Cognitive behavioural therapy with optional graded exercise therapy in severely fatigued patients with myotonic dystrophy type 1: a single-blind randomised trial

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Supplemental Data

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Contributions

BGMvE, JG, HK and ST conceptualized the study and coordinated funding. Recruitment and data collection were performed at four clinical sites by KO (Nijmegen), CJ-M (Newcastle), SW (Munich) and FD (Paris), coordinated by BGMvE (Nijmegen), BS (Munich), GB (Paris), HL and GG (Newcastle). HK, MC and BGMvE designed the intervention. BGMvE, BS, GB, HL, GG, CF and MC designed the outcome measures. PD and AH performed pre and post-trial statistical analysis. SC and DGM devised and conducted the genetic analyses. RL and ST coordinated trial design, randomisation and data collation. MC contributed to the design and utilisation of triaxial accelerometery, measure selection, data cleaning, analytics and result interpretation. All authors were actively involved throughout in the design, implementation and completion of the study. KO wrote the first draft; all authors reviewed the manuscript for intellectual input, and all authors were involved in revisions.

Summary

Background

Myotonic dystrophy type 1 (DM1) is the most common form of muscular dystrophy in adults and leads to severe fatigue, significant physical functional impairment, and restricted social participation. In this study, we aimed to determine whether cognitive behavioural therapy (CBT) optionally combined with graded exercise compared to standard care alone improved the health status of patients with DM1.

Methods

In this, prospective 16-month trial, we randomly assigned in a 1:1 ratio, 255 severely fatigued adult DM1 patients to CBT compared to standard care. We defined severe fatigue as a score of ≥35 on the checklist individual strength, subscale fatigue severity (CIS-fatigue). Patients were recruited at four neuromuscular referral centres - with experience in treating DM1 patients - located in Paris, France, Munich, Germany, Nijmegen, the Netherlands and Newcastle, the United Kingdom. Randomisation was performed by local trial staff via a central, GCP-compliant, web-based system, developed by the Tayside Clinical Trials Unit. CBT focused on addressing reduced initiative, increasing physical activity, optimizing interaction with significant others, regulating sleep-wake pattern, addressing pain behaviours and beliefs and beliefs about fatigue and DM1. CBT was delivered by experienced and specifically trained CBT therapists over a 10-month period in 10-14 sessions, with the majority of session given in the first four to five months. A physical therapist supervised graded exercise module aimed at increasing physical fitness could be added to CBT, in two of the study centres. The primary end point was 10-month change on the DM1-Activ-c scale, a disease-specific Rasch-built measure of capacity for activity and social participation that has a 0-100 interval range. Only outcome adjudicators were blind to treatment allocation. Statistical analysis of primary outcome of change in DM1-Activ-c score was intention-to-treat, utilising mixed effects linear regression models with baseline as a covariate.

Findings

255 patients were randomised between April 2014 and May 2015, 128 to the intervention and 127 to standard care alone. At 10 months, the adjusted mean DM1-Activ-c score in the intervention group had improved 1·53 points (95% CI -0·14 to 3·20) and had worsened 2·02 (-4·02 to -0·01) points in the standard care group, with a mean difference in favour of the intervention groupof 3.27 points (0·93 to 5·62, p = 0·007). We recorded 244 and 155 adverse events (AE); and 24 and 23 serious adverse events (SAE) in the intervention and standard care groups, respectively. AE and SAE were distributed equally across groups, with the exception of falls occurring more frequently in the intervention group compared to the standard care group, 160 versus 72 falls, respectively. In the intervention group, 5 falls classified as SAE versus 1 in the standard care group. Most frequently occurring non-fall AE and SAE involved cardiac, pulmonary-thoracic or gastro-intestinal systems, and were in the latter two often of infectious nature.

Interpretation

CBT increased the capacity for activity and social participation in DM1 patients at 10 months. With no curative and few symptomatic treatments available, CBT could be considered for use in severely fatigued DM1 patients.

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Background

Myotonic dystrophy type 1 (DM1) is an autosomal dominant chronic progressive multi-system disorder and the most common form of muscular dystrophy in adults.[1] The disease leads to significant physical impairment, which in combination with the neuropsychological impacts of the condition, results in severely restricted social participation.[2-6] No curative treatment exists, and evidence for the efficacy of rehabilitative approaches is largely lacking, resulting in considerable unmet need for treatment that aims to improve health status.[7]

A DM1-specific model of factors determining health status was empirically derived from the findings of our longitudinal study.[8] This model predicts that improvement of patient reported health status can be achieved by addressing reduced initiative, optimizing physical activity, and alleviating experienced fatigue. Previous studies have shown that fatigue is a highly prevalent and debilitating symptom in DM1.[9,10] Cognitive behavioural therapy (CBT) has been found effective in relieving fatigue in chronic fatigue syndrome and type 1 diabetes.[11,12] In facioscapulohumeral muscular dystrophy, CBT reduced fatigue and increased objective activity (as measured with actometry) and social participation.[13] In addition, there is accumulating evidence supporting the beneficial effects of low-to-moderate-intensity strength and aerobic exercise training and an active lifestyle in neuromuscular diseases.[14,15] Nevertheless, recent reviews conclude that studies evaluating graded activity in neuromuscular diseases are limited in number and quality, and that there is a need for disease-specific, randomised, controlled trials investigating the effect on health status.[14,16] We therefore conducted a large international, multi-center, randomised trial to determine whether CBT plus optional graded exercise improved health status of patients with DM1 compared to standard care alone.[17]

