that there is insufficient evidence of effectiveness and safety of drug treatment in myotonic syndromes.³

Based on this review, the Healthcare Insurance Board (CVZ) decided to discontinue coverage of drugs for NDM patients. However, absence of evidence of effectiveness should not be confused with evidence of absence of effectiveness, and this decision might deprive NDM patients of substantial benefits. Indeed, CVZ has acknowledged that in the case of rare diseases, it is unreasonable to demand level 1 evidence (CVZ report 2007). As more than 7000 rare diseases in Europe and the USA suffer from this lack of treatment evidence, an innovative trial design is urgently needed.

The objective of our project is to provide an evidence base for mexiletine in NDM patients, and to further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient basis for coverage decisions on drugs for rare diseases. As reported in our Cochrane review, there is no level 1 evidence of classic RCTs available for treatment of myotonia in NDMs.³ However, evidence from single case reports and expert opinion point towards the class I antiarrhythmic agents with mexiletine as the (off-label) drug of choice in patients with NDMs.⁴ Drug efficacy of mexiletine will be tested in our study on NDM patients.

2. OBJECTIVES

Primary Objective: The objective of this project is to further refine N-of-1 trial methodology, and explore whether Bayesian analysis of multiple N-of-1 trials can serve as a sufficient basis for coverage decisions on drugs for rare diseases.

The previously mentioned will be tested in combined N-of-1 trials using mexiletine vs. placebo in NDM patients. The secondary objective of this proposal is to assess whether mexiletine improves myotonia measured (both quantitatively and qualitative) in patients with non-dystrophic myotonia.

3. STUDY DESIGN

Study design: Bayesian hierarchical approach of N of 1 trials

N-of-1 trials have initially been developed to optimize individual patient management. More recently, results of multiple N-of-1 trials have been used to produce an evidence base for drug effectiveness at group level, using Bayesian hierarchical modeling.^{5,6} Bayesian methodology is highly appropriate for this, since the Bayesian concepts of 'borrowing strength' and 'shrinkage' (see e.g. Zucker et al. (1997)⁵, Spiegelhalter (2004)⁷) seem very appropriate for combining the N-of-1 trials while still respecting their heterogeneity and individuality. Moreover, it allows for an estimate of the probability that wrong inferences are made on the basis of available data (e.g., concluding that a drug is effective, whereas in reality it is not, or vice versa). For this, we will test robustness of the method, by comparing results when using noninformative or informative priors. Furthermore we will compare the results of our study with the results of the worldwide multi-center trial 'Phase II therapeutic trial of mexiletine in Non-Dystrophic myotonia' of the consortium of Clinical Investigation of Neurological Channelopathies (CINCH) with dr. Robert Griggs (University of Rochester) and dr. Richard Barohn (University of Kansas Medical Center) as the principal investigators. NDM provides an excellent model, since prior probability estimates can be based on the detailed knowledge of the pathophysiology of the disease and mechanism of action of the various drugs

Each N-of-1 trial consists of a minimum of one, and a maximum of 4 treatment sets, each comprising a 4-week period of active treatment (Mexiletine) and a 4-week period of treatment with placebo, in random order, with one week for wash-out in between (see Figure 1). Total study enrolment will be maximally 44 weeks per patient and minimally 11 weeks. Patients will be enrolled in two cohorts, each consisting of ten patients. Patients in one cohort will be treated and followed up in parallel. Thus, all N-of-1 trials can be conducted within 88 weeks.

After completion of the N-of-1 trial, patients will be followed up for 3 months, to monitor clinical progression, drug compliance and any adverse events (in case of active treatment), and quality of life. At the start of the first set the patient will receive a blinded, randomly-ordered treatment kit that holds medication for the entire set. This treatment kit will be prepared by the department of pharmacy of our hospital. A programmer in the department of HTA statistics will perform computer-generated randomization, and the resulting randomization plans will be sent to the pharmacy where drug packaging and labelling will take place. In each set, patients will receive 4-week treatment with Mexiletine, 200 mg 1 times a day PO (day 1, week 1), 200 mg 2 times a day PO (day 2, week 1) and 200 mg 3 times a day

PO (remaining days of week 1, week 2, week 3 and week 4), or Placebo in a similar build-up scheme with placebo tablets PO.

An initial screening visit will be performed 1-4 weeks prior to start of the study. Allowing for up to 4 weeks will allow the participant to schedule all visits at the time of the screening visit. For participants currently taking antiarrhythmics or medication that may affect sodium channels, a wash-out period will be required before the baseline visit. If the patient is currently on phenytoin or flecainide acetate for myotonia the wash-out period must be at least 5 days. If they are currently on mexiletine or carbamazepine for myotonia the wash-out period must be at least 3 days. If the patient is on propafenone, procainamide, disopyramide, quinidine or encainide for myotonia the wash-out period must be at least 2 days.

The primary outcome measure will be changes in stiffness as measured by the Interactive Voice Response Diary (IVR), and secondary outcome measures will include changes in pain, weakness, and fatigue on IVR, clinical myotonia assessment, quantitative grip myotonia, INQoL, SF-36 (adults), biceps force test and needle EMG.

Schedule of Assessments:

Initial screening will occur at 1-2 weeks prior to baseline visit and will include consent forms, medical history, SMA7 (blood urea nitrogen, serum chloride, carbon dioxide, creatinine, blood glucose, serum potassium, serum sodium), ECG and EMG recordings, and urine pregnancy testing for females. Serum pregnancy testing can be performed if, in the opinion of the investigator, the urine pregnancy test is inconclusive. Prior use of phenytoin, carbamazepine or mexiletine will be documented. This documentation will include dosage, duration and date of last use.

Patients will be asked to visit the department of Neurology between 4-16 visits (depending on number of treatment sets necessary to obtain enough evidence) during the study enrolment (see table 1). Each visit will approximately cost 2 hours; within each visit two questionnaires need to be filled, clinical and electrophysiological myotonia test need to be performed and venous blood collection will take place for measurement of mexiletine blood plasma levels. A needle-EMG will be recorded at the end of each treatment or placebo period to monitor the size and frequency of myotonic discharges that can be evoked from the muscle. An ECG will be recorded at the end of each treatment or placebo period to monitor possible ECG-changes in PR-, QRS- and QTc-interval. After ECG's are performed they will be sent by fax to an independent cardiologist. The cardiologist will read and interpret each. The cardiologist will document the findings and any abnormalities at screening. Furthermore, the cardiologist will compare follow-up ECG's (Weeks 4, 9, 15, 20, 26, 31, 37 and 42) to the screening ECG (week 0) and any abnormalities will be noted. These findings will then be sent to the DSMB-

board and principal investigators. The cardiac adverse events will be reported to the METC by using ToetsingOnline.

In addition, patients will have to call in to a interactive voice response (IVR) system to report their daily self-assessed stiffness measure. The IVR diary will be completed on a weekly basis during the first two weeks in every treatment period and on a daily basis during the last two weeks of every treatment period. Participants will be encouraged to call into the IVR system immediately after taking their first dose in the morning. During the week (Monday through Friday) the study coordinators will need to check the database to evaluate if the participant is calling into the IVR diary. If not, the participant will automatically receive a sms-text message to encourage them to call into the IVR system. The primary endpoint is the mean stiffness measure of daily calls during weeks 3, 4, 8, 9, 14, 15, 19, 20, 25, 26, 30, 31, 36, 37, 41 and 42. The data collected from the remaining will be used as a secondary outcome measure. On the last visit, the participant will be asked to fill out and mail in a questionnaire on their experience with the IVR system.

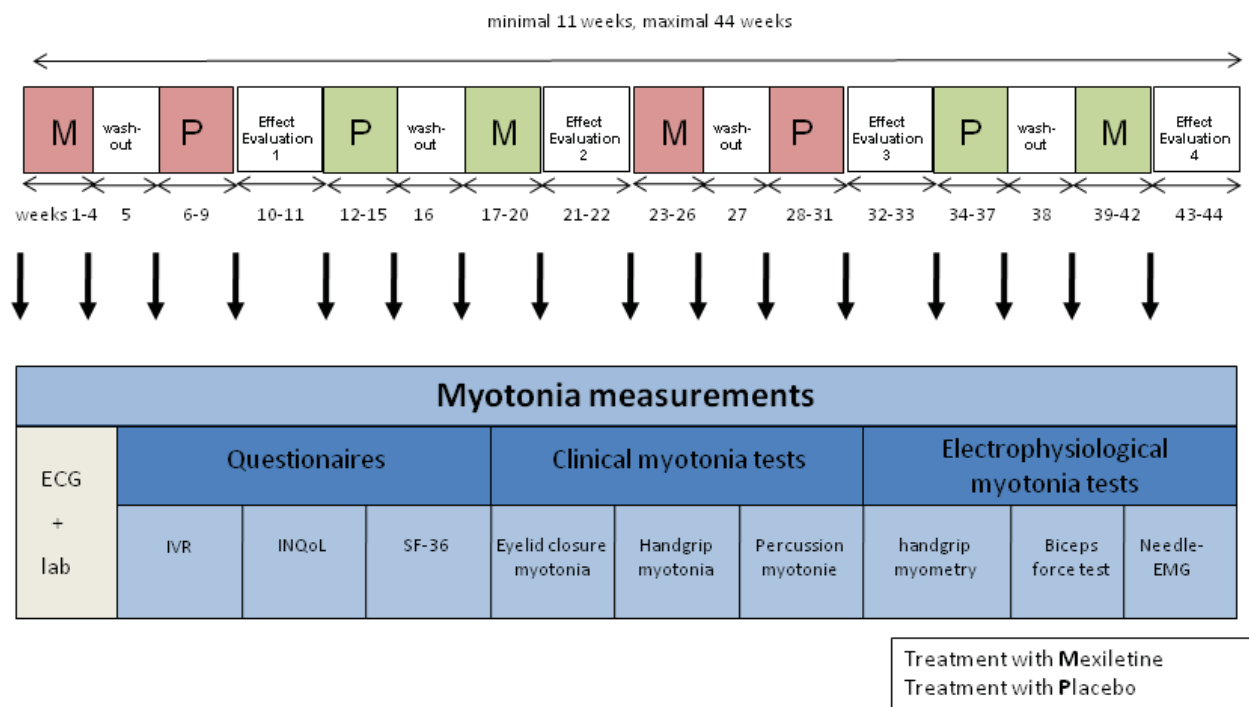


Figure 1: study design

Actions	Screening	Mexiletine or placebo (treatment set 1) (period 1)				Wash-out and cross-over	Mexiletine or placebo (treatment set 1) (period 2)				Effect evaluation 1		Mexiletine or placebo (treatment set 2) (period 3)				Wash-out and cross-over
		Week 1, day 1	Week 2, day 1	Week 3, day 1	Week 4, day 7	Week 5	Week 6, day 1	Week 7, day 1	Week 8, day 1	Week 9, day 7	Week 10	Week 11	Week 12, day 1	Week 13, day 1	Week 14, day 1	Week 15, day 7	Week 16
Lab test	X																
Pregnancy test	X																
Consent	X																
Medical history	X																
ECG	X				X				X						X		
Needle EMG	X				X				X						X		
IVR		X	X	X*	X*		X	X	X*	X*		X	X	X*	X*		
INQoL/SF-36		X			X		X		X			X			X		
Clinical myotonia tests		X			X		X		X			X			X		
Quantative grip myotonia		X			X		X		X			X			X		
Biceps force test		X			X		X		X			X			X		
Mexiletine blood plasma levels		X			X		X		X			X			X		
Dispense drug/placebo		X					X					X					
Collect medication bottles					X				X						X		

