

Clinical Study Protocol

DM-IMT - Controlled, randomized, three-arm interventional study on the safety and efficacy of regular respiratory muscle training in patients with myotonic dystrophy type 1

Version 1.2 (26. June 2019)

Study site	Friedrich-Baur-Institute Department of Neurology Klinikum der Universität München Ziemssenstr. 1 80336 Munich Germany
Principal Investigator	Dr. med. Stephan Wenninger Neurologist Department of Neurology Klinikum der Universität München Ziemssenstr. 1 80336 Munich Germany Tel: +49 89 4400 57400 Fax: +49 89 4400 57402
Principal Investigator Back-up	Dr. med. Kristina Stahl Medical intern for neurology Department of Neurology Klinikum der Universität München Ziemssenstr. 1 80336 Munich Germany Tel: +49 89 4400 57400 Fax: +49 89 4400 57402

This protocol was designed and will be conducted, recorded, and reported in accordance with the principles of Good Clinical Practice (GCP) as stated in the International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use and any applicable national and regional laws.

I have read and agree to abide by the requirements of this protocol.

Investigator Name (print) and Signature

Date

1 SYNOPSIS

TITLE: DMIMT - Controlled, randomized, three-arm interventional study on safety and efficacy of regular respiratory muscle training in patients with myotonic dystrophy type 1
PROTOCOL-NUMBER: Version 1.2 (26. June 2019)
STUDY CENTRE/CLINIC/INSTITUE: Friedrich-Baur-Institute, Klinikum der Universität München, Ziemssenstr. 1, 80336 Munich, Germany
OUTCOME MEASURE: The primary objective of this study is to investigate the safety of repetitive respiratory muscle training on respiratory muscle strength measured by MIP (maximum inspiratory pressure) in the upright position. The secondary objectives are <ul style="list-style-type: none">• Efficacy and safety of repetitive inspiratory strength muscle training in 15 patients with myotonic dystrophy type 1,• Efficacy and safety of repetitive inspiratory endurance muscle training in 15 patients with myotonic dystrophy type 1,• Measurement of the effect on the quality of life and muscular performance in patients with myotonic dystrophy type 1 during respiratory muscle training or in patients without respiratory muscle training, measured using the questionnaires "DM1-Activ", "Respicheck" and "FDSS-Fatigue and Daytime Sleepiness-Scale".• Measurement of the influence on CO₂ and O₂ values in capillary blood gas analysis of patients with myotonic dystrophy type 1 during respiratory muscle training or in patients without respiratory muscle training.• Measurement of the impact of respiratory muscle training on the 6-minute walking test in patients with DM1.
METHODS: This is a monocentric, three-arm, controlled, randomized interventional study for patients with myotonic dystrophy type 1. The patient is not blinded regarding his therapy. The patient must provide informed consent prior to performing any protocol-related procedure. Eligible patients will be randomized and either perform <ul style="list-style-type: none">(a) a nine-month respiratory strength training of respiratory muscles; or(b) a nine-month respiratory endurance training of the respiratory muscles, or(c) no respiratory muscle training. Lung function tests (FVC, FEV1, MIP, MEP), capillary blood gas analysis (pO ₂ , pCO ₂ , pH, Hb), 6-minute walking tests including oxygen saturation and patient questionnaires on quality of life and respiratory symptoms will be performed on scheduled visits throughout the treatment period. Adverse events (AEs) and concomitant medications / therapies are continuously monitored throughout the whole study period. Patients who are withdrawn from the trial for safety reasons or who withdraw their participation will not be replaced (i.e. a patient's study number will not be reused); however, it is planned to recruit additional patients if patients terminate participation prematurely.
NUMBER OF PATIENTS: A total of 45 patients are planned to be enrolled in the study. 15 patients per group will be randomized by the MUSCULAR IMPAIRMENT RATING SCALE (MIRS), age and gender.
INCLUSION- AND EXCLUSION CRITERIA: <u>Inclusion criteria:</u> A patient must meet all of the following criteria to be eligible for this study: <ol style="list-style-type: none">1. the patient is willing and able to provide signed informed consent.2. the patient is ≥ 18 years old.3. the diagnosis of myotonic dystrophy type 1 has been confirmed by molecular genetics.

4. the patient is able and willing to perform pulmonary function tests (PFT) and blood sampling for capillary blood gas analysis (pO₂, pCO₂) throughout the study, to fill in a diary and to complete questionnaires.

Exclusion criteria:

A patient who meets one of the following criteria will be excluded from this study or not randomized to the study:

1. the patient requires invasive ventilation (non-invasive ventilation is allowed).
2. the patient uses non-invasive ventilation longer than 16h/day.
3. the patient participates in another clinical trial where therapy is provided.
4. the patient cannot perform pulmonary function tests (PFT).
5. the patient is diagnosed with central sleep apnea in polysomnography and not sufficiently treated by NIV ventilation.
6. the patient is diagnosed with obstructive sleep apnea and is not sufficiently treated with NIV ventilation.
7. the patient cannot meet the requirements of the study, according to the investigator.

STUDY PROCEDURES:

After provided consent to participate in the study, the following diagnostic procedures will be performed:

- At screening, the eligibility of the patient is evaluated and the allocation to one of the two treatment groups (1, 2) or the "placebo group" (3) without respiratory muscle training will be done.
- At baseline, all patients will be assessed for a respiratory function status with FVC, FEV1, MIP, MEP, capillary blood gas analysis, 6-minute walking test including oxygen saturation and questionnaires ("DM1-Activ", "Respicheck" and "FDSS-Fatigue and Daytime Sleepiness-Scale") as well as a clinical examination (including MIRS).
- Patients of the groups 1 and 2
 - will perform a respiratory muscle training (IMT, inspiratory muscle training) for nine months.
 - During training (between months 3 and 9), inspiratory resistance will be increased at each visit (10-20% of baseline MIP), measured by the Borg scale.
 - Patients will be asked fill in a diary about their performed respiratory muscle training
- Patients of group 3 will not perform respiratory muscle training.
- At every visit, all patients will perform the following assessments every two months:
 - Pulmonary function tests, including FVC, FEV1, MIP, MEP (6 times including screening visit)
 - Functional assessments (6-minute walk test + Borg scale at screening, month 1, month 5 and month 9).
 - Clinical examination including MIRS at screening and month 9.
 - Patients are asked to complete the following questionnaires at defined times: three questionnaires on health status in myotonic dystrophy type 1, effects of fatigue and daytime fatigue on everyday life and one questionnaire on clinical symptoms of respiratory insufficiency (DM1-ACTIV, FDSS - FATIGUE AND DAYTIME SLEEPINESS SCALE und RESPICHECK).

STATISTICAL METHODS:

All patients who participate in this study will be included in the analysis. Data collected in this study will be documented using summary tables, figures, and patient data listings. For continuous variables, descriptive statistics (n, mean, median, standard deviation, minimum, and maximum) will be presented. For categorical variables, frequencies and percentages will be presented. Graphical displays will be presented as appropriate.