Methods

Study design and participants

Four European clinical sites (Munich, Germany; Nijmegen, the Netherlands; Newcastle, UK; Paris, France) collaborated in this study. Eligible patients with a confirmed genetic DM1 diagnosis who provided written informed consent were randomly assigned to study groups. There were up to five assessment visits: eligibility screening followed by baseline, five, 10 and 16 months post-randomisation, with the primary outcome being measured at 10 months. The study protocol has previously been published.[17]

We recruited DM1 patients aged 18 years and older who were severely fatigued as measured by the checklist-individual strength subscale fatigue (CIS-fatigue, score ≥35)[18], able to walk independently (walking aids permitted) and undergo trial interventions (Table S1 in the Web Extra material, available at thelancet.com). The study was approved by the institutional review boards at each of the four clinical sites and conducted in accordance with the provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. Patients were recruited by invitation via DM1 registries, from clinics via their treating neurologists, or independently through study awareness by patient organizations. We invited the patients' caregiver to participate, as described previously.[17]

Randomisation and masking

Eligible patients were randomised in a 1:1 ratio via a central, GCP-compliant web-based system called the Tayside Randomisation System (TRuST) developed by the Tayside Clinical Trials Unit at the University of Dundee, UK. Trials Unit statisticians and data management staff programmed TRuST to implement the randomisation described in the OPTIMISTIC protocol namely that randomisation was stratified by site (location of inclusion) and minimized for baseline DM1 severity (as assessed by the muscular impairment rating scale (MIRS)) and for baseline involvement of a caregiver.[19] Immediate family members (i.e parents, children, siblings) were allocated as a cluster to avoid treatment contamination. Only outcome adjudicators were blind to treatment allocation, patients could not be blinded to allocation. Outcome adjudicators were instructed to refrain from interactions with the patient

that could disclose treatment allocation. During therapy, patients were discouraged from disclosing their treatment allocation to outcome adjudicators.

Study procedures and interventions

Patients in the comparison group received standard care applicable to each individual's country (table S2 in the Web Extra material). In addition to receiving standard care, all patients randomised to the intervention arm also received CBT (details in table S3 in the Web Extra material).[17] In a process of shared-decision making on the basis of therapist assessment and questionnaire evaluation, CBT was customized to the individual participant by the selection of one or more appropriate treatment modules: regulating sleep-wake pattern, compensating for a reduced initiative, formulating helpful beliefs about fatigue and DM1, optimizing social interactions and coping with pain. In addition, CBT included a graded activity module for every patient. To ensure a high degree of treatment integrity, CBT was manual-based, delivered by experienced CBT therapists with extensive training prior to start of the trial, and monitored during the delivery of the intervention (table S3). The treatment manual is available upon request (see table S3 for details). We evaluated treatment integrity of CBT as given during the conduct of the trial by means of evaluation of therapist-recorded case report forms from each session from every CBT participant, and by the assessment of audio records of CBT sessions that were recorded during the intervention (details in Web Extra material, S8).

If considered appropriate through a process of shared-decision making between CBT therapist and participant, a graded exercise module supervised by a physical therapist could optionally be added to CBT in the participants randomised to intervention (table S4 in the Web Extra material). Although we planned this in all four centres, differences in standard care meant we could implement the graded exercise in two out of four sites (Nijmegen and Newcastle). As it was not possible to offer the graded exercise module as an option within the French and German care pathways for DM1 patients, this constituted a protocol

deviation, as listed in the Web Extra material. The graded exercise module constitutes a structured exercise program aimed at increasing physical fitness. The program was individually defined, but targeted incorporating moderate intensity exercises (e.g. walking, cycling, jogging or dancing) for at least half an hour, three times a week. The graded exercise module was given during the intervention period. The overall intervention (*i.e.* CBT and GET when applicable) was scheduled for a duration of 10 months, starting directly after randomisation. Patients were to receive 10-14 sessions of CBT (no specific duration specified), with the majority delivered in the first 4-5 months. We planned for a minimum of 5 face-to-face sessions, but other communication formats, such as telephone or video calls were acceptable.

Onsite and remote visits to assess protocol compliance and adherence to good clinical practice guidelines were performed during the conduct of the study by local trial staff and by staff from the coordinating Trials Unit in Dundee, United Kingdom.