Actions	Mexiletine or placebo (treatment set 2) (period 4)				Effect evaluation 2		Mexiletine or placebo (treatment set 3) (period 5)				Wash-out and cross-over	Mexiletine or placebo (treatment set 3) (period 6)				Effect evaluation 3	
	Week 17, day 1	Week 18, day 1	Week 19, day 1	Week 20, day 7	Week 21	Week 22	Week 23, day 1	Week 24, day 1	Week 25, day 1	Week 26, day 7	Week 27	Week 28, day 1	Week 29, day 1	Week 30, day 1	Week 31, day 7	Week 32	week 33
ECG				X						X				X			
Needle EMG				X						X				X			
IVR	X	X	X*	X*			X	X	X*	X*		X	X	X*	X*		
INQoL/SF-36	X			X			X			X		X			X		
Clinical myotonia tests	X			X			X			X		X			X		
Quantative grip myotonia	X			X			X			X		X			X		
Biceps force test	X			X			X			X		X			X		
Mexiletine blood plasma levels	X			X			X			X		X			X		
Dispense drug/placebo	X						X					X					
Collect medication bottles				X						X				X			

Actions	Mexiletine or placebo (treatment set 4) (period 7)				Wash-out and cross-over	Mexiletine or placebo (treatment set 4) (period 8)				Effect evaluation 4	
	Week 34, day 1	Week 35, day 1	Week 36, day 1	Week 37, day 7	Week 38	Week 39, day 1	Week 40, day 1	Week 41, day 1	Week 42, day 7	Week 43	Week 44
ECG				X					X		
Needle EMG				X					X		
IVR	X	X	X*	X*		X	X	X*	X*		
INQoL/SF-36	X			X		X			X		
Clinical myotonia tests	X			X		X			X		
Quantative grip myotonia	X			X		X			X		
Biceps force test	X			X		X			X		
Mexiletine blood plasma levels	X			X		X			X		
Dispense drug/placebo	X					X					
Collect medication bottles				X					X		

X*= daily collection of IVR data

Table 1: Schedule of trial assessments

4. STUDY POPULATION

4.1 Population (base)

As a center of reference for this disease, we have access to the majority of NDM patients in the Netherlands, all registered in our database. This enables us to quickly and easily recruit the requisite number of patients.

NDM is caused by mutations in the skeletal sodium channel (sodium channelopathies; NaCh) or skeletal chloride channel (chloride channelopathies; ClCh). Unlike ClCh, NaCh display a broad spectrum of clinical phenotypes, with paramyotonia congenita (PMC) and sodium channel myotonia (SCM) as the two most common phenotypes within the spectrum of NaCh. The ClCh can be subdivided into two phenotypes as well, namely Becker's myotonia congenita (BMC) and Thomson's myotonia congenita (TMC).

4.2 Inclusion criteria

1. At least 18 years of age
2. Genetically confirmed diagnosis of NDMs
3. Participation in the "Genetical variability of the Non-dystrophic Myotonia" study of J. Trip or a new patient with genetically confirmed NDM.

4.3 Exclusion criteria

1. Inability or unwillingness to provide informed consent.
2. Other neurological conditions that might affect the assessment of the study measurements.
3. Genetic confirmed DM1 (CTG > 50 repeats), or DM2.
4. Patients with existing cardiac conduction defects, evidenced on ECG including but not limited to the following conditions: malignant arrhythmia or cardiac conduction disturbances (such as second degree AV block, third degree AV block, or prolonged QT interval >500 ms or QRS duration > 150 msec).
5. Current use of the following antiarrhythmic medication for a cardiac disorder: lecainide acetate, encainide, disopyramide, procainamide, quinidine, propafenone or mexiletine.
6. Women who are pregnant or lactating.
7. Patients currently on medications for myotonia such as phenytoin and flecainide acetate within 5 days of enrollment, carbamazepine and mexiletine within 3 days of enrollment, or propafenone, procainamide, disopyramide, quinidine and encainide within 2 days of enrollment.

8. Patients with renal or hepatic disease, heart failure, history of myocardial infarction, or seizure disorders.

4.4 Sample size calculation

The IVR measure for stiffness is our primary endpoint. As this measure is not commonly used in clinical practice (in fact, we use it here in order to be able to compare the results of our study to those of the worldwide multi-center trial 'Phase II therapeutic trial of mexiletine in Non-Dystrophic myotonia' of the consortium of Clinical Investigation of Neurological Channelopathies (CINCH)), it is difficult to find guidance with respect to what would constitute a clinically meaningful difference. However, the IVR measures stiffness on a 9-points scale, and from the statistician of the international study we know that they obtained a mean IVR score of 4.62 on placebo. Therefore we think that 0.75 would be a clinically relevant mean difference (this would correspond to an effect size of 0.34). Like in the international study, IVR measurements will be taken daily during the last 2 weeks of each 4 week treatment period,^{8,9} and we assume that we will get an average of 10 IVR measurements during the last 2 weeks of every treatment period.

The data will be analyzed using a hierarchical Bayesian model (as in Zucker et al. (1997))⁵, also see section 9.1. However, at the moment no formula-based methodology exists to determine the number of N-of-1 trials that should be conducted and the number of treatment pairs that should be offered within each trial when such a procedure is used. Therefore we have done simulations to provide estimations of our model's performance in a combined N-of-1 trial.

We have performed a simulation-based sample size calculation using a procedure as described in Wang and Gelfand (2002)¹⁰, and based on the model structure that is outlined in the appendix of Zucker et al. (2006) (also see section 9.1). That is to say, as in Wang and Gelfand (2002), for every sample size calculation (we did more than one, see below) we have performed the following five steps a thousand times. (1) A thousand times a random realization was drawn from the prior distribution for the mean treatment effect (i.e., for the mean of the random slope, see below) that was elicited from one of the treating physicians (see section 9.2). (2) For each of these realizations, we have simulated data for 30 N-of-1 trials using R software, where the data for each N-of-1 trial consists of 2x10x2 or 2x10x3 simulated observations (for 2 treatment arms, 10 observations per arm per treatment pair, and for either 2 or 3 completed treatment pairs (see below for the reason)). These simulations were performed using the model structure from Zucker et al. (2006), i.e. with a random intercept and a random slope for different individuals and a residual within-person

error. More details about how simulations were performed can be found below. (3) Each simulated data set of 30 N-of-1 trials was analyzed using the model from Zucker et al. (2006). We ran the required Bayesian analyses in R by using the R package R2WinBUGS. We have combined each of the simulated data sets with the prior distribution ($N(1.75, 0.89)$, see section 9.2) that was elicited from one of the treating physicians. (4) Each of these Bayesian analyses resulted in a (marginal) posterior distribution for the mean treatment effect β_0 . (5) For each of these posterior distributions we determined the posterior probability of a substantial treatment effect (i.e. $P_{\text{post}}(\beta_0 > 0.75)$) as in the fourth performance criterion from Wang and Gelfand (2002).

As mentioned before, for the simulations in step 2 we have used the model structure from Zucker et al. (2006). For the required parameter values we used estimates that we obtained directly from the statistician of the international mexiletine trial that he obtained while fitting (using standard frequentist methods) the same model structure to their data: a model structure with a random intercept and a random slope and a (common) residual within person error. Thus we obtained the following parameter estimates: 4.62 for the overall placebo IVR average (the mean of the random intercept α_0)¹; 2.19 for the corresponding standard deviation τ_α ; 1.77 for the standard deviation of the random slope τ_β ; and 0.827 for the standard deviation of the residual, within person error. We did not use the estimate for the mean of the random slope β_0 from the international study, instead we used the drawings from the (elicited) prior distribution for this variable in step 1 (as in Wang en Gelfand (2002)). Simulated observations smaller than 1 and larger than 9 were truncated to 1 and 9, respectively. This model structure does not exactly match the statistical model from section 9.1 since here we ignore the fixed effects. The reason for this is that the estimates we obtained from the international study did not distinguish between the channelopathy subgroups or centers (of course their centers would also have been irrelevant to ours). We think that this is not a big problem since taking into account the fixed effects would probably only have reduced the variance components that we have used here, and thus improved our model performance.

After having performed the above procedures 1000 times, this resulted in 1000 posterior probabilities of a substantial treatment effect. From these 1000 probabilities we have determined the mean, which corresponds to an estimate of the expected (with respect to the prior distribution that was drawn from in step (1)) posterior probability of a substantial treatment effect (as in the 4th performance criterion from Wang and Gelfand (2002)).

¹ Here we use the notation from the appendix of Zucker et al. (2006).

We would also like to have a sufficiently large expected posterior probability of a substantial treatment effect in case we use a non-informative prior in our analysis instead of the elicited prior for the mean treatment effect. Therefore, we repeated the above calculations after replacing the $N(1.75, 0.89)$ prior in step (3) with a $N(1.75, 10)$ vague prior (see section 9), while leaving the sampling prior from step (1) unchanged. (Wang and Gelfand (2002) distinguish between a *design prior* as used in our step (1) and an *analysis prior* as used in our step (3). These two priors do not have to be the same.)

As mentioned above, we performed simulations with data for 2 completed treatment pairs per N-of-1-trials and 3 completed treatment pairs per N-of-1-trials. The reason for this was to anticipate missing data. All participants would be subjected to a minimum of 1 and a maximum of 4 treatment pairs, where after each treatment pair of each N-of-1 trial an interim analysis resulted in advice on stopping or continuing the N-of-1 trial.

Therefore, we ended up doing $2 \times 2 = 4$ sample size calculations, namely for each of the combinations of a clinical prior or a non-informative prior and 2 treatment pairs or 3 treatment pairs. The results are displayed in the table below. We find the results satisfactory, in fact, these values are quite similar to the cut-off for sufficient evidence that we use in the interim analyses (0.8).

Expected Posterior Probability >0.75	2 treatment periods	3 treatment periods
clinical prior	0.817	0.821
non-informative prior	0.782	0.784

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Mexiletine intervention:

Three times a day 200 mg tablet.