Power and Sample Size:

This is an exploratory study about efficacy and safety of respiratory muscle training in patients with Myotonic Dystrophy Type 1 and is not powered to make other statistical inferences.

Analysis-Sets:

Full Analysis Set: This analysis set consists of all patients who performed respiratory muscle therapy for at least 9 months or who did the check-ups throughout the 9 months without respiratory muscle training. All analyses will be based on this analysis set

Demographics and Baseline Characteristics:

Demographic and baseline data on medical/surgical history and disease history including length of repeats will be summarized using descriptive statistics for continuous variables and frequency distribution for categorical variables.

Safety:

A deterioration of >15% of FVC in comparison with baseline measurements will be defined as an AE, as well as developing unusual myalgia of respiratory muscles for more than 12 hours. The Adverse events will be collected from enrollment (=signed informed consent) through month 9 plus 7 days. Adverse events will be coded using the Medical Dictionary for Regulatory Activities, and categorized by system organ class and preferred term. All AEs will be displayed in patient listings. Adverse events will be categorized and tabulated for the treatment group overall by severity, seriousness, and relationship to study treatment

Efficacy:

Observed measurements and changes from baseline to each study time point in respiratory function parameters (% predicated sitting and supine FVC, forced expiratory volume in the 1st second of the FVC maneuver [FEV1], maximal inspiratory pressure [MIP], maximal expiratory pressure [MEP], and peak expiratory flow [PEF]); and blood gas analysis (pH, pCO₂, pO₂) as well as oxygen saturation and six-minute-walk-test with Borg scale will be summarized using descriptive statistics. In addition, 95% confidence intervals will be used to estimate the change from baseline at each study visit. Graphical displays showing data over time will be presented as appropriate.

REFERENCE TREATMENT:

There is no reference treatment to respiratory muscle training.

2 TABLE OF CONTENTS

1 SYNOPSIS	2
2 TABLE OF CONTENTS	5
3 ABBREVIATIONS.....	7
4 INTRODUCTION	8
5 RISKS AND BENEFITS.....	9
5.1 Summary of Potential Risks.....	9
5.2 Summary of Potential Benefits	9
6 STUDY OBJECTIVES	10
7 INVESTIGATIONAL PLAN	10
7.1 Discussion of study design, including choice of control group	10
7.2 End Points	11
7.2.1 Safety end points	11
7.2.2 Efficacy end points.....	11
7.2.3 Completion of a patient's participation in the study	11
7.2.4 Premature Patient Discontinuation from the Study	11
7.3 Patient Population and Selection.....	11
7.4 In- and Exclusion Criteria	11
7.4.1 Inclusion criteria	11
7.4.2 Exclusion criteria.....	12
7.5 Respiratory Muscle Training (RMT).....	12
7.6 Training Discontinuation.....	13
7.7 Prior and Concomitant Medications and Therapeutic Procedures	13
7.8 Blinding and Randomization	13
7.9 Therapy Compliance	14
8 EFFICACY ASSESSMENTS.....	14
8.1 Study Schedule of Events	14
8.2 Demographic and Screening Assessments	14
8.3 Efficacy Assessments.....	14
8.3.1 Physical Examination	14
8.3.2 Vital signs	14
8.3.3 Pulmonary Function Testing	14
8.3.4 Six minute walk test and Borg Scale	15
8.3.5 Patient-Questionnaires.....	15
8.3.6 Clinical Laboratory Tests (blood analysis)	16
8.4 Safety Assessments	16
9 ADVERSE EVENTS REPORTING (AE)	16
10 STATISTICAL METHODS AND PLANNED ANALYSES	17
10.1 General Considerations.....	17

10.2 Determination of Sample Size	17
10.3 Demographics and Baseline Characteristics	17
10.4 Patient Accountability	17
10.5 Study Training and Compliance.....	17
10.6 Efficacy Analyses	17
10.7 Physical Examination and Vital Signs.....	17
10.8 Missing or Invalid Data	18
11 SPECIAL REQUIREMENTS AND PROCEDURES	18
11.1 Institutional and Ethics Review	18
11.2 Changes to the Conduct of the Study or Protocol	18
11.3 Patient Informed Consent	18
11.4 Case Report Forms	18
11.5 Record Retention	18
11.6 Clinical Study Report	19
12 APPENDIX A: Schedule(s) of Study Events.....	20
13 APPENDIX B: RANDOMIZATION IN STUDY GROUPS.....	22
14 REFERENCES	23

3 ABBREVIATIONS

Abbreviation	Term
6MWT	6-minute walk test
AE	adverse event
COPD	chronic obstructive pulmonary (lung) disease
CRF	Case report form
FEV1	forced expiratory volume in the 1st second of the FVC maneuver
FVC	forced vital capacity
GCP	Good Clinical Practice
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMT	Inspiratory muscle training
MEP	maximal expiratory pressure
MIP	maximal inspiratory pressure
pCRF	paper case report form
PFT	pulmonary function test
RMT	Respiratory Muscle Training
SAE	serious adverse event
FDSS	Fatigue Daytime Sleepiness Scale
DM1-Activ	Rasch-built myotonic dystrophy type 1 activity and participation scale
BGA	Blood gas analysis

4 INTRODUCTION

Myotonic dystrophy type 1 (DM1, Myotonia congenita Curschmann-Steinert) is an autosomal dominant transmitted, rare, progeroid disease with slow progression (Bird 1993, Mateos-Aierdi, Goicoechea et al. 2015). With a prevalence of 10/100,000, it is the most common muscular dystrophy in adulthood (Norman, Floyd et al. 1989, Norwood, Harling et al. 2009). According to current knowledge, the expansion of the CTG trinucleotide repeat on chromosome 19q13.3 leads to an accumulation of transcription aggregates in the cell nuclei, which indirectly influences the RNA metabolism. The length of this expansion influences both the age of onset of the disease and the manifestation of the symptoms and thus the severity of the disease with increasing age (Meola 2013, Meola and Cardani 2015, Santoro, Masciullo et al. 2017). The different symptoms are currently best explained by incorrect splicing mechanisms in subordinated effector genes (Gladman, Mandal et al. 2013).