Outcomes measures

The primary outcome was the change in DM1-Activ-c at the end of the 10-month intervention period (Web Extra material, table S5). The Rasch-built DM1-Activ-c is a DM1 specific patient-reported outcome measure of capacity for activity and social participation.[20,21] The DM1-Activ-c with a 0-100 score range is the updated version of the DM1-Activ scale that had a 0-40 score range. We based our power calculation on the DM1-Activ and planned it to be the primary outcome measure. However, deviating from the study protocol (Web Extra – list of protocol deviations), we decided to use the DM1-Activ-c after criticism of the DM1-Activ had led to the publication of an updated version that was available to us before the start of the study.[21]

Predefined secondary outcome measures categorized into five groups were collected: physical activity and exercise capacity: six-minute walk test (6MWT) with Borg scale assessment, myotonic dystrophy health index (MDHI), physical activity measured with an

accelerometer (Web Extra S9); fatigue and sleepiness: fatigue and daytime sleepiness scale (FDSS), CIS-fatigue; quality of life: individualised neuromuscular quality of life questionnaire (InQoL); depressive symptoms: Beck-depression inventory-fast screen (BDI-fs) ;and cognition: Apathy evaluation scale – clinician version (AES-c) and Stroop test interference score (Table S5 and study protocol paper).[17] The Borg scale is a subjective measure of perceived exertion taken immediately after the 6MWT; we utilised the 0-10 scale, as recommended previously.[22] For accelerometry, we calculated mean 24h activity levels, and levels of activity during the 5 most active and 5 least active hours of the day. Adverse events (AE) and serious adverse events were reported continuously during the study and reviewed at each study visit.[17]

Statistical analysis

The agreed statistical analysis plan (SAP) was made publicly available at www.optimistic-dm.eu prior to completion of the study (available from: www.optimistic-dm.eu: http://www.optimistic-dm.eu/images/com_projectfork/progress/OPTIMISTIC_SAP.pdf). Analyses were done by the trial statistician (A.H.), and checked by a second statistician (P.T.D). Based on a minimum clinically important mean difference of 1.4 on the 40-item DM1-Activ scale, a standard deviation of 3.5, effect size = 0.4, 80% power at the 5% significance level, a total sample size of 200 patients was required.[17] We accounted for the potential of clustering of DM1 family members in identical treatment arms by inflating the sample size to 208. The trial was also fully powered for 6MWT, a secondary outcome assessing exercise capacity.[23] The recruitment target was set at 296 to allow for a potential drop-out rate of up to 30% based on previous pilot studies in DM1 patients.[24] Full details of the sample size calculations have been described previously (see full trial protocol and SAP).[17]

The primary outcome analysis was conducted according to the principles of intention-to-treat as outlined on the ICH E9 ‘Statistical Principles for Clinical Trials’. We utilized mixed effects

regression models with baseline scores as a covariate to assess the change in DM1-Activ-c score at 10 months. Priorly, the raw sum scores of the DM1-Activ-c scale were translated into a log-odds units (logit) scale, using the Rasch-model.[25] Since logits are difficult to interpret intuitively, the logits were converted into a centile metric score with values ranging from 0 (most severe activity and social participation limitations) to 100 (no activity and social participation limitations). The mixed effects models included the intervention (as a binary variable), age and the minimisation variables (MIRS score and involvement of the caregiver at baseline (as a binary variable) as fixed effects and site as random effect. Random effects were included for each subject in the repeated measures analyses, as well as for correlation within family group. Results are presented as model-derived means and 95% CIs. Planned subgroup analyses were carried out by testing for a subgroup by intervention interaction, as detailed previously (SAP).[17] Predefined subgroups were implemented for number of CBT sessions attended, clinical site, severity of DM1 as defined by MIRS score, involvement of the caregiver, age, sex, and addition of the graded exercise module to CBT. All these analyses were repeated for all the secondary outcome measures. In addition, we performed post-hoc repeated measures analysis for primary and secondary outcomes at all timepoints. We used SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) for statistical analyses.

Role of the funding source

The funder of this trial had no role in the study design, data collection, analysis, interpretation of data, writing the report, or decisions regarding when to submit publications. All authors were involved in design and/or conduct of the study and in the preparation of the manuscript. All authors had full access to all data in the study and all authors take full responsibility for the decision to submit the paper for publication. They attest to the accuracy, completeness of the data and analyses. Researchers wishing to get access to the data collected in the OPTIMISTIC study are requested to contact the last author at Baziel.vanEngelen@Radboudumc.nl and sign a data access agreement. Requests for

access will be reviewed by a panel consisting of one representative of the 4 clinical sites each, chaired by Baziel van Engelen.

Results

Study patients

Patients were randomised between April 2, 2014 and May 29, 2015, with follow-up continuing until October 17, 2016 when the last patient underwent the 16-month assessment. A total of 255 patients underwent randomisation, 128 patients were allocated to the intervention and 127 allocated to standard care alone (Figure 1). Baseline characteristics between both groups were similar (Table 1). Thirty-three out of the 128 (26%) patients randomised to intervention were involved in the additional graded exercise module. There was no cross-over from standard care to intervention; four patients randomised to CBT considered it too much burden and did not attend any sessions, but remained in the trial. At 10 months, 231 (91%) patients completed the primary outcome evaluation, with similar losses to follow-up across both groups. By the end of the study at 16 months, 225 (88%) patients remained in the trial, with a total of 14 formal withdrawals in the intervention group and 16 in the standard care group. The reasons given for trial withdrawal included the burden of travelling to clinical site for trial measurements and the number of questionnaires to be completed at each visit.