Placebo intervention:

Three times a day a placebo tablet.

5.2 Use of co-intervention (if applicable)

For participants currently taking antiarrhythmics or medication that may affect sodium channels, a wash-out period will be required before the baseline visit. If the patient is currently on phenytoin or flecainide acetate for myotonia the wash-out period must be 5 days. If they are currently on mexiletine or carbamazepine for myotonia the wash-out period must be 3 days. If the patient is on propafenone, procainamide, disopyramide, quinidine or encainide for myotonia the wash-out period must be 2 days. If patients do not agree with temporary discontinuation of antiarrhythmics or medication that may affect sodium channels, they will be excluded from this study. During the study period patients are not allowed to deviate from the study medication regime as supplied in the treatment kits. They are also not allowed to take co-medication in the form of antiarrhythmics or medication that may affect sodium channels which are not in the treatment kit.

5.3 Escape medication

There is no specific antidote for Mexiletine. There are a few cases of mexiletine intoxication reported in literature (see table 2).^{11,12,13,14,15,16} The lowest known dose in a fatality case was 4.4 g with postmortem serum Mexiletine level of 34 to 37 ug/ml.¹¹ However, patients have completely recovered from ingestion of 4 g to 18 g of Mexiletine.^{8, 10, 12} As escape medication/procedures for mexiletine (1) minimizing drug absorption can be considered with gastric lavage and administration of activated charcoal shortly after the intake of mexiletine, (2) followed by close observation and monitoring of vital signs at an intensive care unit. If hypotension and bradycardia occur, depending on the patient's clinical condition, atropine and transcutaneous pacing can be initiated for bradycardia. Aggressive fluid resuscitation and dopamine infusion can be started for hypotension.^{8,11,12} (3) Generalized convulsions can initially be treated with administration of i.v. benzodiazepines, phenobarbital and pyridoxine.¹⁰ Hemodialysis has been successfully performed in cardiovascular unstable patients with a nearly fatal mexiletine intoxication.⁸

Mexiletine indication	Tablets / dosage	Plasma level *	Signs of intoxication	Resuscitation	Follow-up	Reference
Lethal intoxication						
-	-	44.8 ug/ml	-	-	Lethal intoxication	Rohrig et al. (1994)
-	-	38 ug/ml	-	-	Lethal intoxication	Kempton et al. (1994)
Arrhythmia	<u>Tablets:</u> 22 x 200 mg <u>Total dosage:</u> 4.4 g	34-37 ug/ml	Tongue paraesthesiae, generalized convulsion, hypotension, bradycardia, asystolia	Intubation, external cardiac massage, emergency pacing, adrenaline and isoprenaline.	Lethal intoxication	Jequier et al. (1976)
Complete recovery						
Myotonia	<u>Tablets:</u> 20 x 200 mg <u>Total dosage:</u> 4 g	-	Hypotension, bradycardia, dysarthria.	Gastric lavage, activated charcoal, atropine, transcutaneous pacing, dopamine and hemodialysis.	Complete recovery	Akinci et al. (2010)
Arrhythmia	<u>Tablets:</u> 90 x 200 mg <u>Total dosage:</u> 18 g	20 ug/ml	convulsive status epilepticus.	i.v. diazepam 100 mg, phenobarbital 1 g and pyridoxine 5 g.	Complete recovery	Nelson et al. (1994)
Arrhythmia	<u>Tablets:</u> 62 x 200 mg <u>Total dosage:</u> 12.4 g	-	Mental obtundation, vomiting, tonic-clonic seizure, AV-block, cardiovascular collapse.	i.v. calcium gluconate, fluid resuscitation, i.v. phenylephrine, dopamine and epinephrine.	Complete recovery	Frank et al. (1991)

* Highest plasma level of mexiletine reported

Table 2. Overview of details of known mexiletine intoxication cases from literature.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1 Name and description of investigational medicinal product(s)

Mexiletine (Mexitil): Class 1B anti-arrhythmic

Mexiletine and tocainide are both lidocaine derivated and belong to the class of 1B antiarrhythmic agents (Vaughan-Williams Classification of Antiarrhythmica). Class I antiarrhythmica have membrane-stabilizing properties. Drugs in this class work by interfering with the fast influx of sodium by inhibition of sodium ionchannels during the fast depolarization phase, thereby decreasing the maximal voltage and upshoot phase of the actionpotential.

In contrast to Class IA (kinidine, disopyramide) and Class IC agents (flecainide, encainide), Class IB agents neither increase the actionpotential duration by elongation of the repolarisation phase, nor have inhibiting properties on actionpotential conduction. Instead, Class IB agents decrease the actionpotential duration.^{17,18}

6.2 Summary of findings from non-clinical studies

In-vitro and animal studies Mexiletine

In-vitro studies using cell culture systems on mexiletine, as a sodium channel blocker, has shown that the efficacy of mexiletine on skeletal sodium channels is due to the open-channel block of persistent late Na(+) currents, which arise during the pathological conditions of myotonia in NDMs patients with sodium channel mutations.¹⁹ Takahashi et al. showed that mexiletine especially blocks mutations involving the putative binding site of mexiletine in S6 segments of the sodium channel (V445M, S804F, V1293I, V1589M and M1592V).²⁰

Mexiletine does not directly acts on the skeletal chloride channel. Nevertheless, in cell culture, mexiletine has been showed to be effective on the skeletal chloride channel by indirectly reducing the membrane hyperexcitability by affecting extracellular–intracellular ionic ratios.²¹

Animal models of chloride channel NDM have shown that mexiletine improved the righting reflex, as indicator of muscle stiffness, in the ADR mouse, a model for severe Becker's type Myotonia Congenita.²²

6.3 Summary of findings from clinical studies

As concluded in our recent Cochrane review, there is insufficient evidence of effectiveness and safety of drug treatment in non-dystrophic myotonic syndromes.³

For mexiletine, five clinical trials (three randomized- and two N-of-1 trials) and five case-reports, have been performed in patients with myotonic syndromes using different outcome measurements to measure electrophysiological myotonia (short exercise test, repetitive stimulation, EMG and quantitative handgrip myometry) or clinical myotonia (clinical bedside test and questionnaires) (see table 3).^{23,24,25,26,27.}

Overall, the methodological quality of these studies is considered poor. Most studies lack basic information on treatment duration, dosage, randomization and blinding. Only the recently published study by Logigian et al. (2010) in patients with dystrophic myotonia type 1 had a washout interval, was placebo-controlled, reported methods of randomization and blinding and reported data from each treatment period and can thereby be considered as the only Class I evidence study in myotonic dystrophy.²¹

None of the clinical trials with mexiletine treatment in NDM reported thus far can meet the criteria for a Class I evidence of the efficacy of mexiletine in NDM.

Clinical trials in non-dystrophic myotonia using Mexiletine

Pouget et al. (1983) were the first to demonstrate an improvement in electrophysiological myotonic discharges (measured after repetitive stimulation) and muscular weakness (measured with ergometry) by mexiletine 400 mg/day. Unfortunately, treatment period was not stated and treatment effect was only compared to baseline (not placebo-controlled).¹⁸

In 1986, Kratz et al. performed a placebo-controlled, double-blind crossover study in a total of 6 patients with myotonic dystrophy or myotonia congenita. Mexiletine 600 mg/day was compared to placebo by measuring myotonia with different clinical bedside test and the length of myotonic discharges. However the study lacked a washout period, the treatment period was not stated and the results were presented as number of patients that improved without giving insight in data.²²

Kwiecinsky et al. (1992) measured the efficacy of mexiletine in a randomized, single-blind study in 22 patients with myotonic dystrophy or myotonia congenital. At beginning, a crossover trial of phenytoin and placebo was performed, followed by randomization for disopyramide, tocainide or mexiletine. Myotonia was measured using clinical bedside tests and EMG relaxation time and placebo treatment was compared to each treatment period. Mexiletine treatment period; Mexiletine 400 mg/day for two week and 600 mg/day last 2 weeks. Based upon their analysis the researchers concluded that mexiletine and tocainide were the most potent anti-myotonic agents. Limitations of this study include a randomization

method that is not further specified, and results from the first treatment arm that were not presented.²⁰

In 1994, Jackson et al. demonstrated the effectiveness of mexiletine in a patient with paramyotonia congenital using a N-of-1 trial design. This was the first report of mexiletine in a patient with a molecularly-defined NDM subtype. They demonstrated improvement on the short exercise test following mexiletine therapy. The mexiletine dose in this report was 300 mg - 850 mg. Treatment duration was not reported and treatment effect was compared to baseline (not placebo controlled).¹⁹

Clinical trials in dystrophic myotonia using Mexiletine

Logigian et al. (2010) performed two randomized, double-blind, placebo-controlled crossover trials, each involving 20 ambulatory myotonic dystrophy type 1 participants with grip or percussion myotonia on examination. The initial trial compared 150 mg of mexiletine 3 times daily to placebo, and the second trial compared 200 mg of mexiletine 3 times daily to placebo. Treatment periods were 7 weeks in duration separated by a 4- to 8-week washout period. The primary measure of myotonia was time for isometric grip force to relax from 90% to 5% of peak force after a 3-second maximum grip contraction.

The authors reported a significant reduction in grip relaxation time with both 150 and 200 mg dosages of mexiletine. Treatment with mexiletine at either dosage was not associated with any serious adverse events, or with prolongation of the PR or QTc intervals or of QRS duration. Mild adverse events were observed with both placebo and mexiletine treatment. Mexiletine at dosages of 150 and 200 mg 3 times daily was shown to be effective, safe, and well-tolerated over 7 weeks as an antimyotonia treatment in myotonic dystrophy.²¹

Case reports of NDM patients using mexiletine as antimyotonic treatment

In addition to the clinical trials, five case reports of treatment with mexiletine in patients with non-dystrophic myotonia have been reported.^{28,29, 30,31,32}

In all case-reports treatment effect of mexiletine is not further objectified and consist out of a subjective change in clinical observation of myotonia by a neurologist. Mexiletine dosage ranges from 130-200 mg (resp. Gay et al. 2008, Rosenfeld et al. 1997).^{24,27}

All case reports concludes that mexiletine treatment improves myotonia, except for Rosenfeld et al. In this study it was shown that a patient with sodium channel myotonia (a subtype of NDM caused by a mutation in the skeletal sodium channel) was treatment resistant for mexiletine. No serious adverse events or prolongation of PR, QTc intervals or QRS duration was reported in the case-reports mentioned above.

