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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List of protocol deviations
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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 S8); 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 S5a and S5b). 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 S6). 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 S6). 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 S6).

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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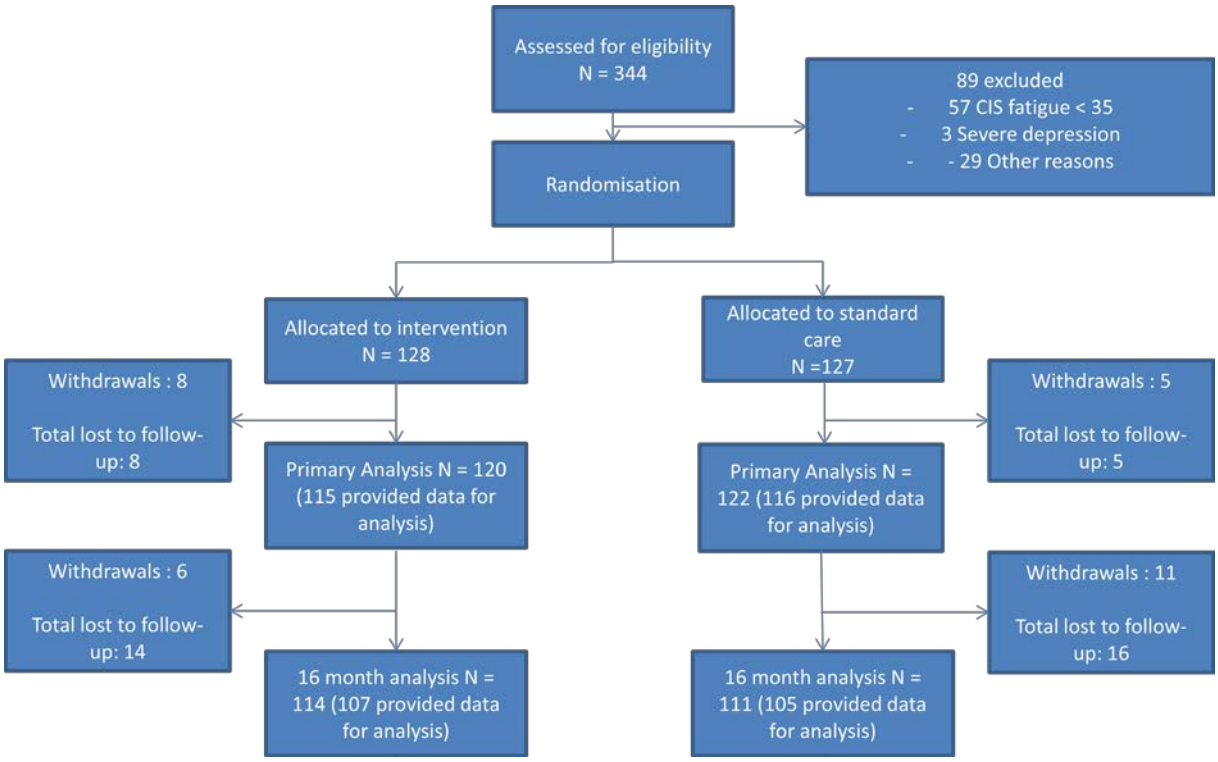

Figure 1. **Screening, randomisation, treatment, and follow-up in the trial**

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 BORG	128	389·29 (123·20) 4·56 (2·28)		127	400·69 (119·74) 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 7·776)	76	47·21 (24·93)	-3·897 (-8·366 to 0·572)	8·36 (2·62 to 14·10)	0·005
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 which 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.