Protocol deviations

During the conduct of the study, some protocol violations occurred; these are listed in the Web Extra Material available at thelancetneurology.com. Most importantly, we made use of DM1-Activ-c scale, an updated version of the DM1-Activ scale. Whereas the original scale DM1-Activ was published in 2010, criticism led to its revision and publication of an updated version in 2015.[20,21] As DM1-Activ-c was available before inclusion of the first patient, this updated version was used in the trial.[21] In addition, although we planned to offer graded

exercise in all centres, we were only able to provide graded exercise in Nijmegen and Newcastle, thus limiting the availability of this add-on to CBT. Other deviations that occurred are listed in the Web Extra material.

Primary and secondary outcomes

After 10 months, the DM1-Activ-c scale, demonstrated an adjusted mean increase of 1·53 (95%CI: -0.14 to 3.20) points in the CBT group compared with an adjusted mean decrease of 2·02 (95%CI: -4.02 to -1.01) points in the standard care group (Table 2). In our predefined primary outcome analysis of DM1-Activ-c, there was a difference between both groups of 3·27 points (95%CI: 0·93 to 5·62, p = 0·007) in favour of the intervention group at 10 months. Differences at 10 months in favour of CBT were also found for total distance on 6MWT, the fatigue and daytime sleepiness scale (FDSS), CIS-fatigue and daily activity levels (24 hours and most active 5 hours, average of seven consecutive days) measured by accelerometry (Table 2). Although MDHI and InQoL-quality of life scores decreased from baseline to 10 month follow-up in the intervention and standard care group, no significant between-group differences were found. Three secondary outcomes measures (*i.e.* apathy evaluation scale, Stroop interference, BDI-FS), demonstated no change over time and no between-group differences (Table 2).

With one exception (i.e. the effect of site on FDSS at 10 months), pre-specified subgroup analyses yielded no significant interactions of age, sex, site, MIRS, involvement of caregiver, number of CBT sessions or the addition of a supervised graded exercise module to CBT on primary or secondary outcomes at 10 months, after Bonferroni correction for multiple testing (Web Extra tables S6a and S6b). In a post-hoc analysis, scores on the CIS-fatigue scale at 10 months had decreased to <35 in 47 out of 112 (42%) and 20 out of 106 (19%) patients in the intervention and standard care groups, respectively.

For DM1-Activ-c, post-hoc repeated measures analysis demonstrated improved scores compared to baseline in the intervention group at five months, maximizing at 10 months and

continuing until 16 months, although there was a drift towards the standard care group scores at 16 months (Web Extra table S7). The difference between intervention and standard care groups over all time periods was in favour of the intervention (p = 0·004). Similar temporal patterns were seen for 6MWT, MDHI, FDSS, CIS-fatigue, accelerometry (mean 24 hours and highest 5 hours of activity) and InQoL (quality of life domain) (Web Extra table S7). Of these, 6MWT, FDSS, CIS-fatigue and accelerometry demonstrated significant between-group differences. BDI-fs and AES-c scores were relatively stable across timepoints and we detected no significant between-group differences. Although Stroop interference scores improved with time in both groups, no between-group differences were found (Web Extra table S7).

Adverse events

We recorded a total of 399 adverse events (AE) in 128 subjects, with 244 events in 65 patients in the intervention group compared to 155 events in 63 patients in the standard care group (Table 3). A total of 226 (56·6%) AE were related to falls, 155 in the intervention and 71 in the standard care group. 51 AE (12·8%) were related to infections and infestations, 32 in the intervention versus 19 in the standard care group (table 3), these AE comprised mostly upper respiratory tract infections, influenza and infections in the oral cavity. We recorded 5 and 12 AE related to the respiratory tract, thorax and mediastinum, in intervention and standard care group, respectively. All other AEs were distributed equally between groups (table 3). A total of 47 serious adverse events (SAE) occurred in 34 patients during the conduct of the study (Table 4). SAE occurred with similar frequency in the intervention group and the standard care group; 24 versus 23 events in 19 and 15 patients, respectively. Distribution of SAE across both groups was similar, with the exception of SAE related to falls, which occurred more frequently in the intervention group (five versus one).

Discussion

The multi-system and progressive nature of DM1 leads to severe physical impairment, restricted social participation and premature death, yet no FDA approved therapies are available.[3,26-28] Experienced fatigue is a highly prevalent and debilitating symptom that has been shown to have the greatest impact on the lives of patients with DM1.[10] Data from this prospective trial, in which severely fatigued adult DM1 patients were randomly assigned to CBT compared to standard care, show that CBT by month 10 increased capacity for activity and participation as measured with the DM1-Activ-c scale. In addition, CBT was superior to standard care on several secondary outcome measures of experienced fatigue (CIS-fatigue and FDSS), exercise capacity (6MWT), and objective physical activity as measured with accelerometry. At 10 months, improvements in outcome measures for quality of life (InQoL – quality of life subdomain) and disease burden (MDHI) were not significantly different between groups. It should be noted the trial was not powered for any of the secondary outcome measures except the 6MWT.