Disease	Genotype	Phenotype	Mexiletine treatment	Outcome measure	Treatment effect	NI	Reference
Clinical trials							
MD (type 1)	CTG-repeats	(1) Handgrip myotonia	450 mg - 600 mg	<u>Test:</u> Quantitative handgrip myometry	Improvement of electrophysiological myotonia	40	Logigian et al. (2010)
BMC TMC MD	- - -	- - -	400 mg - 600 mg	<u>Test:</u> Eyelid and hand action myotonia, stair test, EMG relaxation time	Improvement of electrophysiological and clinical myotonia	12 9 9	Kwiecinski et al. (1992)
MC MD	- -	- -	600 mg	<u>Test:</u> Handgrip strength, hand action myotonia, length of myotonic discharges	Improvement of electrophysiological and clinical myotonia	2 4	Kratz et al. (1986)
N-of-1 trials							
PMC	T1313M (SCN4A)	(1) Cold-induced handgrip myotonia (2) Cold-induced jaw myotonia (3) No muscle weakness	300 mg - 850 mg	<u>Test:</u> Repetitive stimulation test and short exercise test	Improvement of electrophysiological myotonia	1	Jackson et al. (1994)
BMC	-	(1) Muscle weakness improved by exercise	400 mg	<u>Test:</u> Repetitive stimulation test	Improvement of electrophysiological myotonia	1	Pouget et al. (1983)
Case reports							
PMC	N1297K (SCN4A)	Neonatal onset; (1) Cold-induced myotonia (2) Presence of muscle weakness >> Severe hypoxia and consciousness	130 mg	Clinical observation	Improvement of myotonia	1	Gay et al. (2008)
SCM	G1306G (SCN4A)	(1) Myotonia permanens: severe potassium-aggravated myotonia	-	Clinical observation	Improvement of myotonia	1	Van den Bergen et al. (2006)
PMC	R672C (SCN4A)	(1) No potassium-aggravation of myotonia	-	Clinical observation	Improvement of myotonia	7	Miller et al. (2004)
SCM	V445M (SCN4A)	(1) Painful myotonia	200 mg	Clinical observation	No improvement of myotonia	1	Rosenfeld et al. (1997)
TMC	-	Neonatal onset; frequent crises of apnoea, cyanosis, vomiting.	-	Clinical observation	Improvement of myotonia	1	Ceccarelli et al. (1992)

NI= Number of patients included

PMC = Paramyotonia Congenita

SCM = Sodium Channel Myotonia (previously PAM = Potassium Aggravated Myotonia)

MC = Myotonia Congenita (not further specified)

BMC = Becker's Myotonia Congenita

TMC= Thomson's Myotonia Congenita

MD = Myotonic Dystrophy

Table 3. Overview of clinical studies with mexiletine in myotonic syndromes.

6.4 Summary of known and potential risks and benefits

6.4.1 Benefits of mexiletine

Ventricular arrhythmias after myocardial infarction

Two major considerations have prompted the prophylactic use of antiarrhythmic agents after acute myocardial infarction; (1) the increased risk of developing potentially fatal ventricular fibrillation during the early acute stage of myocardial infarction, and (2) the increased risk of sudden death, presumably arrhythmia related, in those survivors who have ventricular arrhythmias.^{33,34}

These observations have led to the traditional "arrhythmia suppression hypothesis" that prophylactic antiarrhythmic therapy during and after acute myocardial infarction should prevent potentially fatal ventricular arrhythmias, thereby decreasing mortality. This hypothesis has formed the theoretical basis for a large number of randomized clinical trials conducted with a wide range of antiarrhythmic agents from Class I-4 of the Vaughan-Williams Classification of Antiarrhythmics, including mexiletine as a Class IB antiarrhythmic (600-1200 mg/day). In general, these trials showed a limited effect in suppression of ventricular arrhythmia on ECG.^{35,36,37,38,39,40,41}

However, since the report of significant increased mortality in patients with non-severe ventricular arrhythmia after myocardial infarction due to a pro-arrhythmic effect of Class IC antiarrhythmics: encainide and flecainide (the CAST-trial; see text below *risk of mexiletine*), all Class I antiarrhythmics are now reserved only for the treatment of severe life-threatening arrhythmias in patients with cardiac morbidity.

Myotonic syndromes

Treatment of mexiletine in a dose of approximately 400 - 600 mg / day, has shown to improve myotonia in the clinical trials, N-of-1 trials and case-reports in patients with myotonic syndromes as mentioned above (see 4.6; Summary of findings from clinical studies).²⁰⁻²⁹

Pain syndromes

Both intravenous lidocaine and mexiletine are increasingly used to treat pain syndromes. Mexiletine appears effective in the treatment of diabetic neuropathy (225-675 mg/day)⁴², primary allodynia (titrated till maximum of 1350 mg/day)⁴³, erythromelalgia (900 mg/day)⁴⁴ and headache syndromes such as refractory chronic daily headache (600-1500 mg/day).^{45,46}

6.4.2 Risks of mexiletine

Pro-arrhythmic effect of anti-arrhythmics (the CAST-trial)

The CAST-trial (The Cardiac Arrhythmia Suppression Trial) demonstrated increased mortality due to arrhythmia and deaths due to shock after acute recurrent myocardial infarction in patients treated with intravenous Class 1C antiarrhythmics, encainide and flecainide. The CAST-trial investigated only a specific patient population, namely patients with asymptomatic or mild symptomatic ventricular arrhythmia as a result of a recent myocardial infarction (with remaining left ventricle dysfunction).^{47,48}

However, except for the CAST-trial, no other trial with Class I antiarrhythmics, mexiletine trial included, showed a statistically significant difference in mortality between active and control treatments.⁴⁹

In response to the CAST-trial, a meta-analysis performed by Teo et al. (JAMA, 1993) examined the collective evidence of prophylactic antiarrhythmic drug therapy (Class I-IV) in acute myocardial infarction. Within, mortality data from 138 trials on 98000 patients were combined. The overall effect of Class I antiarrhythmic agents (total of 59 trials) was a statistically significant increase in risk of death in those patients given these agents prophylactically after myocardial infarction (OR, 1.14; 95% CI, 1.01 to 1.28; P=.03), mostly contributed to by the overall effect of the Class IA (OR, 1.19%; 95% CI, 0.99 to 1.44; P=.07) and IC antiarrhythmics (OR, 1.31; 95% CI, 0.95 to 1.79; P=.10). The overall OR was 1.06 for trials of class IB agents (95% CI, 0.89 to 1.26; P=.50).⁴⁶

This said, we do not expect any cardiac abnormalities upon mexiletine treatment in the patients with NDMs that will be included in our trial upon because; (1) upon subgroup meta-analysis of mexiletine-trials alone by Teo et al., the trend towards an excess in mortality in the treatment group is reversed towards an mild protective effect of mexiletine (OR, 0.99; 95% CI, 0.72 to 1.36; P=.95)⁴⁶ and (2) no serious cardiac events (such as arrhythmia) or cardiac abnormalities on ECG has ever been reported in all performed trials with patient without cardiac comorbidity receiving mexiletine in the dosage used in our study (600 mg/day) or a much higher dose (1500 mg/day).^{20-29, 33-37}

Suspected adverse events

Toxic side effects of mexiletine occur with greater frequency at the higher dosages required to control arrhythmias and neuropathic pain. These dosages are typically two to three times higher than the dosages used in the present study. Patients taking these higher dosages of mexiletine (600-3200mg/day) have a significantly increased incidence of upper gastrointestinal distress, 41%, lightheadedness and tremor, 12.5%. These symptoms are dose related, generally not serious, and disappear after dose reduction or discontinuation of treatment.^{50,51,52}

In the recently published therapeutic trial (Logigian et al. Neurology 2010) in which myotonic dystrophy patients received mexiletine in a similar dosage as in our trial (200 mg TID) mexiletine was generally well-tolerated and there were no significant adverse events at either dosage. Adverse events were mild, and slightly more common with mexiletine treatment than with placebo treatment. Again, adverse events that seemed to be more common with mexiletine were mild upper gastrointestinal distress and lightheadedness.²¹

6.5 Description and justification of route of administration and dosage

Patients enrolled in this study receive no pre-treatment with one of the medications. As mexiletine has a half life of approximately 10-12 hours, we expect a sufficient protective serum concentration can be reached within 5 doses. Furthermore it has been shown that serum mexiletine is relatively stable and maximally increased on the third day after initiation of mexiletine treatment.

6.6 Dosages, dosage modifications and method of administration

Treatment conditions:

- (1) Mexiletine (Mexitil) 200 mg three times daily orally
- (2) Three times daily tablets placebo orally

6.7 Preparation and labelling of Investigational Medicinal Product

Oral capsules containing mexiletine or placebo with identical appearance will be provided by the department of Clinical Pharmacy of the Radboud University Nijmegen Medical Centre and this will be stocked at the department of Neurology at controlled temperature (15-25 °C).

6.8 Drug accountability

The department of Clinical Pharmacy of our University Medical Centre will provide the medicinal products (mexiletine and placebo) used in this trial and will stored these medicinal

products under GMP conditions. Compliance to the treatment will be checked by pill counting. The completed drug accountability of all involved medicinal products will be documented by the investigator on specially designed drug accountability form.

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

The primary outcome measure is the mean stiffness measure of daily phone calls (IVR), during weeks 3, 4, 8, 9, 14, 15, 19, 20, 25, 26, 30, 31, 36, 37, 41 and 42.

7.1.2 Secondary study parameters/endpoints (if applicable)

The secondary outcome measures will include changes in pain, weakness, and fatigue on IVR, clinical myotonia assessment, quantitative grip myotonia, INQoL, SF-36 (adults), blood plasma levels of mexiletine, biceps force test and needle EMG. The data collected by the IVR system from the remaining weeks and the washout periods will also be used as a secondary outcome measure.

7.1.3 Other study parameters (if applicable)

Not applicable

7.2 Randomisation, blinding and treatment allocation

This study is a combined N-of-1 trial. With each N-of-1 trial being a double-blind randomized placebo-controlled trial. The code will only be broken after all patients have completed their N-of-1 trial and thus the experiment will be powered sufficiently. However in case of any serious adverse event, if necessary, the individual code for the concerning participant will be broken, to enable and facilitate possible medical treatment.

7.3 Study procedures

Interactive Voice Response Diary (IVR):

The IVR is an automated centralized phone-system in rating scale ranking severity of symptoms and the frequency of symptoms (hours) for stiffness, pain, weakness, and fatigue. Using the telephone key pad participants will call in on a weekly or daily basis to rate their symptoms on an ordinal scale (1-9). The IVR used for this study will be developed by OrcaGroup communication solution (Heesch, the Netherlands).