References

1. Harper PS. Myotonic dystrophy. 3rd ed. / with a chapter on molecular and cell biology by J. David Brook and Emma Newman. ed. London: W.B. Saunders; 2001.
2. Laberge L, Mathieu J, Auclair J, Gagnon E, Noreau L, Gagnon C. Clinical, psychosocial, and central correlates of quality of life in myotonic dystrophy type 1 patients. *European neurology* 2013; **70**(5-6): 308-15.
3. Kierkegaard M, Harms-Ringdahl K, Holmqvist LW, Tollback A. Functioning and disability in adults with myotonic dystrophy type 1. *Disability and rehabilitation* 2011; **33**(19-20): 1826-36.
4. Gourdon G, Meola G. Myotonic Dystrophies: State of the Art of New Therapeutic Developments for the CNS. *Front Cell Neurosci* 2017; **11**: 101.
5. Sansone V, Gandossini S, Cotelli M, Calabria M, Zanetti O, Meola G. Cognitive impairment in adult myotonic dystrophies: a longitudinal study. *Neurological sciences : official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology* 2007; **28**(1): 9-15.
6. Winblad S, Samuelsson L, Lindberg C, Meola G. Cognition in myotonic dystrophy type 1: a 5-year follow-up study. *European journal of neurology : the official journal of the European Federation of Neurological Societies* 2016; **23**(9): 1471-6.
7. Turner C, Hilton-Jones D. Myotonic dystrophy: diagnosis, management and new therapies. *Current opinion in neurology* 2014; **27**(5): 599-606.
8. Kalkman JS, Schillings ML, Zwarts MJ, van Engelen BG, Bleijenberg G. The development of a model of fatigue in neuromuscular disorders: a longitudinal study. *Journal of psychosomatic research* 2007; **62**(5): 571-9.
9. Kalkman JS, Schillings ML, van der Werf SP, et al. Experienced fatigue in facioscapulohumeral dystrophy, myotonic dystrophy, and HMSN-I. *Journal of neurology, neurosurgery, and psychiatry* 2005; **76**(10): 1406-9.
10. Heatwole C, Bode R, Johnson N, et al. Patient-reported impact of symptoms in myotonic dystrophy type 1 (PRISM-1). *Neurology* 2012; **79**(4): 348-57.
11. Malouff JM, Thorsteinsson EB, Rooke SE, Bhullar N, Schutte NS. Efficacy of cognitive behavioral therapy for chronic fatigue syndrome: a meta-analysis. *Clinical psychology review* 2008; **28**(5): 736-45.
12. Menting J, Tack CJ, van Bon AC, et al. Web-based cognitive behavioural therapy blended with face-to-face sessions for chronic fatigue in type 1 diabetes: a multicentre randomised controlled trial. *Lancet Diabetes Endocrinol* 2017; **5**(6): 448-56.
13. Voet N, Bleijenberg G, Hendriks J, et al. Both aerobic exercise and cognitive-behavioral therapy reduce chronic fatigue in FSHD: an RCT. *Neurology* 2014; **83**(21): 1914-22.
14. Cup EH, Pieterse AJ, Ten Broek-Pastoor JM, et al. Exercise therapy and other types of physical therapy for patients with neuromuscular diseases: a systematic review. *Archives of physical medicine and rehabilitation* 2007; **88**(11): 1452-64.
15. Favejee MM, van den Berg LE, Kruijshaar ME, et al. Exercise training in adults with Pompe disease: the effects on pain, fatigue, and functioning. *Archives of physical medicine and rehabilitation* 2015; **96**(5): 817-22.
16. Voet NB, van der Kooi EL, Riphagen, II, Lindeman E, van Engelen BG, Geurts AC. Strength training and aerobic exercise training for muscle disease. *The Cochrane database of systematic reviews* 2013; **7**: CD003907.
17. van Engelen B, Consortium O. Cognitive behaviour therapy plus aerobic exercise training to increase activity in patients with myotonic dystrophy type 1 (DM1) compared to usual care (OPTIMISTIC): study protocol for randomised controlled trial. *Trials* 2015; **16**(1): 224.
18. Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. *Journal of psychosomatic research* 2017; **98**: 40-6.
19. Mathieu J, Boivin H, Meunier D, Gaudreault M, Begin P. Assessment of a disease-specific muscular impairment rating scale in myotonic dystrophy. *Neurology* 2001; **56**(3): 336-40.