The clinical presentation of DM1 is very variable. The inconsistent combination of muscular and extramuscular symptoms often complicates early diagnosis and leads to an early reduction of quality of life, chronic disability, reduced ability to work and reduced life expectancy in affected patients. Leading muscle symptoms are myotonia, a slowly progressive and distal emphasized tetraparesis with reduced muscular endurance and performance, associated with muscular atrophy. The progressive muscle weakness includes not only the extremities, but also the trunk and respiratory muscles in various forms. In the majority of patients, respiratory muscle weakness leads to an early start of mechanical ventilation (Babacic, Goldina et al. 2018). A central respiratory regulation disorder, such as a central sleep apnea with concentration disorders, fatigue, headache and reduced physical and/or muscular endurance and performance, can appear in some of these patients as well (Boentert, Wenninger et al. 2017, Evangelista, Dias et al. 2017). Among high variability of extramuscular symptoms, neuropsychological symptoms such as chronic fatigue syndrome with excessive daytime sleepiness, depressive disorders, as well as reading and spelling difficulties have been observed (Stahl, Wenninger et al. 2016). These symptoms partly overlap with those of chronic respiratory insufficiency, with the consequence that diagnosis and therapy may be delayed (Boentert, Wenninger et al. 2017). Accordingly, recommendations for regular lung function diagnostics in patients with myotonic dystrophy and recently also a special questionnaire on symptoms of respiratory insufficiency were published (Sansone and Gagnon 2015). Cardiac (arrhythmia) and endocrine diseases (diabetes mellitus, thyroid metabolism), cataracts and gastrointestinal symptoms are regular accompanying symptoms. The combination of muscular and extramuscular symptoms leads to severe functional deficits, causing impaired quality of life at an early stage of the disease and may endanger the ability to work (Kierkegaard, Harms-Ringdahl et al. 2011, Laberge, Mathieu et al. 2013).

At the moment, there is no causal therapy for this autosomal dominant inherited disease, so the focus of patient care is on symptomatic therapy. Modafinil and Ritalin have long been used with moderate success in cases of excessive daytime sleepiness (Hilton-Jones, Bowler et al. 2012, Puymirat, Bouchard et al. 2012). High-frequency physiotherapy and occupational therapy can positively influence gripping function and thus self-sufficiency; an (intermittent) mechanical mask ventilation (NIV - non-invasive ventilation) is established with increasing restrictive ventilation disorder (Sansone and Gagnon 2015, Boentert, Wenninger et al. 2017); peripheral muscle relaxants or Mexiletin can reduce myotonia and pain caused by muscular

tension (Smith and Gutmann 2016); regular physical activity can decelerate the slowly progressing muscular degradation and prevent secondary complications - especially of joint function (Cup, Pieterse et al. 2007, Schilling, Forst et al. 2013, Voet, van der Kooi et al. 2013).

In contrast to other neuromuscular diseases with an early involvement of the respiratory muscles such as glycogen storage disease type II (Pompe disease) or Duchenne muscular dystrophy, there are no meaningful clinical studies for myotonic dystrophy type 1 that could prove a positive or negative effect of regular respiratory muscle training. On the other hand, it could be shown that early and regular respiratory muscle training can significantly improve inspiratory respiratory muscle strength and delay the onset of ventilation in Pompe's disease and Duchenne muscular dystrophy (Martin, Stern et al. 1986, Rodillo, Noble-Jamieson et al. 1989, Aslan, Gurses et al. 2014, Eidenberger and Nowotny 2014, Ferreira, Costa et al. 2016, Jones, Crisp et al. 2016, Human, Corten et al. 2017, Wenninger, Greckl et al. 2018). Only one case study from 2006 presented a lack of improvement of the symptoms of respiratory insufficiency after respiratory muscle training in one patient (de Freitas Fregonezi, Resqueti et al. 2006). Due to the lack of results from high-quality studies, respiratory muscle training has not yet been included in the current recommendations for patients with myotonic dystrophy type 1.

5 RISKS AND BENEFITS

5.1 Summary of Potential Risks

Study specific procedures and associated risks are bulleted below:

- Functional testing (six-minute-walk-test): falls, shortness of breath, muscle soreness, myalgia and fatigue
- Pulmonary function testing: dizziness, shortness of breath, discomfort
- Blood draws for oximetry: momentary discomfort, bruising, excessive bleeding, infection
- Respiratory muscle strength training: dizziness, myalgia of respiratory muscles, fatigue, shortness of breath, discomfort
- Respifit S®: Study results on respiratory muscle training in patients with the muscle disease M. Pompe ("Safety and efficacy of short- and long-term inspiratory muscle training in late-onset Pompe disease (LOPD): a pilot study". Wenninger S. et al (2018)) have provided no evidence that the use of the Respifit S device can cause relevant side effects or health risks so far.

5.2 Summary of Potential Benefits

Respiratory muscle training (RMT) is well known and established in patients with chronic obstructive lung disease (COPD) and can improve symptoms in these patients within four weeks of training (Borge, Hagen et al. 2014). While training, patients might improve their respiratory muscle function and symptoms related to respiratory insufficiency might vanish or improve. The quality of life, performance and fatigue may also improve. The need for (non-)invasive ventilation can also be reduced or delayed.

6 STUDY OBJECTIVES

The primary objective of this study is to determine the safety of repetitive respiratory muscle training on respiratory muscle strength as measured by MIP (maximum inspiratory pressure) in the upright position.

The secondary objectives are to evaluate the

- efficacy and safety of repetitive inspiratory strength respiratory muscle training in 15 patients with myotonic dystrophy type 1,
- efficacy and safety of repetitive inspiratory endurance respiratory muscle training in 15 patients with myotonic dystrophy type 1,
- Measurement of the effect on the quality of life and muscular performance in patients with myotonic dystrophy type 1 during respiratory muscle training or in patients without respiratory muscle training, using the questionnaires "DM1-Activ", "Respicheck" and "FDSS-Fatigue and Daytime Sleepiness-Scale",
- Measurement of the effect on the values CO₂ and O₂ in capillary blood gas analysis of patients with myotonic dystrophy type 1 during respiratory muscle training or in patients without respiratory muscle training,
- Measurement of the effect on muscular endurance performance in patients with myotonic dystrophy type 1 during respiratory muscle training or in patients without respiratory muscle training, measured by the 6-minute walking test.

7 INVESTIGATIONAL PLAN

This is a monocentric, three-arm, controlled interventional study for patients with myotonic dystrophy type 1. The patient is not blinded regarding his group assignment (group 1 and 2: respiratory muscle therapy, group 3 control group without respiratory muscle therapy). The patient must provide signed informed consent prior to the study. Suitable patients will either perform

- (a) A nine-month strength training of respiratory muscles (group 1: strength training); or
- (b) A nine-month endurance training of the respiratory muscles (group 2: endurance training);
- (c) Or will not perform any respiratory muscle training for nine months (Group 3: control group).

Lung function tests (FVC, FEV1, MIP, MEP), capillary blood gas analysis (pO₂, pCO₂), 6-minute walking tests, oxygen saturation, and patient questionnaires on quality of life and respiratory symptoms are performed on scheduled visits throughout the entire treatment period. Adverse events (AE) and concomitant medication / therapies will continuously be monitored throughout the whole study. Patients who must be excluded from the trial for safety reasons or who withdraw their participation will not be replaced (i.e. a patient's study number will not be reused); however, it is planned to recruit additional patients if patients terminate participation prematurely.