INQoL:

There are no quality of life studies examining the impact of NDM. NDM patients experience stiffness, pain, and weakness. The Individual Neuromuscular Quality of Life questionnaire (INQoL) is a quality of life instrument used to examine issues specific to patients with a neuromuscular disease.^{53,54}

SF36:

This is a generic questionnaire that is suitable for prospective assessment in NDM.⁵⁵ The Dutch Language version of the SF-36 has been shown to have a good validity and reliability.⁵⁶

Clinical Myotonia test:

Myotonia will be sought on physical examination using the following techniques:

1. Eye closure myotonia. The participant will be instructed to close the eyes tightly for three seconds and then to open the eyes. Eye closure myotonia is present if there is difficulty fully opening the eyelids. This will be repeated for a total of 5 times. Each attempt will be timed.
2. Hand-grip myotonia. The participant will be instructed to forcefully close the fingers in a fist for three seconds and then rapidly open the fist and extend the fingers. Hand-grip myotonia is present if the fingers cannot be immediately extended. The time it takes (in seconds) for the fingers to be fully extended will be recorded. This will be repeated for a total of 5 times. Each attempt will be timed.
3. Percussion myotonia. This will be tested in two sites:
 - a. Thenar eminence. With the hand supinated, the thenar eminence will be struck with a reflex hammer. If contraction of the thenar muscles draws the thumb medially and this does not relax immediately, then percussion myotonia is present.
 - b. Extensor digitorum (EDC) muscle. With the forearm supported, allowing the hand to hang down, the EDC muscle is struck with a reflex hammer about 3 cm distal to the lateral epicondyle of the elbow, and 1 cm medial. If the wrist/third finger is extended and does not relax immediately, then percussion myotonia is present.

Quantative grip myotonia:

Quantitative Grip Myotonia: Maximum Voluntary Isometric Contractions (MVIC's) of the long finger flexors and the subsequent relaxation time (myotonia) will be measured using a technique developed at the University of Rochester (Figure 2).^{57,58} To measure the extent of grip myotonia of resting forearm muscle, each participant will squeeze the grip handle with a maximum grip for 3 seconds then relax until the force returns to baseline. The time required for relaxation (the relaxation time (RT)) following this initial MVIC will be used to calculate the

degree of myotonia. To determine if repeated muscle contractions shorten the time required for full muscle relaxation, eg., warm-up, a series of five MVICs will be made, each for three seconds duration followed by a ten second period of rest. The measurement of warm-up will be made by comparing relaxation time for the initial MVIC compared to the relaxation time following the final contraction in the series of five contractions used as warm-up exercise. Myotonia will be assessed using three different measurements of the relaxation phase: 1.) time required to fall from 90% of MVIC to 10% MVIC, 2.) Time required to fall from 90% MVIC to 50% MVIC; 3.) Time required to fall from 90% MVIC to 75% MVIC. Each participant will perform three sets of MVIC testing. Each set will be separated by a 10- minute rest period.

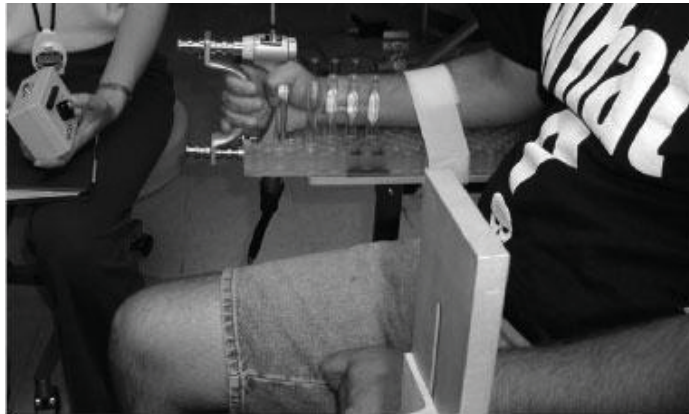


Figure 2: Measurement of handgrip myotonia in a NDM patient using handgrip myometry.

Biceps force recording

Biceps force recording has been proved to be a successful technique to detect hyperexcitability of the skeletal muscle cell membrane. Especially in isometric contractions at 60% of maximal voluntary contraction (MVC), disturbances of the skeletal muscle cell membrane can be seen by an irregular force pattern with intermittent decline in force.⁵⁹

The experimental protocol starts with a short measurement of the MVC, which is carried out three times. The peak performance of this measurement is taken as the MVC. Subsequently isometric contractions at 60% of the MVC are performed for at least 30 seconds. Every measurement will be followed by a 10 minute period of rest.

For the recording of the voluntary contraction of the biceps brachii the left arm is placed in a horizontal position with the elbow in 90 degrees abduction and is fixed in an arm flexor dynamometer supplied with strain gauges. The hand will be in a middle position. The force will be recorded isometrically and on a PC monitor this force is visually fed back to the subject.

Needle EMG

Concentric needle EMG will be performed in the rectus femoris muscles. These muscle were chosen based on the data from the NDM natural history study as performed in Jeroen Trip his PhD-thesis, and will be consistent throughout this study. According to established criteria myotonic discharges will be defined and quantified: Myotonic discharges must be at least 500 msec and elicited in three areas of the muscle outside of the endplate zone.

Grading of myotonic discharges: 1+: fulfills minimal requirements; 2+: myotonic discharges in more than ½ of needle locations; 3+: myotonic discharges with each needle movement in all examined areas.⁶⁰

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.4.1 Specific criteria for withdrawal (if applicable)

Intercurrent illness or event that precludes further visits to the study site or ability to evaluate disease (e.g.-mental status change, large pleural effusion).

7.5 Replacement of individual subjects after withdrawal

An intent-to-treat approach will be used. All data acquired prior to termination for the reasons outlined below will be included in the primary analysis unless patient withdraws consent. Every effort will be made to conduct a final study visit with the participant, and participants will be followed clinically until, if applicable, all adverse events resolve.

7.6 Follow-up of subjects withdrawn from treatment

Subjects who withdraw from treatment will be contacted, within seven days, to an exit-interview concerning their withdrawal. Furthermore, possible side effects or adverse events of the treatment will be reported.

7.7 Premature termination of the study

This study may be suspended or closed if:

1. Early stopping rules have been met.
2. The study objectives have been met.
3. The Study Chair / Study Investigators believe it is not safe for the study to continue.
4. The DSMB suspends or closes the trial.

In case of an unexpected and unforeseen complication or medicinal side-effect which is related to our study, continuation of the protocol will be discussed with responsible investigators and local ethics committee. The safety and wellbeing of the subjects is our highest priority. As described in more detail further on in this protocol a DSMB will be established.

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 Adverse and serious adverse events

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to mexiletine treatment. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- is a new event of the trial likely to affect the safety of the subjects, such as an unexpected outcome of an adverse reaction, lack of efficacy of an IMP used for the treatment of a life threatening disease, major safety finding from a newly completed animal study, etc.

All SAEs will be reported through the web portal *ToetsingOnline* to the accredited METC that approved the protocol.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.1 Suspected unexpected serious adverse reactions (SUSAR)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are adverse reactions, of which the nature, or severity, is not consistent with the applicable product information (e.g. Investigator's Brochure for an unapproved IMP or Summary of Product Characteristics (SPC) for an authorised medicinal product).

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern. The expedited reporting of SUSARs through the web portal *ToetsingOnline* is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

8.2.2 Annual safety report

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, Medicine Evaluation Board and competent authorities of the concerned Member States.

This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.3 Follow-up of adverse events

All adverse events will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

8.4 Data Safety Monitoring Board (DSMB)

We will establish a Data Safety Monitoring Board, consisting of three independent members (a cardiologist, a clinical pharmacologist and a biostatistician). The DSMB will judge all results regarding ECG, plasma drug levels of mexiletine and adverse events or reactions after every treatment set within each individual N-of-1 trial.

The DSMB will also judge causality of (severe) adverse events for all N-of-1 trials. All adverse events will be reported to the CMO as soon as possible, in accordance with the GCP guideline. If a severe side-effect or AE occurs in the first treatment set and the DSMB judges it undesirable to expose the patient to the offending drug any further, the DSMB has the obligation to break the blinding code in order to eliminate the treatment with this drug in the second period of treatment. (See figure 3. for more detailed DSMB decision guidelines)

The DSMB will be notified of every cardiac event (AE/SAE) within 24 hours of submission to the METC. If the accumulated serious adverse events deemed related to the study are equal to or more than 10% (three patients) of the study population or if two or more of the same cardiac event (AE/SAE) occur the DSMB will convene and review the data in order to make a determination about the continuation/stopping of the study. After completion and debinding of the trial all safety analyses will be performed on the complete research population and reported in a peer reviewed scientific publication.

Documentation of the DSMB meetings will be made by one of the DSMB members and sent to the PI within 5 days after the DSMB meeting.

The DSMB do not work with the sponsor of the project and do not participate in this study.

Therefore the members of the DSMB have no conflict of interest and the DSMB will form an independent committee.

DSMB decision guidelines:
<p><u>ECG:</u></p> <ol style="list-style-type: none">1. Occurance of conductance disturbances (second degree AV block, thrid degree AV-block, prolonged QT-interval >500 ms or QRS-duration >150 ms2. Other abnormalities on ECG described as serious by the independent trial cardiologist → Stop individual N-of-1 trial
<p><u>Drug levels of Mexiletine:</u></p> <ol style="list-style-type: none">1. Drug levels of serum mexiletine exceeding the therapeutic range (> 2 ug/ml)2. Drug levels of serum mexiletine within the range of non-compliance (0-0,25 ug/ml) → Stop individual N-of-1 trial
<p><u>Adverse reactions/events:</u></p> <ol style="list-style-type: none">1. Occurance of a cardiac event (AE/SAE) → Stop individual N-of-1 trial2. Occurance of cardiac events (AE/SAE) in more than 10% (three patients) of the study population or two or more of the same cardiac event (AE/SAE) → Convene and review data → Decision to continue/stop the study

Figure 3. DSMB decision guidelines

9. STATISTICAL ANALYSIS

9.1 Multivariate analysis

The key question that this study aims to answer is: What is the probability that Mexiletine, when used in patients with non-dystrophic myotonia (NDM), is clinically effective? The appropriate way to address this question is through Bayesian analysis, which allows for estimation of such a probability directly. Moreover, a Bayesian analysis on multiple N-of-1 trials allows for answering the above question on an individual as well as on a population level, which is important since we are dealing with a rare disease with substantial heterogeneity between patients.

To combine the results of the multiple N-of-1 trials, a hierarchical (multi-level) model will be used, with the IVR measure for stiffness as the dependent variable, and where patient, subgroups of patients (Cl channelopathy and Na channelopathy, type 1 and 2), and centre will be used as the structural grouping factors (or the levels of the model). Patient will be treated as a random effect (both a random intercept and a random slope), while centre and subgroup of patients will be treated as fixed effects. A common within person residual variance was assumed. For this multi-level model, Bayesian methods will be used to combine the data from the individual N-of-1 trials. Thus, we will obtain (marginal) posterior distributions for the mean treatment effect at the population level and for the between-patient variation, as well as posterior distributions for the treatment effects at the individual level, that will exhibit borrowed strength from the population estimates through shrinkage to the population mean. For details of the procedure to be used, see Zucker et al. (2006, especially the appendix).