In DM1, few, if any fully validated disease-specific outcome measures exist, complicating the conduction of clinical trials in DM1.[29] The sensitivity to change for DM1-specific outcome measures, including the DM1-Activ-c scale, was unknown during the design phase of the trial. Nonetheless, we selected the best outcome measures available at that time, after careful consideration in our consortium and based on consensus literature in the international DM1 community.[30] We think the clinical relevance of a 3·27 point difference on the DM1-Activ-c at 10 months, is supported by concurrent changes in the secondary outcome measures in favour of the intervention group that measured activity, exercise capacity, and fatigue. In particular, the 26·5 meter difference between groups at 6MWT at 10 months would be beyond the minimal clinically important change in DM1, which was previously defined as a 6% change in walking distance between assessments.[23] In the intervention group alone, the increase in walking distance from 389 to 421 meters means an increase of approximately 8%. The outcomes at follow-up showed a tendency for a decrease of the beneficial effects of CBT over time. We suggest that booster sessions of CBT may help to maintain beneficial

effects to their maximum.[31] Intriguingly, despite the increase in activity and exercise capacity, our study did not demonstrate changed levels of apathy. This may be explained by the nature of the CBT module dealing with apathy, in which we aimed to teach patients how to compensate for reduced initiative (but did not aim to increase levels of initiative per se).

Subgroup analysis demonstrated that treatment effects were largely independent of age, sex, clinical site, the addition of a graded exercise supervised by a physical therapist, MIRS score at study entry or involvement of a caregiver. This means that despite differences in health-care systems, favourable effects can be achieved in different settings. The lack of additive benefit with the addition of the graded exercise module means that CBT alone is capable of increasing activity levels and exercise capacity in DM1 patients. However, it should be noted that the group of patients that were involved with the graded exercise module was relatively small, which means care is needed when interpreting this result. Moreover, our results do not at all preclude a beneficial effect of exercise therapy per se (i.e. without CBT) in DM1 patients, that was suggested in previous literature.[32,33] Finally, we are suprised to find that the involvement of a caregiver with the study did not affect outcome, as we had expected better outcomes through supportive effects when caregivers were involved with the study.

With regards to CBT safety, the equal distribution of SAE across groups is reassuring. However, falls were more frequent in the intervention group. Falls are a common complication in natural DM1 history, but the increased risk of less serious falls linked to the intervention underlines the importance of monitoring and where possible addressing this issue in clinical practice and future clinical trials.[34,35] Furthermore, patients may underreport DM1 related complications, such as falls, as a result of reduced disease awareness.[36] The excess fall frequency in the CBT group might be partly explained by a better recall resulting from more frequent contacts with trial staff (i.e. CBT therapists). Another explanation is a true increase in fall frequency as a result of spending more time being active, during which time a higher number of falls may occur. Other factors that we did not evaluate, such as the occurence of cataracts, may have influenced our results. It should be noted that the total

number of falls (i.e. 226) recorded in our study is relatively low in comparison with the recent Swedish study reporting falls in DM1 (which reported more than 200 falls occuring over a 1 year period in 43 DM1 patients). This could be due to differences in fall evaluation and the fact that less severely affected patients (as defined by MIRS score) were excluded from the other study.[35] Nevertheless, it seems reasonable to conclude that increasing activity levels in people with DM1 will lead to more falls, though most are minor. Balancing this potential harm against the potential benefit of increased activity levels needs to be a shared decision between patient, carers and health professionals.

This trial was characterized by high recruitment and low drop-out rates, in contrast to a previous study in this patient population.[24] The selection of severely fatigued DM1 patients increases the generalisability of our results, as a previous study found severe fatigue in 74% of otherwise unselected DM1 patients, using the same instrument and cut-off score (*i.e.* CIS-fatigue ≥35).[9]

The trial has some limitations. The lack of information on respiratory muscle involvement can be considered a limitation of our study, as this may influence fatigue, physical activity and exercise capacity. Possibly, more frequent contact with trial staff for patients in the intervention group might have led to desirability bias: more desirable answers on patient-reported outcome measures in comparison with the standard care group. Nevertheless, the statistically significant differences on objective physical activity, as measured with accelerometry and the six-minute walk test, a measure of exercise capacity, argue against desirability bias as a sole explanation for our favourable results. In common with other studies employing accelerometry, there were missing data.[37,38] However, the quantity of missing data did not differ significantly between groups; with comparable reasons of noncompliance and device loss or failure, to those reported in the literature.[37,38]