7.1 Discussion of study design, including choice of control group

This is a monocentric, three-arm, controlled interventional study for patients with myotonic dystrophy type 1. The patient is not blinded regarding his group assignment (group 1 and 2:

respiratory muscle therapy, group 3 control group without respiratory muscle therapy). The efficacy and safety of regular training of the respiratory muscle on the patient's health status is to be investigated.

The endpoints for this study are changes from baseline to month 9 after repetitive training.

7.2 End Points

7.2.1 Safety end points

Routine safety assessments are considered as primary endpoints of this study and are described in the sections 8, 9, 10 and 11.

7.2.2 Efficacy end points

Efficacy assessments are not considered to be primary endpoints of this study and are described in Section 8 and 10.

7.2.3 Completion of a patient's participation in the study

The length of a patient's participation will be from the time the informed consent form is signed until last planned assessment/visit and will be 9 months + 7 days follow-up period. A patient will be considered "completed" when the visit month 9 has occurred successfully according to the protocol.

7.2.4 Premature Patient Discontinuation from the Study

Patients are free to withdraw consent and/or discontinue participation in the study at any time, without prejudice to further treatment. A patient's participation in the study may also be discontinued at any time at the discretion of the Investigator.

Patients who are prematurely withdrawn from the study will be asked to complete all discontinuation assessments prior to withdrawal, if possible. Post-study serious adverse events (SAEs) will be reported according to Section 8 and 9. A patient will be considered early terminated if the patient does not complete the study after enrollment.

Patients who are withdrawn from the study will not be replaced (i.e., a patient's study number will not be reused); however, additional patients may be enrolled to offset patient dropouts.

7.3 Patient Population and Selection

A total of 45 patients are planned to be enrolled in the study. 15 patients will be randomized into 3 groups on the basis of the MUSCULAR IMPAIRMENT RATING SCALE (MIRS) age and gender.

7.4 In- and Exclusion Criteria

7.4.1 Inclusion criteria

A patient must meet all of the following criteria to be eligible for this study:

1. The patient is willing and able to provide signed informed consent.
2. The patient is ≥ 18 years of age.
3. The diagnosis myotonic dystrophy type 1 has been confirmed by molecular genetics.
4. The patient is able and willing to perform pulmonary lung function tests (PFT) throughout the entire study as well as capillary blood draws for oximetry, fill in a diary and answer questionnaires.

7.4.2 Exclusion criteria

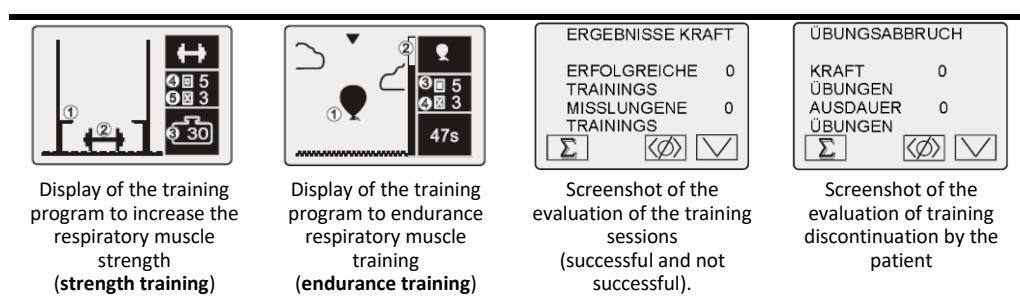
A patient who meets any of the following criteria will be excluded from the trial or not randomized to the trial:

1. the patient requires invasive ventilation (non-invasive ventilation is allowed).
2. the patient uses non-invasive ventilation longer than 16h/day.
3. the patient participates in another clinical trial using investigational treatment.
4. the patient cannot perform pulmonary function tests (PFT).
5. the patient is diagnosed with central sleep apnea in polysomnography and not sufficiently treated with NIV ventilation.
6. the patient is diagnosed with obstructive sleep apnea and not sufficiently treated with NIV ventilation.
7. the patient cannot meet the requirements of the study, according to the investigator.
8. the patient is unable to complete a 6-minute walking test.

7.5 Respiratory Muscle Training (RMT)

Respiratory muscle training (RMT) is known and established in patients with chronic obstructive pulmonary disease (COPD) (Borge, Hagen et al. 2014). Several publications point to a positive effect on patients with neuromuscular diseases studied in small populations in patients with amyotrophic lateral sclerosis, Duchenne muscular dystrophy, Pompe disease and myotonic dystrophy (Jones, Crisp et al. 2014, Ferreira, Costa et al. 2016, Jones, Crisp et al. 2016).

Myotonic dystrophy type 1 affects both inspiratory and expiratory muscles. Group 1 patients will perform inspiratory muscle strength training (IMT) in this study. Group 2 patients will perform inspiratory muscle endurance training. Both serve to improve ventilation by increasing respiratory coordination, endurance and strength. Using the "Respifit S®" training device, the two study groups can be treated with different training programs. The "Respifit S®" respiratory therapy device was chosen as it can train both, the strength and endurance of the respiratory muscles, in two separate programs and enables an evaluation of the successfully completed and unsuccessfully completed training sessions. The latter is necessary for the assessment of the efficacy of the respiratory training on completed training units. In addition, compliance can be evaluated. The complete RespifitS®-System contains a patient handset, a digital device displaying patient's efforts and remaining training series and an electronic patient identity card storing patient's trainings and results.



7.5.1 Respiratory Endurance Training

The Respifit S® offers a pressure measurement working as feedback control during inspiration, which is visually displayed to the test person. In endurance mode, the respondent breathes in

and out regularly through the hand set with the aim that a balloon on the screen is held for 60 seconds in the middle part of the screen. The inhalation resistance is determined by the predetermined respiratory minute volume of the test person. The training consists of 7 intervals (1 min each) with pauses of 1 min each. The training should be carried out at least 5 days a week. Patients are asked to fill in a diary of their training sessions. After each training session, patients are asked to indicate how strenuous their breathing training was using the BORG scale (Borg 1982).

7.5.2 Respiratory Strength Training

Patients perform the most common resistance training. A pressure-loaded inhalation valve and an unloaded exhalation flap valve only increase inhalation resistance, which provides a training of the inspiratory muscle strength. The resistance value of the inspiration valve is initially set to 30% of the maximum inspiratory pressure (MIP) measured at the beginning of the study. The intensity will be increased monthly by 10-20%, depending on the individual subjective exertion measured on the BORG scale (Borg 1982). The training consists of 7 intervals (2min) with 6 breaks (1min) in between. Patients should take 15 breaths at each interval. Training should be performed at least 5 days a week. Patients are asked to fill in a diary about their training sessions.