We will also investigate whether we find evidence for interactions between treatment effect and treatment pair, and between treatment effect and treatment order.

The secondary endpoints will be analyzed in the same way.

Prior elicitation and non-informative priors

We will require prior distributions for all model parameters. We will use two types of priors: non-informative priors and 'clinical priors', i.e. priors elicited from expert physicians (as there are only two neurologists in the Netherlands that have experience with this patient group our priors are only based on two neurologists' expert opinion). We will use clinical priors from the participating physicians for the parameters of main interest: for each patient's individual treatment effect, and for the overall mean treatment effect. For all other model parameters we will use (almost) non-informative priors, since it is very hard to elicit parameters such as random effect variations from physicians, and because the estimates for these parameters are only instrumental in estimating our main parameters (see Spiegelhalter (2004), ch. 5).

For our non-informative priors it will suffice to use vague or almost non-informative priors. We have two types of model parameters: means (such as the mean for the random intercept: the placebo mean) and variances. For all mean parameters we will use normal prior distributions with very large standard deviations (e.g. the placebo mean prior will follow a normal distribution with mean=5 and SD=10). For the variation parameters we will use inverse gamma distributions with both shape and scale parameters equal to 0.001, which is a very common choice for a non-informative prior (see e.g. Spiegelhalter (2004), section 5.7.3). An important reason to opt for normal and inverse gamma distributions for our priors is that these distributions are conjugate with a normal likelihood (see e.g. Gill (2008)) so that we know to what class of distributions our posterior will belong. This greatly facilitates the interim analyses where we want to use the posterior distribution obtained after the first treatment pair as our prior distribution for the analysis of our second treatment pair, etc.

From one of our participating neurologists we have already elicited a prior distribution for the mean of the random slope (the mean treatment effect): a normal distribution with mean 1.75 and a standard deviation of 0.89, and we have used this prior in our sample size calculation. At the start of the study we will also elicit prior distributions for each individual treatment effect from that particular patient's treating physician. Prior elicitation for these variables will be done by assuming normally distributed priors and by eliciting 2.5- and 97.5-percentiles, which allows for determining the corresponding normal distributions (see Spiegelhalter (2004), p.141)

To check for robustness with respect to prior distributions, we will also replace the elicited prior distributions with non-informative priors in our analyses.

9.2 Interim analysis

After treatment pair 1, 2 and 3 of each N-of-1 trial it will be investigated whether the existing evidence at that moment is sufficient to be able to conclude that one of the two treatments is more effective for that particular individual. This will be done by a statistician who will be blinded for treatment allocation and who will use Bayesian methods to do so. For every patient prior distributions will be combined with the data from his/her N-of-1 trial as expressed in the form of a likelihood function, to produce a posterior distribution. On the basis of the (marginal) posterior distribution for the real treatment effect for this particular patient, the patient and the treating physician will be advised to continue or discontinue the N-of-1 trial. We have determined two stopping criteria based on the posterior probability of treatment effects larger than 0.75, as this is our cut-off for what we consider to be a

substantial effect (our clinically relevant difference). When the posterior probability that the treatment effect is larger than 0.75 is at least 80%, the physician will be advised to discontinue the N-of-1 trial. Similarly, if the posterior probability that the treatment effect is larger than 0.75 is no more than 20%, the physician will also be advised to discontinue the N-of-1 trial. In all other cases the physician will be advised to continue the N-of-1 trial. Taking into account this advice, the physician and patient will discuss the effects of treatment, as observed by the physician and experienced by the patient, and together they will decide whether or not to continue the N-of-1 trial. For a simple flowchart of the interim situation see figure 5.

For our interim analyses we will use non-informative priors only, as we prefer our stopping advice to be only based on the available data, especially because after one or two treatment pairs there are not a lot of data yet, and an elicited prior distribution could have considerable impact on the posterior distribution and therefore on the stopping advice.

Note that this interim procedure is different from a usual interim analysis. Here multiple interim analyses will be performed during (and with respect to the (dis)continuation of) a single N-of-1 trial. No interim analysis will be performed with respect to the (dis)continuation of the combined trial as a whole. Also, by themselves these interim analyses will not be decisive, they will merely play an advisory role.

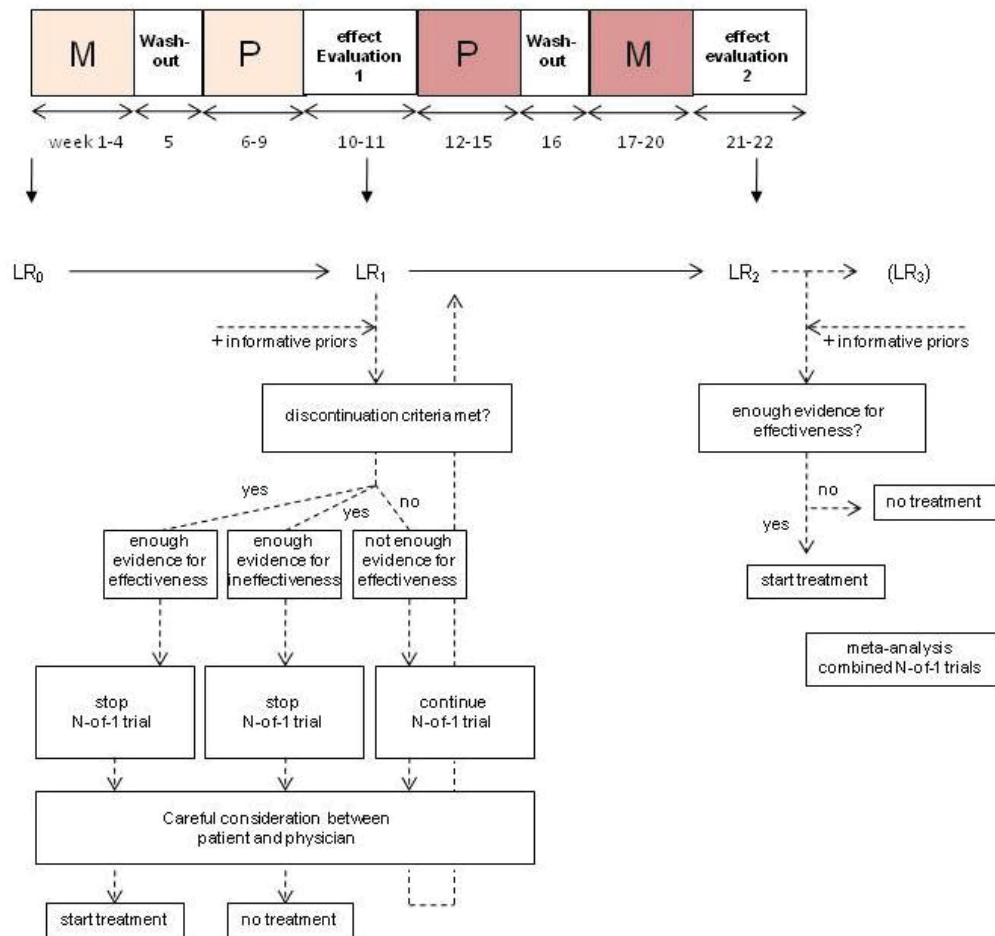


Figure 4. Likelihood Ratio (LR) calculation during trial.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki (version October 2008) and in accordance with the Medical Research Involving Human Subjects Act (WMO)

10.2 Recruitment and consent

The Nijmegen NDM database has been recently developed with help of all neurologists across the Netherlands as well as the Dutch Patient Association for Neuromuscular Diseases (VSN). They were requested to report all patients with NDM to our research group for a full year. All reported patients aged 18 years and over were invited to the neurology outpatient clinic of the Radboud University Nijmegen Medical Centre and seen once for clinical assessment, needle-EMG, and collection of blood samples for genetic analysis. Using inclusion and exclusion criteria (see below), we will identify potentially eligible patients from the Nijmegen NDM database (see figure 5). We expect that a maximum of ca. 15% may not be eligible to participate, for instance for reason of cardiac conditions, diabetes mellitus, or neurological diseases other than NDM. From the remaining patients, random stratified samples will be taken, resulting in 15 CICH patients, 10 PMC (NaCh) patients, and 10 SCM (NaCh) patients. These patients will be contacted by telephone and asked to participate in the study. When interested, they will be sent information about the study and scheduled for an appointment. During this screening visit, further explanation about the N-of-1 trial will be given, and patients will be asked to give informed consent in writing. Eligibility will then be checked by taking medical history and by conducting SMA7 (blood urea nitrogen, serum chloride, carbon dioxide, creatinine, blood glucose, serum potassium, serum sodium), ECG, and urine pregnancy testing for females. Serum pregnancy testing can be performed if, in the opinion of the investigator, the urine pregnancy test is inconclusive. Prior use of phenytoin, carbamazepine or mexiletine will be documented. This documentation will include dosage, duration and date of last use. We expect that this procedure will lead to inclusion of **20 NDM patients** from the Radboud University Nijmegen Medical Center: 10 patients with CICH and 10 patients with NaCh (5 PCM en 5 SCM). Should this not be the case, we will select further patients from the registry, following the same procedure. At the Maastricht University Hospital, a similar, though smaller (n = 20) registry of NDM patients exists. Here, the same procedure will be followed, resulting in inclusion of an additional group of **10 NDM patients**: CICH (n=5), PMC (n=2) and SCM (n=3).

In total, **30 NDM patients** will be included in the multicenter-study between the Radboud University Nijmegen Medical Center and the Maastricht University Hospital. Characteristics of patients who were ineligible or who refused participation will be documented, in order to estimate the external validity of the findings of our study.

Patient study enrollment:

The 20 NDM patients included from the RUNMC will be first enrolled into the study; Patients will be divided into two parallel groups of 10 NDM patients (5 CICH and 5 NaCh), that will be

enrolled one after the other. All measurements will take place at the RUNMC (primary trial location).

The 10 NDM patients included from the Maastricht University Hospital will also be enrolled in a parallel group of 10 NDM patients after study completion of the 20 NDM patients from the RUNMC. All measurements of this parallel group will take place at the Maastricht University Hospital.

(see Figure 6.)