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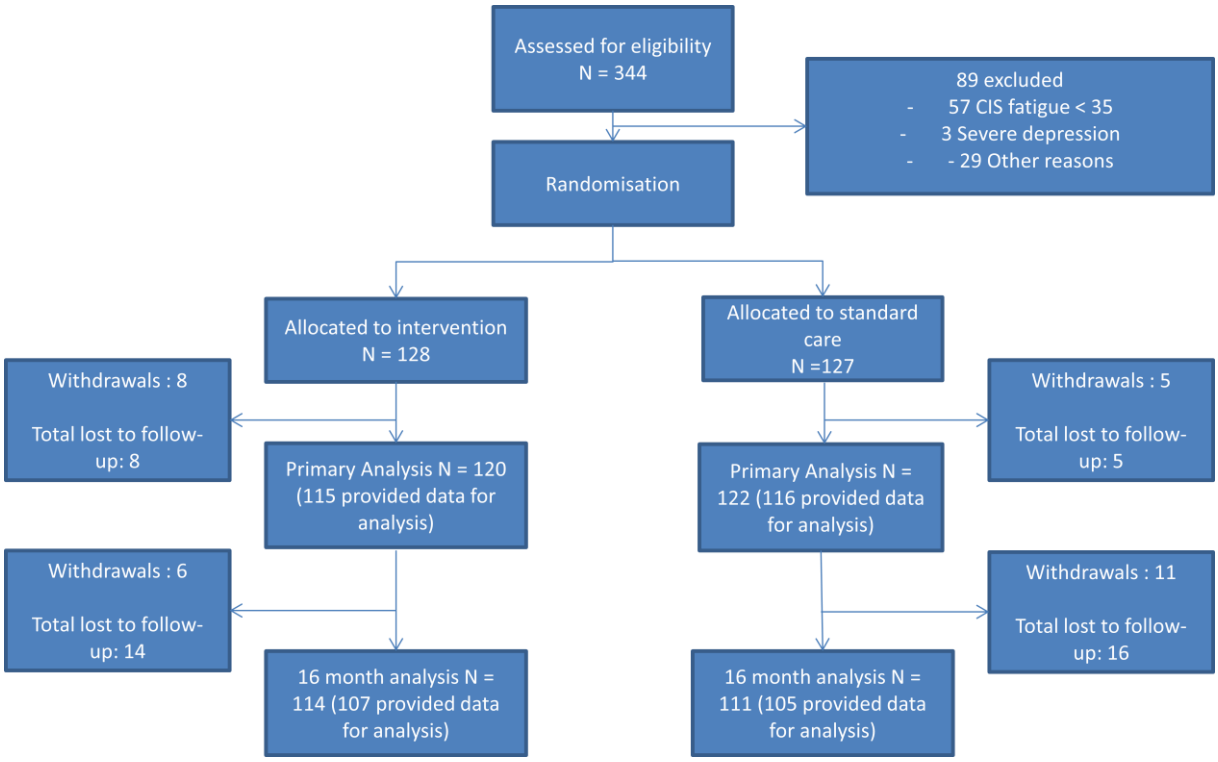

Figure 1. **Screening, randomisation, treatment, and follow-up in the trial**

Abbreviations: CIS-fatigue: checklist individual strength, subscale fatigue

Table 1. **Characteristics of patients at study entry**

Characteristic*	**Intervention group (N = 128)**	**Standard care group (N = 127)**
Clinical characteristics		
Age in years - mean	44·8 ± 11·7	46·4 ± 11·3
Sex male/female – no. (%)	70 / 58 (55% / 45%)	67 / 60 (53% / 47%)
BMI in kg/m^2	26·5 ± 6·1	26·2 ± 5·3
Age at disease onset in years	24·9 ± 12·6	26·2 ± 13·3
Duration of disease in years	19·7 ± 9·6	19·4 ± 10·5
Participants with a family member in the study – no. (%)	12 (9%)	18 (14%)
Location of enrollment – no (%)		
- Paris, France	37 (29%)	34 (27%)
- Munich, Germany	33 (26%)	33 (26%)
- Newcastle, United Kingdom	25 (20%)	27 (21%)
- Nijmegen, the Netherlands	33 (26%)	33 (26%)
Years of education	14·0 ± 3·5	14·6 ± 4·2
MIRS – median, ranges	3 (1 to 5)	3 (1 to 5)
Use of walking aids – no. (%)		
- Walking with aids†	23 (18%)	25 (20%)
- Intermittent use of wheelchair†	18 (114%)	20 (16%)

CIS-fatigue	44·9 ± 5·92	44·9 ± 6·3
BDI-FS	4·3 ± 3·1	4·0 ± 3·2
Involvement of caregiver† – no. (%)	56 (44%)	50 (39%)
Employment – no. (%)	46 (36%)	49 (39%)
Concomitant condition and therapy		
Presence of cardiac condition – no. (%)		
- Cardiac condition – not further specified	6 (5%)	2 (2%)
- Cardiac arrhythmia or conduction defect	37 (30%)	41 (33%)
- Cardiomyopathy	3 (2%)	3 (2%)
Presence of pacemaker and/or ICD – no. (%)	23 (18%)	21 (17%)
Regular use of assistive ventilatory device – no. (%)	23 (18%)	16 (13%)
Medication – no. (%)		
- Psychostimulant drug use (total)	25 (20%)	25 (20%)
- Modafanil	20 (16%)	19 (15%)
- Ritalin	2 (2%)	1 (1%)
- Antidepressants	3 (2%)	5 (4%)
Genetics		
Estimated progenitor CTG repeat length – median (range)	233·0 (50 to 789)	211·5 (61 to 726)
Modal CTG repeat length – mean, median		

(SD)	508·9, 482·0 ± 276·1	512·3, 470·0 ± 292·2

Table 1. **Characteristics of patients at study entry**

* Plus-minus values are observed means ± SD.

† one missing value for walking with aids, intermittent wheelchair use, involvement of the caregiver.