7.6 Training Discontinuation

A patient's study participation may be discontinued at any time at the patient's request or at the discretion of the Investigator. The following may be justifiable reasons for the Investigator to discontinue a patient from treatment:

- The patient was erroneously included in the study (i.e., was found to not have met the inclusion/exclusion criterion).
- The patient experiences an intolerable or unacceptable AE.
- The patient is unable to comply with the requirements of the protocol.
- The patient participates in another investigational study without the prior written authorization of the investigator.
- The patient becomes lost to follow-up.

Discontinuation of treatment does not imply withdrawal from the study, if applicable, the patient is suitable for admission to the control group. The investigator will document the reason(s) for treatment discontinuation on the CRF. Additional patients may be enrolled to offset effects of premature discontinuations.

7.7 Prior and Concomitant Medications and Therapeutic Procedures

Medications and therapies taken by the patient during the course of the study will be recorded in the Concomitant Medication CRF and Concomitant Therapies CRF, respectively.

7.8 Blinding and Randomization

This is a controlled, randomized, three-arm interventional study on the safety and efficacy of repetitive respiratory muscle training in patients with myotonic dystrophy type 1. As the disease is quite rare and the study is performed as pilot study, with 15 patients included in each group. The randomization software "Randoulette" of the LMU Munich is used for the randomization. The patients will be randomized in 3 groups of 15 patients each, age-, gender- and symptom-corrected according to the MUSCULAR IMPAIRMENT RATING SCALE (MIRS).

7.9 Therapy Compliance

The patient's compliance is monitored by a patient's diary, digital recording of the respiratory therapy device, and a successful performance of lung function testing. Missed or incomplete respiratory muscle training or function tests are clearly documented and considered in the analysis.

8 EFFICACY ASSESSMENTS

8.1 Study Schedule of Events

The study will be conducted as outlined in the following sections. Appendix A summarizes the study events at each visit.

8.2 Demographic and Screening Assessments

The patient's medical/surgical history and DM disease history including molecular genetics will be obtained to determine the patient's eligibility for the study, per inclusion and exclusion criteria in Section 7, prior to randomization. Demographic data, height, and weight will also be recorded at the Screening visit.

8.3 Efficacy Assessments

The efficacy of training will be evaluated using results from lung function tests (FVC, FEV1, MIP, MEP), capillary blood gas analysis (pH, pCO₂, pO₂), functional assessments (6-minute walk test, oxygen saturation and Borg scale), and questionnaires on quality of life and symptoms of respiratory failure.

8.3.1 Physical Examination

A complete physical examination will be conducted at the time points specified in Appendix A. The examination will include an assessment of the patient's general appearance; skin; head, eyes, ears, nose, and throat; examinations of lymph nodes, heart, lungs, abdomen, extremities/joints, neurological, mental status, and reflexes. Whenever possible, the same physician should perform the examination at each study visit. Any clinically significant abnormal findings that meet the definition of an AE per Section 8 and 9 (e.g., that result in an alteration in medical care, diagnostic or therapeutic) will be recorded on the AE page of the pCRF. The Investigator will continue to monitor the patient until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

8.3.2 Vital signs

Vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be taken prior to and after the performance of the 6MWT. Any clinically significant abnormal findings that meet the definition of an AE per Section 8 and 9 (e.g., that result in an alteration in medical care, diagnostic or therapeutic) will be recorded on the AE page of the pCRF. The Investigator will continue to monitor the patient until the parameter returns to baseline or until the Investigator determines that follow-up is no longer medically necessary.

8.3.3 Pulmonary Function Testing

PFT will be performed at time points specified in Appendix A. The PFT administration protocol will be standardized in accordance with the American Thoracic Society (ATS) guidelines (American Thoracic Society/European Respiratory 2002). PFT will include the assessment of

forced vital capacity (FVC), forced expiratory volume in the 1st second of the FVC maneuver (FEV1), maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), and peak expiratory flow (PEF) in the upright and supine positions.

FVC is the maximal volume of gas that can be exhaled with the patient breathing forcefully to obtain maximal airflow rates. For this measurement, the patient is instructed to inspire completely until the lungs are fully inflated. A nose clip is used to prevent leakage. Then the patient exhales as far as possible until the lungs are almost empty and the measured volume is recorded. Data are reported in liters and percent of predicted normal values based on age, gender, race, and height (Hankinson, Odencrantz et al. 1999).

Respiratory status will be assessed by spirometry using the KoKo PFT System © 2010 nSpire Health Inc. spirometer. FVC and FEV1 will both be measured in upright and supine position. In addition, the function of the respiratory muscles will be evaluated by the maximal respiratory pressures MIP for maximum inspiratory pressure and MEP for maximum expiratory pressure. For MIP and MEP in upright position, the CareFusion digital manometer from microRPM™ will be used with a flanged mouthpiece, as recommended by the American Thoracic Society (ATS) (American Thoracic Society/European Respiratory 2002). Calibration of software and spirometry devices will be done daily, as described in software manuals (Bolliger, Mathur et al. 2002).

8.3.4 Six minute walk test and Borg Scale

The six-minute walk test (6MWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface. The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway. The 6MWT has been used with a variety of other conditions than chronic obstructive pulmonary disease (COPD) such as heart failure and stroke, and is widely used in neuromuscular diseases. The six-minute-walk-test will be conducted as recommended by the American Thoracic Society (American Thoracic Society/European Respiratory 2002) The Borg scale is a self-reported questionnaire designed to subjectively assess dyspnea and exertion during activity (Borg 1982). The Borg scale rates dyspnea on a scale of 0 to 10 incorporating nonlinear spacing of verbal descriptors of the level of intensity of dyspnea. A higher Borg score indicates more severe dyspnea. The Borg scale will be administered prior to starting the 6MWT (≤ 15 minutes) and after completing the 6MWT (≤ 5 minutes).

8.3.5 Patient-Questionnaires

8.3.5.1 DM1-Activ-c-questionnaire

This questionnaire explores the possible relationship between a patient's health status and the implementation of activities of daily life (ADL). The responses provide information on the extent to which the underlying myotonic dystrophy type 1 disease affects everyday and social activities, so that the extent of the limitations can be assessed. The questionnaire includes 25 questions, which are answered with the options 1-3 ("I am not able to do this", "...I am able to do it, but only with difficulties" and "...it is no problem for me") (Hermans, Faber et al. 2010).

8.3.5.2 FDSS

The Fatigue and Daytime Sleepiness Scale (FDSS) questionnaire is a questionnaire of 12 questions on daytime sleepiness and symptoms associated with sleep disorders. The FDSS consists of the topics ESS, DSS and FSS. The 12 items selected for the final FDSS scale met all

expectations of the Rasch model, and the hierarchy of items was invariant in DM1 patients of different age, gender, disease type, educational level and use of psychostimulants, as well as between patients from different countries (Hermans, Merkies et al. 2013).