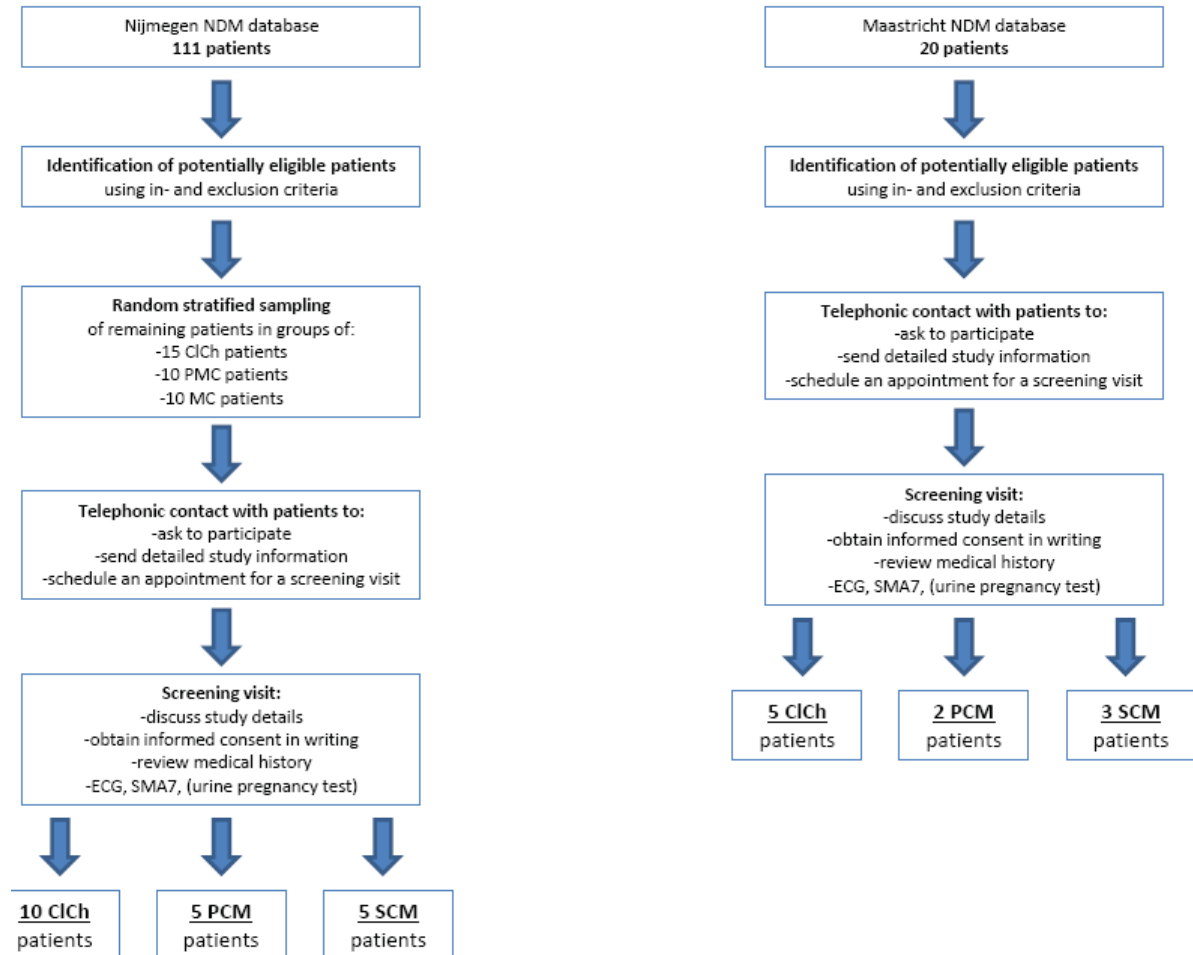


Figure 5: Flowchart patient inclusion

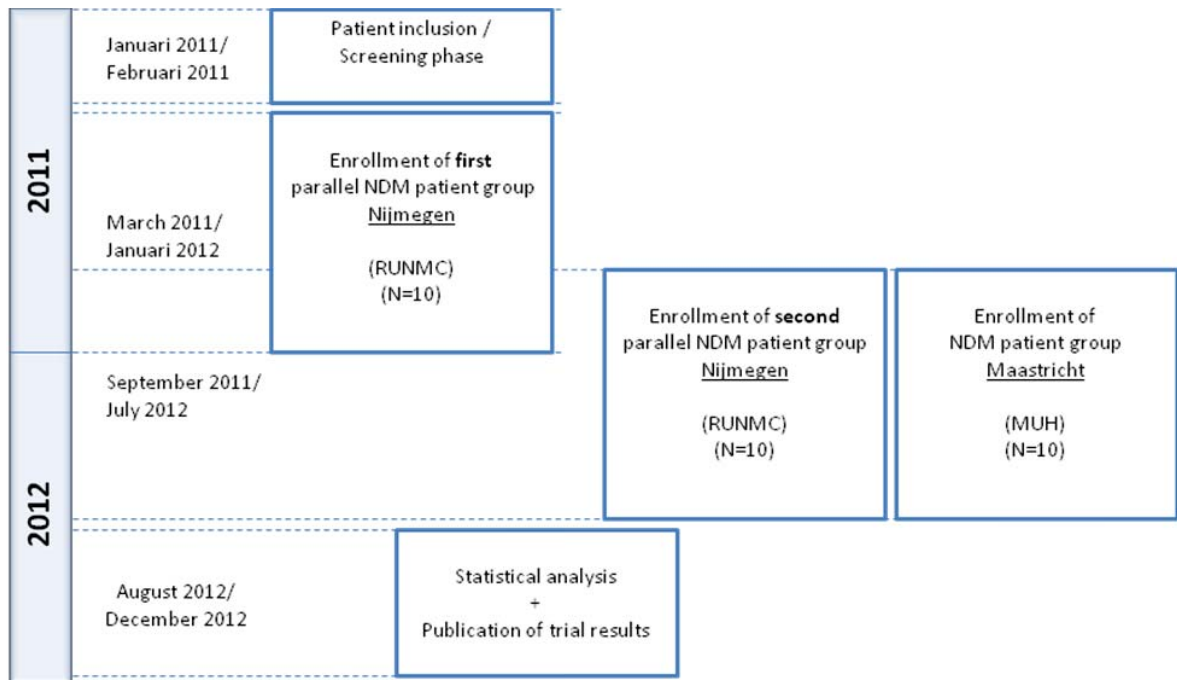


Figure 6: Time schedule of trial activities

10.3 Objection by minors or incapacitated subjects (if applicable)

Not applicable

10.4 Benefits and risks assessment, group relatedness

Testing Related Risk:

EMG testing may be painful. It may be uncomfortable for some participants. The patient may feel some pain or discomfort when the needles are inserted, but most people are able to complete the test without significant difficulty. Afterward, the muscle may feel tender or bruised for a few days. The risks associated with blood drawing include discomfort from the needle stick, bruising, and rarely, an infection from the needle stick.

Other measurements are non-invasive and are not associated with any risks.

Pregnancy Related Risk:

It is not known how Mexiletine will affect an unborn or nursing child. There may be risks to an unborn or nursing child that have not yet been identified. There are no adequate and well-controlled studies in pregnant women. Because the drug(s) in this research study may affect an unborn child, pregnant patients will be excluded from this study. If a patient becomes pregnant during the study the patient must immediately inform the primary investigator and visit a doctor. If female patients have not been surgically sterilized, or have not undergone menopause at least 1 year ago, they must practice a method of birth control during the trial. Examples of birth control include: birth control pills, implant, intrauterine device, (IUD), or a barrier method such as a diaphragm with intravaginal spermicide, cervical cap, male or female condom

Possibility of Unknown Risks

There may be other risks that have not yet been identified and unexpected side effects that have not been previously observed may occur

New findings statement:

You will be informed if any significant new findings develop during the course of the study that may affect your willingness to participate in this study.

Benefits

Because of the proposed design of combined N-of-1 trials, each patient is treated with several treatment periods with mexiletine and placebo. Thereby, patients could directly benefit from participation in this study. Information on adverse events from therapy can

already be registered and if therapy significantly decreases complaints of myotonia, the trial could be preliminary ended and treatment with mexiletine could be started.

10.5 Compensation for injury

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

The sponsor (also) has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

1. € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
2. € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
3. € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as 'verrichter' in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.6 Incentives (if applicable)

Reasonable out-of pocket expenses for items such as transportation and/or parking for visits that are required as part of participation to this study will be reimbursed (such as travel expenses and parking costs for the visits; twice the distance between their home address and the RUNMC, 0.28 cent/kilometer).

11. ADMINISTRATIVE ASPECTS AND PUBLICATION

11.1 Handling and storage of data and documents

All research outcomes will be archived in the personal medical file of each participant. This medical file will never leave the Radboud University Nijmegen Medical Centre. This source document can only be viewed by trial monitors and investigators involved in trials for which subject's signed informed consent has been obtained. The following data will be archived in the source document: Copy of signed informed consent form, ECG's, laboratory values, subject study code, each visit date and all study outcomes and possible adverse events, (serious) adverse events. In addition to the source document, a case report form (CRF) will be completed. The CRF is anonymised (only contains subjects initials and subject study code) and may leave the hospital for data management or monitoring purposes. A copy of this CRF remains at the RUNMC for 15 years.

The following data will be archived in the CRF: Subject study code; data; ECG's, laboratory values, all study outcomes and possible adverse events, (serious) adverse events. A subject code log will be archived in a locked site in the trial master file. Furthermore we will file the drug accountability forms in the trial master file together with the approved version of the protocol, correspondence with the METC and CVs of all involved investigators.

11.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 End of study report

The investigator will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the investigator will notify the accredited METC, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.5 Public disclosure and publication policy

Not applicable

12. REFERENCES

- ¹ Trip J, Drost G, Verbove DJ, et al. In tandem analysis of CLCN1 and SCN4A greatly enhances mutation detection in families with non-dystrophic myotonia. *Eur J Hum Genet* 2008; 16:921-929.
- ² Trip J, de Vries J, Drost G, Ginjaar HB, van Engelen BGM, Faber CG. Health status in non-dystrophic myotonias: close relation with pain and fatigue. *J Neurol* 2009;256:939-947.
- ³ Trip J, Drost G, van Engelen BG, Faber CG. Drug treatment for myotonia. *Cochrane Database Syst Rev* 2006; (1):CD004762.
- ⁴ Conravey A, Santana-Gould L. Myotonia Congenita and Myotonic Dystrophy: Surveillance and Management. *Current Treatment Options in Neurology* (2010). 12:16-28.
- ⁵ Zucker DR, Schmid CH, McIntosh MW et al. Combining Single Patient (N-of-1) Trials to Estimate Population Treatment Effects and to Evaluate Individual Patient Responses to Treatment. *J Clin Epidemiol* 1997; Vol. 50, No. 4, 401-410.
- ⁶ Zucker DR, Ruthazer R, Schmid CH et al. Lessons Learned Combining N-of-1 Trials to Assess Fibromyalgia Therapies. *Journal of Rheumatology* 2006;33:10.
- ⁷ Spiegelhalter DJ, Abrams KR en Myles JP (2004): "Bayesian Approaches to Clinical Trials and Health-Care Evaluation", Wiley.
- ⁸ Walsh RJ, Wang Y, Statland J, Bandi B, Barohn R, CINCH Study Group. The nondystrophic myotonias; genotype-phenotype correlation and longitudinal study: Clinical Phenotype Characterization. *Neurology*. 2007; 68 (Suppl 1): A297.
- ⁹ Wang Y, Walsh RJ, Statland J, Barohn R, CINCH Study Group. Interactive voice response diary and objective myotonia measurement as endpoints for clinical trials in nondystrophic myotonia. *Neurology*. 2007; 68 (Suppl 1): A297.
- ¹⁰ Wang F en Gelfand AE (2002): "A Simulation-based Approach to Bayesian Sample Size Determination for performance under a Given Model and for Separating Models", *Statistical Science* 17(2), 193-208.
- ¹¹ Rohrig TP, Harty LE. Postmortem distribution of mexiletine in a fatal overdose. *J Anal Toxicol*. 1994 Oct;18(6):354-6.
- ¹² Akinci E, Yuzbasioglu Y, Coskun F. Hemodialysis as an alternative treatment in mexiletine intoxication. *Am J Emerg Med* 2010 (epub ahead of print).