Abbreviations: BMI: body mass index, MIRS: muscular impairment rating scale, CIS-fatigue: checklist individual strength, subscale fatigue, BDI-FS: Beck depression inventory fast-screen, ICD: implantable cardioverter-defibrillator

Table 2. **Changes in primary and secondary outcomes between baseline and 10 months**								
	Intervention group (N=128)			**Standard care group (N=127)**			**Mean (95%CI) difference between groups**	
	N	**Mean (SD)** **Unadjusted**	**Mean change (95%CI) from baseline** **Adjusted***	**N**	**Mean (SD)** **Unadjusted**	**Mean change (95%CI) from baseline** **Adjusted***	**Adjusted***	**p-value**
Primary Outcome								
DM1-Activ-c score [higher is beneficial]								
Baseline	128	61·22 (17·35)		127	63·00 (17·35)			
10 months	115	63·92 (17·41)	1·53 (-0·14 to 3·20)	116	60·79 (18·49)	-2·02 (-4·02 to -0·01)	3·27 (0·93 to 5·62)	0·007
Secondary Outcomes∫								
Total distance (m) in 6 MWT [higher is beneficial]; end-of-test BORG score [lower is beneficial][&]								
Baseline 6MWT	128	389·29 (123·20)		127	400·69 (119·74)			

BORG		4·56 (2·28)			4·58 (2·14)			
10 months 6MWT BORG	111 	 420·65 (134·84) 4·22 (2·01)	 22·61 (10·60 to 34·61) -0·21 (-0·59 to 1·76)	99 	 401·10 (133·49) 4·60 (2·05)	 -4·39 (-14·49 to 5·72) 0·235 (-0·17 to 1·79)	 26·5 (11·1 to 41·8) -0·42 (-0·89 to 0·06)	 0·0009 0·083
MDHI score [lower is beneficial]								
Baseline	128	37·49 (18·33)		127	35·64 (16·08)			
10 months	112	31·78 (19·35)	-5·30 (-7·44 to -3·15)	106	33·05 (17·72)	-2·07 (-4·36 to 0·22)	-2·35 (-5·35 to 0.65)	0·126
Accelerometry (ENMO) - Mean (24h) physical activity† [higher is beneficial]								
Baseline	128	19·92 (9·53)		127	21·33 (12·72)			
10 months	88	21·22 (9·91)	0·977 (-0·292 to 2·247)	76	19·32 (8·85)	-2·192 (-3·831 to -0·554)	3·23 (1·47 to 5·00)	0·0005
Accelerometry (ENMO) - Mean (most active 5 hours) physical activity† [higher is beneficial]								
Baseline	128	48·80 (26·19)		127	51·01 (34·56)			
10 months	88	53·60 (29·93)	3·439 (-0·897 to	76	47·21 (24·93)	-3·897 (-8·366 to	8·36 (2·62 to	0·005

			7·776)			0·572)	14·10)	
Accelerometry (ENMO) - Mean (least active 5 hours) physical activity†								
Baseline	128	3·86 (0·79)		127	4·29 (2·38)			
10 months	88	3·88 (0·78)	0·038 (-0·142 to 0·217)	76	3·80 (0·66)	-0·541 (-1·154 to 0·073)	0·181 (-0·059 to 0·422)	0·141
FDSS score [lower is beneficial]								
Baseline	128	45·87 (9·72)		126	46·52 (11·54)			
10 months	109	38·38 (10·27)	-7·44 (-9·20 to -5·68)	104	43·22 (10·78)	-3·50 (-5·16 to -1·84)	-4·15 (-6.30 to -2.00)	0·0002
CIS-fatigue score [lower is beneficial]								
Baseline	128	44·89 (5·92)		127	44·88 (6·34)			
10 months	113	36·27 (10·91)	-8·38 (-10·29 to -6·46)	106	40·62 (8·46)	-4·34 (-5·82 to -2·85)	-3·93 (-1·58 to -6·28)	0·001
InQoL – QoL domain score [lower is beneficial]								
Baseline	128	78·14 (31·94)		127	72·72 (34·82)			
10 months	113	69·21 (35·95)	-8·15 (-12·96 to -3·34)	105	70·26 (34·80)	-2·27 (-8·00 to 3·47)	-4·52 (-11·35 to 2·31)	0·196

BDI-FS‡ score [lower is beneficial]								
Baseline	128	4·31 (3·10)		127	4·03 (3·15)			
10 months	110	4·06 (3·44)	-0·330 (-0·91 to 0·241)	105	3·60 (3·14)	-0·277 (-0·794 to 0·240)	0·064 (-0·644 to 0·772)	0·859
AES-c score [lower is beneficial]								
Baseline	128	38·87 (9·07)		127	37·33 (8·65)			
10 months	109	36·31 (8·47)	0·74 (-0·57 to 2·04)	103	37·24 (9·84)	-0·41 (-1·73 to 0·90)	0·63 (-0·98 to 2·25)	0·444
Stroop interference score‡ [lower is beneficial]								
Baseline	128	92·19 (72·26)		127	90·27 (51·99)			
10 months	115	73·95 (40·15)	-16·093 (-26·815 to -5·370)	105	77·75 (51·41)	-9·995 (-17·127 to -2·863)	-0·035 (-0·115 to 0·045)	0·389

Table 2. **Changes in Primary and secondary outcomes between baseline and 10 months**

* Adjusted for baseline value, MIRS, site, caregiver involvement and age.

† As measured with accelerometry – unit measure total ENMO.

‡ Log-transformed in mixed model.