8.3.5.3 Respicheck

The Respicheck questionnaire was developed at the 207th working session on respiratory insufficiency in myotonic dystrophies. This questionnaire is very simple and contains 27 Yes / No questions for nine groups of symptoms related to respiratory insufficiency (Sansone and Gagnon 2015).

8.3.6 Clinical Laboratory Tests (blood analysis)

At the initial examination and every two months a capillary blood analysis will be performed, using epoc blood analysis system, which consists of epoc® BGEM Test Card, epoc® Host2 Mobile Computer and epoc® Care-FillTM Capillary Tubes. Calibration will be done as recommended in users' manual. The Care-Fill™ Capillary Tubes are designed to collect a blood sample from a skin puncture. The tube fills with a blood sample through a combination of capillary action and gravity flow. When sufficient blood is present, the tube fills readily and preserves the integrity of the blood sample until it can be tested by preventing clotting and alteration of analytic concentrations. For each blood draw, approx. 90µl are needed for sufficient analysis. In total, approx. 540µl are drawn per patient during the whole study. The following parameters will be measured: pH, pCO2, pO2.

Observed measurements and changes from baseline to study time points in month 1,3,5,7 and 9 will be descriptively summarized. All laboratory values will be classified as normal, above normal, or below normal based on normal ranges provided by the laboratory. Frequencies of abnormal values and clinically significant abnormal values will be summarized. All data will be presented in listings along with individual listings of patients with clinically significant abnormal laboratory values.

8.4 Safety Assessments

Safety will be assessed for all enrolled patients from the time of signing the informed consent up to 7 days after the final study visit (month 9). Safety parameters include pulmonary function testing (PFT, including FVC, FEV1, MIP, MEP), physical examination, vital signs and –at decision of investigator- clinical laboratory tests as needed. See also Section 9.

9 ADVERSE EVENTS REPORTING (AE)

A deterioration of >15% of FVC in comparison to baseline measurements will be defined as an AE, as well as developing unusual myalgia of respiratory muscles for more than 12 hours. AEs and SAEs will be coded using the Medical Dictionary for Regulatory Activities and summarized by primary system organ class and preferred term. Detailed listings of patients who experience AEs or SAEs will be presented. The incidence of treatment-emergent AEs and SAEs will be tabulated (frequencies and percentages) by severity, and by relationship to treatment. Adverse event severity will be categorized as mild, moderate, or severe. In tabulating severity of AEs on a per patient basis, the greatest severity will be assigned to a patient should there be more than one occurrence of the same AE with different reported severities. Relationships of the AE to treatment will be categorized as not related, unlikely related, possibly related, or related. The highest level of association will be reported in patients with differing relationships

for the same AE. Listings of AEs and SAEs for all patients will be provided, which will include severity and relationship to treatment, as well as actions taken regarding treatment, and patient outcome. A separate listing for patients who withdraw from the study due to AEs will be provided. The incidence of AEs leading to study discontinuations will also be summarized.

10 STATISTICAL METHODS AND PLANNED ANALYSES

10.1 General Considerations

Data collected in this study will be reported using summary tables, figures and patient data listings. Summary statistics (n, mean, median, standard deviation, minimum and maximum) will be calculated for the continuous variables and shift tables and/or frequencies, and percentages will be produced for the categorical variables. Due to the exploratory nature of this study, no formal inferential statistical tests will be performed.

10.2 Determination of Sample Size

Approximately 45 patients will be enrolled in this study. No formal sample size calculations have been performed. This is an exploratory study and is not powered to make any statistical inferences.

10.3 Demographics and Baseline Characteristics

Demographic and baseline data on medical/surgical history and DM1 disease history including molecular genetics will be summarized using summary statistics for continuous variables and frequency distribution for categorical variables. All data will be presented in by-patient listings.

10.4 Patient Accountability

Data from all patients who are enrolled in the study will be included in the summary of patient accountability. The frequency and percentage of patients who are enrolled in the study, discontinued from the study, and completed the study, along with reasons for discontinuation, will be summarized.

10.5 Study Training and Compliance

The number of days/weeks/months on which the training is carried out and the number of study training sessions carried out by patients are summarised using summary statistics.

10.6 Efficacy Analyses

Observed measurements and changes of the respiratory function parameters (FVC, FEV1 sitting and lying, MIP, MEP) up to the time of the study and health-related questionnaires on quality of life and symptoms of respiratory insufficiency are summarised using summary statistics. In addition, 95% confidence intervals will be used to estimate the change from baseline at each study visit. All data will be presented by study visit in by-patient listings.

10.7 Physical Examination and Vital Signs

Observed measurements and changes from baseline to study timepoints in physical examination findings, vital signs (blood pressure, heart rate, respiratory rate, and temperature) will be summarized. Listings of abnormal findings/values will be presented.

10.8 Missing or Invalid Data

All data will be analyzed as they were collected in the database. It is not planned to impute missing data using statistical methods.

11 SPECIAL REQUIREMENTS AND PROCEDURES

This protocol was designed and will be conducted, recorded, and reported in compliance with the International Conference on Harmonisation (ICH)/Good Clinical Practice (GCP) guideline. These requirements are stated in the ICH Guideline Topic E6 entitled “Guideline for Good Clinical Practice”.

11.1 Institutional and Ethics Review

This protocol and a patient informed consent form (ICF) must be reviewed and approved by an IRB/IEC before enrollment of patients (No. 19-330). Documentation of IRB/IEC and the approved consent form must be received by the Investigator or its designee prior to obtaining the patient's informed consent.

11.2 Changes to the Conduct of the Study or Protocol

Any changes in the study protocol, such as changes in the study design, objectives or endpoints, inclusion and exclusion criteria, and/or procedures (except to eliminate an immediate hazard) will be implemented only after the mutual agreement of the Investigator or designee. All protocol changes must be documented in protocol amendment(s). Protocol amendment(s) must be signed by the Investigator and approved by the IRB/IEC prior to implementation. Any changes in study conduct that result from a pending amendment will be considered protocol deviations until IRB/IEC approval is granted. Documentation of IRB/IEC approval must be returned to the Investigator or designee.

11.3 Patient Informed Consent

Investigators must adhere to Good Clinical Practice, which includes ethical principles that have their origin in the Declaration of Helsinki, when developing the patient informed consent form and when obtaining consent from the patient. Written informed consent is required prior to enrollment in the study. It is the responsibility of the Investigator to document the consent process within the source documents and obtain consent using an IRB/IEC approved consent form.

11.4 Case Report Forms

Data will be entered by the site onto the paper CRFs (pCRF) and locally stored data bases (Excel). Any erroneous entries made on the pCRFs should be corrected. Changes made to the data after initial entry into the pCRF will be unambiguously corrected and signed.