- ¹³ Kempton J, Manoukian A, Levine B, Smialek J. A mexiletine intoxication. *J Anal Toxicol.* 1994 Oct;18(6):346-7.
- ¹⁴ Nelson LS, Hoffman RS. Mexiletine overdose producing status epilepticus without cardiovascular abnormalities. *J Toxicol Clin Toxicol.* 1994;32(6):731-6.
- ¹⁵ Jequier P, Jones R, Mackintosh A. Fatal mexiletine overdose. *Lancet* 1976; 307;7956: 42.
- ¹⁶ Frank SE, Snyder JT. Survival following severe overdose with mexiletine, nifedipine, and nitroglycerine. *Am J Emerg Med* 1991; 9: 43–46.
- ¹⁷ College voor zorgverzekering (CVZ); Farmacotherapeutisch kompas. Achtergrondinformatie; Tractus circulatorius; anti-aritmica; achtergrondinformatie (www.fk.cvz.nl).
- ¹⁸ College voor zorgverzekering (CVZ); Farmacotherapeutisch kompas. Achtergrondinformatie; Tractus circulatorius; anti-aritmica; membraanstabilerende middelen (www.fk.cvz.nl).
- ¹⁹ Wang GK, Russell C, Wang SY. Mexiletine block of wild-type and inactivation-deficient human skeletal muscle hNav1.4 Na⁺ channels. *J Physiol.* 2004; 554(3): 621-633.
- ²⁰ Takahashi MP and Cannon SC. Mexiletine block of disease-associated mutations in S6 segments of the human skeletal muscle Na⁺ channel. *J Physiol* 2001 537: 701–714,
- ²¹ Gutmann L, Phillips LH. Myotonia congenita. *Semin Neurol* 1991;11:244-8.
- ²² De Luca A, Pierno S, Liantonio A, . New potent mexiletine and tocainide analogues evaluated in vivo and in vitro as antimyotonic agents on the myotonic ADR mouse. *Neuromusc. Disorders.* 2004; 14: 405-416.
- ²³ Pouget J, Serratrice G. Myotonia with muscular weakness corrected by exercise. Therapeutic effect of mexiletine. *Rev. Neurol. (Paris).* 1983;139:11:665-672.
- ²⁴ Jackson CE, Barohn RJ, Ptacek LJ. Paramyotonia congenita: abnormal short exercise test, and improvement after mexiletine therapy. *Muscle Nerve.* 1994; 17: 763-768.
- ²⁵ Kwiecinski H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. *Acta Neurol Scand* 1992;86:371-375.
- ²⁶ Logigian EL, Martens BA, Moxley IV RT et al., Mexiletine is an effective antimyotonia treatment in myotonic dystrophy type 1. *Neurology* 2010; 74; may 4.

-
- ²⁷ Kratz R, Hawley RJ, Jacksons LK et al. Treatment of myotonia with mexiletine. *Muscle and Nerve (Abstract)* 1986;9(Suppl 5):199.
- ²⁸ Ceccarelli M, Rossi B, Siciliano G et al. Clinical and electrophysiological reports in a case of early on myotonia congenita (Thomsen's disease) successfully treated with mexiletine. *Acta Paediatr* 1992;81:453-455.
- ²⁹ Gay S, Dupuis D, Faivre L et al. Severe Neonatal Non-Dystrophic Myotonia Secondary to a Novel Mutation of the Voltage-Gated Sodium Channel (SCN4A) Gene. *Am J Med Genet. Part A* 146A:380-383 (2008).
- ³⁰ Van den Bergen JC, Verbruggen KT, Ginjaar HB et al. A girl with hereditary myotonia due to an exceptional sodium channel mutation. *Ned Tijdschr Geneeskd.* 2006;150:2501-6.
- ³¹ Miller TM, Dias da Silva MR, Miller HA et al. Correlating phenotype and genotype in the periodic paralysis. *Neurology* 2004;63:1647-1655.
- ³² Rosenfeld J, Sloan-Brown K and George Jr AL. A Novel Muscle Sodium Channel Mutation Causes Painful Congenital Myotonia. *Ann Neurol* 1997;42:811-814.
- ³³ Dhurandhar RW, Macmillan RL, Brown KWG. Primary ventricular fibrillation complicating acute myocardial infarction. *Am J Cardiol* 27:347 – 351. 1971.
- ³⁴ Lawrie DM, Higgins MR, Godman MJ. et al. Ventricular fibrillation complicating acute myocardial infarction. *Lancet* 2:523-528. 1968.
- ³⁵ Campbell RWF, Talbot RG, Dolder MA, Murray A, Prescott LF, Julian DG. Comparison of procainamide and mexiletine in prevention of ventricular arrhythmias after acute myocardial infarction. *Lancet.* 1975;1:1257-1260.
- ³⁶ Halinen MO, Pentikainen PJ, Helin MJ, Rehrberg S. Antiarrhythmic efficacy of combined intravenous and oral mexiletine in acute myocardial infarction: a double blind placebo-controlled study. *Eur Heart J.* 1984;5:675-683.
- ³⁷ Campbell RWF, Achuff SC, Pottage A, Murray A, Prescott LF, Julian DG. Mexiletine in the pro-phylaxis of ventricular arrhythmias during acute myocardial infarction. *J Cardiovasc Pharmacol.* 1979;1:43-52.
- ³⁸ Smyllie HC, Doar JW, Head CD, Leggett RJE. A trial of intravenous and oral mexiletine in acute myocardial infarction. *Eur J Clin Pharmacol.* 1984; 26:537-542.

³⁹ Bell JA, Thomas JM, Isaacson JR, Snell NJC, Holt DW. A trial of prophylactic mexiletine in home coronary care. *Br Heart J*. 1982;48:285-290.

⁴⁰ Chamberlain DA, Jewitt DE, Julian DG, Campbell RWF, Boyle DMcC, Shanks RG. Oral mexiletine in high-risk patients after myocardial infarction. *Lancet*. 1980;2:1324-1327.

⁴¹ IMPACT Research Group. International Mexiletine and Placebo Antiarrhythmic Coronary Trial, I: report on arrhythmia and other findings. *J Am Coll Cardiol*. 1984;4:1148-1163.

⁴² Jarvis B, Coukell AJ. Mexiletine. A review of its therapeutic use in painful diabetic neuropathy. *Drugs*. 1998 Oct;56(4):691-707.

⁴³ Wallace MS, Magnuson S, Ridgeway B: Efficacy of oral mexiletine for neuropathic pain with allodynia: a double-blind, placebo-controlled, crossover study. *Reg Anesth Pain Med* 2000, 25:459–467.

⁴⁴ Kuhnert SM, Phillips WJ, Davis MD: Lidocaine and mexiletine therapy for erythromelalgia. *Arch Dermatol* 1999, 135:1447–1449.

⁴⁵ Marmura MJ. Intravenous Lidocaine and Mexiletine in the Management of Trigeminal Autonomic Cephalalgias. *Curr Pain Headache Rep* (2010)14:145-150.

⁴⁶ Marmura MJ, Passero FC, Young WB. Mexiletine for Refractory Chronic Daily Headache: A Report of Nine Cases. *Headache* 2008;48:1506-1510.

⁴⁷ No authors listed. Preliminary report; effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. *N Engl J Med*. 1989 Aug 10;321(6):406-12.

⁴⁸ Echt DS, Liebson PR, Brent Mitchell L et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The cardiac arrhythmia suppression trial. *N Eng J Med* 1991; 324:781-8).

⁴⁹ Teo KK, Yusuf S, Furberg CD. Effects of Prophylactic Antiarrhythmic Drug Therapy in Acute Myocardial Infarction; An Overview of Results From Randomized Controlled Trials.

⁵⁰ Monk JP, Brogden RN: Mexiletine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in the treatment of arrhythmias [published erratum appears in *Drugs* 1991 Mar;41(3):377]. [Review] [178 refs]. *Drugs* 1990; 40: 374 411.

⁵¹ Dejgard A, Petersen P, Kastrup J: Mexiletine for treatment of chronic painful diabetic neuropathy. *Lancet* 1988; 1: 9 11

-
- ⁵² Oskarsson P, Ljunggren JG, Lins PE: Efficacy and safety of mexiletine in the treatment of painful diabetic neuropathy. The Mexiletine Study Group. *Diabetes Care* 1997; 20: 1594-1597
- ⁵³ Rose M, Brooks V, Walburn J, Sanders D, Pandya S, Kissel J, Jackson C. Validation of quality of Life measure for myasthenia gravis. *Neuromusc. Disorders*. 2006; 16(Suppl1): S152.
- ⁵⁴ Vincent KA, Carr AJ, Walburn J, Scott DL, Rose MR. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQOL). *Neurology*. 2007;68:1051-1057
- ⁵⁵ Ware JE Jr, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473-483.
- ⁵⁶ Aaronson NK, Muller M, Cohen PD, et al (1998). Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. *J Clin Epidemiol* 51: 1055-1068.
- ⁵⁷ Martens WB, Blood CL, Logigan EL, . Computerized hand grip myometry reliably measures myotonia and strength in myotonic dystrophy (DM1) and myotonia correlates directly with CTG repeat size of the DM1 gene. *Neurology* 2004;62(Suppl 5);A169.
- ⁵⁸ Torres C, Moxley RT, Griggs RC. Quantitative testing of handgrip strength, myotonia, and fatigue in myotonic dystrophy. *J Neurol Sci* 1983; 60:157-168.
- ⁵⁹ G. Drost, J.H. Blok, D.F. Stegeman, J.P. van Dijk, B.G.M. van Engelen and M.J. Zwarts, Propagation disturbance of motor unit action potentials during transient paresis in generalized myotonia. A high-density surface EMG study. *Brain* **124** (2001), pp. 352-360
- ⁶⁰ Streib EW. AAEE minimonograph #27: differential diagnosis of myotonic syndromes. *Muscle Nerve* 1987;10:603-615.