∫ Abbreviations: 6MWT: six-minute walk test; AES-c: apathy evaluation scale, clinician version; BDS-FS: Beck depression inventory – fast screen; CIS: checklist individual strength; FDSS: fatigue and daytime sleepiness scale; InQoL: individualized neuromuscular quality of life; MDHI: myotonic dystrophy

health index – total score; Stroop interference: Stroop color-word interference test

& 0-10 BORG scale

For score range as outcome measures, please refer to supplemental table S5.

Table 3. **Adverse events**

SOC classification	Intervention group N = 128	Standard care Group N = 127	All patients N = 255
Blood and lymphatics	0 [0]	2 [2]	2 [2]
Cardiac	4 [4]	2 [2]	6 [6]
Ear and labyrinth	0 [0]	1 [1]	1 [1]
Eye disorders	1 [1]	1 [1]	2 [2]
Gastro-intestinal	7 [5]	3 [3]	10 [8]
General disorders	6 [6]	6 [6]	12 [12]
Immune system	0 [0]	1 [1]	1 [1]
Infections and infestations	32 [24]	19 [15]	51 [39]
Injury, poisoning and procedural complications	162 [46]	81 [39]	243 [85]
- Falls	155 [40]	71 [33]	226 [73]
Investigations	1 [1]	1 [1]	2 [2]
Metabolism and nutrition	1 [1]	0 [0]	1 [1]
Muskuloskeletal and connective tissue	14 [14]	12 [9]	26 [23]
Neoplasm	1 [1]	0 [0]	1 [1]
Nervous system	7 [7]	9 [8]	16 [15]

Psychiatric	0 [0]	2 [2]	2 [2]
Reproductive system and breast	1 [1]	0 [0]	1 [1]
Respiratory thoracic mediastinal	5 [5]	12 [9]	17 [14]
Skin subcutaneous	1 [1]	0 [0]	1 [1]
Vascular disorders	1 [1]	3 [3]	4 [4]
Total number of events	**244 [65]**	**155 [63]**	**399 [128]**

Table 3. **Adverse events**

Adverse events were classified according to System Organ Class (SOC) adverse event terminology.[15] Non occurring AE from the SOC list are not listed. Listed are the numbers of AE that occurred, followed by the number of patients in whom these occurred in brackets.

Table 4. **Serious adverse events**			
	Intervention group (N = 128)	**Standard care group (N = 127)**	**All patients (N = 255)**
Total falls	**5 [5]**	**1 [1]**	**6 [6]**
Fall	1 [1]	0 [0]	1 [1]
Fall with fracture (extremity)	1 [1]	0 [0]	1 [1]
Fall with suspected or actual cranial trauma	3 [3]	1 [1]	4 [4]
Total pulmonary and non-cardiac chest	**5 [5]**	**5 [5]**	**10 [10]**
Pneumonia	3 [3]	3 [3]	6 [6]
Chest Infection	1 [1]	0 [0]	1 [1]
Pulmonary embolism	0 [0]	2 [2]	2 [2]
Pneumothorax	1 [1]	0 [0]	1 [1]
Total cardiac	**5 [4]**	**6 [4]**	**11 [8]**
Myocardial infarction	1 [1]	2 [2]	3 [3]
Cardiac arrest	1 [1]	0 [0]	1 [1]
Atypical chest complaints	2 [2]	1 [1]	3 [3]
Tachycardia	0 [0]	2 [1]	2 [1]
Arrhythmia	1 [1]	0 [0]	1 [1]
Pacemaker installation	0 [0]	1 [1]	1 [1]
Total gastro-intestinal	**6 [5]**	**5 [3]**	**11 [8]**
Constipation	0 [0]	2 [1]	2 [1]
Dysphagia	0 [0]	1 [1]	1 [1]
Gallstone attack	1 [1]	1 [1]	2 [2]
Bile cystitis	1 [1]	0 [0]	1 [1]
Peptic Ulcer	0 [0]	1 [1]	1 [1]
Volvulus	1 [1]	0 [0]	1 [1]

GI malignancy (liver)	1 [1]	0 [0]	1 [1]
Ulcerative colitis	1 [1]	0 [0]	1 [1]
Abdominal pain – unknown etiology	1 [1]	0 [0]	1 [1]
Total other	**3 [3]**	**6 [5]**	**9 [8]**
Extremity fracture – not related to falls	1 [1]	1 [1]	2 [2]
Urinary tract infection	0 [0]	1 [1]	1 [1]
Vertigo	0 [0]	1 [1]	1 [1]
Headache of severe intensity	0 [0]	1 [1]	1 [1]
Leg pain – unknown etiology	0 [0]	1 [1]	1 [1]
Back pain - lumbago	1 [1]	0 [0]	1 [1]
(Epileptic) seizure	1 [1]	0 [0]	1 [1]
Wound dehiscence	0 [0]	1 [1]	1 [1]
Overall Total SAE	**24 [19]**	**23 [15]**	**47 [34]**

Table 4. **Serious adverse events**

Number of adverse events and serious adverse events occurring up to 14 days after the final visit (16 months after baseline), followed by number of patients in whom these occurred in brackets. The number in brackets do not always sum up to the totals presented as a consequence of some patients that had multiple SAE.

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