11.5 Record Retention

The Investigator is responsible for oversight and maintenance of the study records and patient source documents. The Investigator must retain study records for at least 10 years after formal termination of the clinical trial or for at least 10 years after the end of the trial. This is defined as the day on which all data to assess the safety and efficacy of respiratory muscle training have been collected, i.e. seven days after the last visit (month 9). However, these documents should be retained for a longer period, if required by other applicable requirements (e.g.,

applicable local regulatory requirement). Patient records or other source data must be kept for the maximum period of time mandated by the hospital, but not less than 10 years.

11.6 Clinical Study Report

A final clinical study report will be produced after study completion.

12 APPENDIX A: Schedule(s) of Study Events

Group 1 and 2:

	Visit 1 Screening month 0	Visit 2 follow-up month 1	Visit 3 follow-up month 3	Visit 4 follow-up month 5	Visit 5 follow-up month 7	Visit 6 final examination month 9
Informed consent	x					
Randomization	x					
Clinical examination including MIRS (Muscular Impairment Rating Scale)	x					x
Pulmonary function test (PFT), sitting and supine	x	x	x	x	x	x
Collection of historical data, especially polysonography and lung function	x					
Maximal expiratory pressure (MEP)	x	x	x	x	x	x
Maximal inspiratory pressure (MIP)	x	x	x	x	x	x
Blood gas analysis (capillary: pO ₂ , pCO ₂ , pH, Hb)	x	x	x	x	x	x
6-minute-walk-test including BORG-scale prior to and after test	x	x		x		x
questionnaire DM1-Activ	x	x	x	x	x	x
questionnaire FDSS (fatigue and daytime sleepiness)	x	x	x	x	x	x
questionnaire "Respicheck" for respiratory insufficiency	x	x	x	x	x	x
Check of patient diary		x	x	x	x	x
Check of data of respiratory training (<i>Respifit S</i> -training device)		x	x	x	x	x
adverse events (AE)		x	x	x	x	x
Instructions for the use of the training device	x	x	x	x	x	x
Increase of resistance by 10%-20%, individually according to BORG scale	start: 30% of MIP	x	x	x	x	

Group 3:

	Visit 1 Screening month 0	Visit 2 follow-up month 1	Visit 3 follow-up month 3	Visit 4 follow-up month 5	Visit 5 follow-up month 7	Visit 6 final examination month 9
Informed consent	X					
Randomization	X					
Clinical examination including MIRS (Muscular Impairment Rating Scale)	X					X
Collection of historical data, especially polysomnography and lung function	X					
Pulmonary function test (PFT), sitting and supine	X			X		X
Maximal expiratory pressure (MEP)	X			X		X
Maximal inspiratory pressure (MIP)	X			X		X
Blood gas analysis (capillary: pO ₂ , pCO ₂ , pH, Hb)	X			X		X
6-minute-walk-test including BORG-scale prior to and after test	X			X		X
questionnaire DM1-Activ	X			X		X
questionnaire FDSS (fatigue and daytime sleepiness)	X			X		X
questionnaire "Respicheck" for respiratory insufficiency	X			X		X
Check of patient diary						
Check of data of respiratory training (<i>Respifit S</i> -training device)						
adverse events (AE)		X	X	X	X	X
Instructions for the use of the training device						
Increase of resistance by 10%-20%, individually according to BORG scale						

13 APPENDIX B: RANDOMIZATION IN STUDY GROUPS

The Randomization Software "Randoulette" of the LMU Munich is used for the randomization. The patients are randomized in 3 groups of 15 patients each, age-, gender- and symptom-corrected according to the MUSCULAR IMPAIRMENT RATING SCALE (MIRS):

Group 1	Group 2	Group 3
Inspiratory strength training	Inspiratory endurance training	No respiratory muscle training
N = 15	N = 15	N = 15

14 REFERENCES

American Thoracic Society/European Respiratory, S. (2002). "ATS/ERS Statement on respiratory muscle testing." Am J Respir Crit Care Med **166**(4): 518-624.

Aslan, G. K., H. N. Gurses, H. Issever and E. Kiyan (2014). "Effects of respiratory muscle training on pulmonary functions in patients with slowly progressive neuromuscular disease: a randomized controlled trial." Clin Rehabil **28**(6): 573-581.

Babacic, H., O. Goldina, K. Stahl, F. Montagnese, V. Jurinovic, B. Schoser and S. Wenninger (2018). "How to Interpret Abnormal Findings of Spirometry and Manometry in Myotonic Dystrophies?" J Neuromuscul Dis **5**(4): 451-459.

Bird, T. D. (1993). Myotonic Dystrophy Type 1. GeneReviews(R). M. P. Adam, H. H. Ardinger, R. A. Pagon et al. Seattle (WA).

Boentert, M., S. Wenninger and V. A. Sansone (2017). "Respiratory involvement in neuromuscular disorders." Curr Opin Neurol.

Bolliger, C. T., P. N. Mathur, J. F. Beamis, H. D. Becker, S. Cavaliere, H. Colt, J. P. Diaz-Jimenez, J. F. Dumon, E. Edell, K. L. Kovitz, H. N. Macha, A. C. Mehta, M. Marel, M. Noppen, J. Strausz and T. G. Sutedja (2002). "ERS/ATS statement on interventional pulmonology. European Respiratory Society/American Thoracic Society." The European respiratory journal **19**(2): 356-373.

Borg, G. A. (1982). "Psychophysical bases of perceived exertion." Medicine and science in sports and exercise **14**(5): 377-381.

Borge, C. R., K. B. Hagen, A. M. Mengshoel, E. Omenaas, T. Moum and A. K. Wahl (2014). "Effects of controlled breathing exercises and respiratory muscle training in people with chronic obstructive pulmonary disease: results from evaluating the quality of evidence in systematic reviews." BMC pulmonary medicine **14**: 184.

Cup, E. H., A. J. Pieterse, J. M. Ten Broek-Pastoor, M. Munneke, B. G. van Engelen, H. T. Hendricks, G. J. van der Wilt and R. A. Oostendorp (2007). "Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review." Archives of physical medicine and rehabilitation **88**(11): 1452-1464.

de Freitas Fregonezi, G. A., V. R. Resqueti and P. Casan (2006). "[Domiciliary respiratory muscle training in myotonic dystrophy]." Archivos de bronconeumologia **42**(11): 605-607.

Eidenberger, M. and S. Nowotny (2014). "Inspiratory muscle training in patients with Amyotrophic Lateral Sclerosis: A systematic review." NeuroRehabilitation **35**(3): 349-361.

Evangelista, M. A., F. A. L. Dias, M. E. T. Dourado Junior, G. C. do Nascimento, A. Sarmento, L. P. Gualdi, A. Aliverti, V. Resqueti and G. A. F. Fregonezi (2017). "Noninvasive assessment of respiratory muscle strength and activity in Myotonic dystrophy." PLoS One **12**(6): e0177318.

Ferreira, G. D., A. C. Costa, R. D. Plentz, C. C. Coronel and G. Sbruzzi (2016). "Respiratory training improved ventilatory function and respiratory muscle strength in patients with multiple sclerosis and lateral amyotrophic sclerosis: systematic review and meta-analysis." Physiotherapy **102**(3): 221-228.

Gladman, J. T., M. Mandal, V. Srinivasan and M. S. Mahadevan (2013). "Age of onset of RNA toxicity influences phenotypic severity: evidence from an inducible mouse model of myotonic dystrophy (DM1)." *PLoS One* **8**(9): e72907.

Hankinson, J. L., J. R. Odencrantz and K. B. Fedan (1999). "Spirometric reference values from a sample of the general U.S. population." *American journal of respiratory and critical care medicine* **159**(1): 179-187.

Hermans, M. C., C. G. Faber, M. H. De Baets, C. E. de Die-Smulders and I. S. Merkies (2010). "Rasch-built myotonic dystrophy type 1 activity and participation scale (DM1-Activ)." *Neuromuscular disorders : NMD* **20**(5): 310-318.

Hermans, M. C., I. S. Merkies, L. Laberge, E. W. Blom, A. Tennant and C. G. Faber (2013). "Fatigue and daytime sleepiness scale in myotonic dystrophy type 1." *Muscle & nerve* **47**(1): 89-95.

Hilton-Jones, D., M. Bowler, H. Lochmueller, C. Longman, R. Petty, M. Roberts, M. Rogers, C. Turner and D. Wilcox (2012). "Modafinil for excessive daytime sleepiness in myotonic dystrophy type 1--the patients' perspective." *Neuromuscular disorders : NMD* **22**(7): 597-603.

Human, A., L. Corten, J. Jelsma and B. Morrow (2017). "Inspiratory muscle training for children and adolescents with neuromuscular diseases: A systematic review." *Neuromuscular disorders : NMD*.

Jones, H. N., K. D. Crisp, T. Moss, K. Strollo, R. Robey, J. Sank, M. Canfield, L. E. Case, L. Mahler, R. M. Kravitz and P. S. Kishnani (2014). "Effects of respiratory muscle training (RMT) in children with infantile-onset Pompe disease and respiratory muscle weakness." *Journal of pediatric rehabilitation medicine* **7**(3): 255-265.

Jones, H. N., K. D. Crisp, R. R. Robey, L. E. Case, R. M. Kravitz and P. S. Kishnani (2016). "Respiratory muscle training (RMT) in late-onset Pompe disease (LOPD): Effects of training and detraining." *Molecular genetics and metabolism* **117**(2): 120-128.

Kierkegaard, M., K. Harms-Ringdahl, L. W. Holmqvist and A. Tollback (2011). "Functioning and disability in adults with myotonic dystrophy type 1." *Disability and rehabilitation* **33**(19-20): 1826-1836.

Laberge, L., J. Mathieu, J. Auclair, E. Gagnon, L. Noreau and C. Gagnon (2013). "Clinical, psychosocial, and central correlates of quality of life in myotonic dystrophy type 1 patients." *European neurology* **70**(5-6): 308-315.

Martin, A. J., L. Stern, J. Yeates, D. Lepp and J. Little (1986). "Respiratory muscle training in Duchenne muscular dystrophy." *Developmental medicine and child neurology* **28**(3): 314-318.

Mateos-Aierdi, A. J., M. Goicoechea, A. Aiastui, R. Fernandez-Torron, M. Garcia-Puga, A. Matheu and A. Lopez de Munain (2015). "Muscle wasting in myotonic dystrophies: a model of premature aging." *Frontiers in aging neuroscience* **7**: 125.

Meola, G. (2013). "Clinical aspects, molecular pathomechanisms and management of myotonic dystrophies." *Acta myologica : myopathies and cardiomyopathies : official journal of the Mediterranean Society of Myology* **32**(3): 154-165.

Meola, G. and R. Cardani (2015). "Myotonic dystrophies: An update on clinical aspects, genetic, pathology, and molecular pathomechanisms." *Biochimica et biophysica acta* **1852**(4): 594-606.

Norman, A. M., J. L. Floyd, A. L. Meredith and P. S. Harper (1989). "Presymptomatic detection and prenatal diagnosis for myotonic dystrophy by means of linked DNA markers." Journal of medical genetics **26**(12): 750-754.

Norwood, F. L., C. Harling, P. F. Chinnery, M. Eagle, K. Bushby and V. Straub (2009). "Prevalence of genetic muscle disease in Northern England: in-depth analysis of a muscle clinic population." Brain **132**(Pt 11): 3175-3186.

Puymirat, J., J. P. Bouchard and J. Mathieu (2012). "Efficacy and tolerability of a 20-mg dose of methylphenidate for the treatment of daytime sleepiness in adult patients with myotonic dystrophy type 1: a 2-center, randomized, double-blind, placebo-controlled, 3-week crossover trial." Clinical therapeutics **34**(5): 1103-1111.

Rodillo, E., C. M. Noble-Jamieson, V. Aber, J. Z. Heckmatt, F. Muntoni and V. Dubowitz (1989). "Respiratory muscle training in Duchenne muscular dystrophy." Archives of disease in childhood **64**(5): 736-738.

Sansone, V. A. and C. Gagnon (2015). "207th ENMC Workshop on chronic respiratory insufficiency in myotonic dystrophies: management and implications for research, 27-29 June 2014, Naarden, The Netherlands." Neuromuscular disorders : NMD **25**(5): 432-442.

Santoro, M., M. Masciullo, G. Silvestri, G. Novelli and A. Botta (2017). "Myotonic dystrophy type 1: role of CCG, CTC and CGG interruptions within DMPK alleles in the pathogenesis and molecular diagnosis." Clinical genetics **92**(4): 355-364.

Schilling, L., R. Forst, J. Forst and A. Fujak (2013). "Orthopaedic Disorders in Myotonic Dystrophy Type 1: descriptive clinical study of 21 patients." BMC musculoskeletal disorders **14**: 338.

Smith, C. A. and L. Gutmann (2016). "Myotonic Dystrophy Type 1 Management and Therapeutics." Current treatment options in neurology **18**(12): 52.

Stahl, K., S. Wenninger, A. Schuller, F. Montagnese and B. Schoser (2016). "[Educational and Professional Qualifications of Adults With Myotonic Dystrophies - A Misleading Perception by the Myopathic Face?]." Fortschr Neurol Psychiatr **84**(4): 211-216.

Voet, N. B., E. L. van der Kooi, Riphagen, II, E. Lindeman, B. G. van Engelen and A. C. Geurts (2013). "Strength training and aerobic exercise training for muscle disease." The Cochrane database of systematic reviews(7): CD003907.

Wenninger, S., E. Greckl, H. Babacic, K. Stahl and B. Schoser (2018). "Safety and efficacy of short- and long-term inspiratory muscle training in late-onset Pompe disease (LOPD): a pilot study." J Neurol.