20. Hermans MC, Faber CG, De Baets MH, de Die-Smulders CE, Merkies IS. Rasch-built myotonic dystrophy type 1 activity and participation scale (DM1-Activ). *Neuromuscular disorders : NMD* 2010; **20**(5): 310-8.
21. Hermans MC, Hoeijmakers JG, Faber CG, Merkies IS. Reconstructing the Rasch-Built Myotonic Dystrophy Type 1 Activity and Participation Scale. *PloS one* 2015; **10**(10): e0139944.
22. Laboratories ATSCoPSfCPF. ATS statement: guidelines for the six-minute walk test. *American journal of respiratory and critical care medicine* 2002; **166**(1): 111-7.
23. Kierkegaard M, Tollback A. Reliability and feasibility of the six minute walk test in subjects with myotonic dystrophy. *Neuromuscular disorders : NMD* 2007; **17**(11-12): 943-9.
24. Orngreen MC, Olsen DB, Vissing J. Aerobic training in patients with myotonic dystrophy type 1. *Annals of neurology* 2005; **57**(5): 754-7.
25. Vanhoutte EK, Hermans MC, Faber CG, et al. Rasch-ionale for neurologists. *J Peripher Nerv Syst* 2015; **20**(3): 260-8.
26. Gagnon C, Mathieu J, Jean S, et al. Predictors of disrupted social participation in myotonic dystrophy type 1. *Archives of physical medicine and rehabilitation* 2008; **89**(7): 1246-55.
27. Minis MA, Kalkman JS, Akkermans RP, et al. Employment status of patients with neuromuscular diseases in relation to personal factors, fatigue and health status: a secondary analysis. *Journal of rehabilitation medicine* 2010; **42**(1): 60-5.
28. Gagnon C, Noreau L, Moxley RT, et al. Towards an integrative approach to the management of myotonic dystrophy type 1. *Journal of neurology, neurosurgery, and psychiatry* 2007; **78**(8): 800-6.
29. Symonds T, Randall JA, Campbell P. Review of patient-reported outcome measures for use in myotonic dystrophy type 1 patients. *Muscle & nerve* 2017; **56**(1): 86-92.
30. Gagnon C, Meola G, Hebert LJ, Laberge L, Leone M, Heatwole C. Report of the second Outcome Measures in Myotonic Dystrophy type 1 (OMMYD-2) international workshop San Sebastian, Spain, October 16, 2013. *Neuromuscular disorders : NMD* 2015; **25**(7): 603-16.
31. Kennedy JC, Dunlop BW, Craighead LW, Nemeroff CB, Mayberg HS, Craighead WE. Follow-up of monotherapy remitters in the PReDICT study: Maintenance treatment outcomes and clinical predictors of recurrence. *Journal of consulting and clinical psychology* 2018; **86**(2): 189-99.
32. Kierkegaard M, Harms-Ringdahl K, Edstrom L, Widen Holmqvist L, Tollback A. Feasibility and effects of a physical exercise programme in adults with myotonic dystrophy type 1: a randomized controlled pilot study. *Journal of rehabilitation medicine* 2011; **43**(8): 695-702.
33. Cudia P, Weis L, Baba A, et al. Effects of Functional Electrical Stimulation Lower Extremity Training in Myotonic Dystrophy Type I: A Pilot Controlled Study. *American journal of physical medicine & rehabilitation / Association of Academic Physiatrists* 2016; **95**(11): 809-17.
34. Wiles CM, Busse ME, Sampson CM, Rogers MT, Fenton-May J, van Deursen R. Falls and stumbles in myotonic dystrophy. *Journal of neurology, neurosurgery, and psychiatry* 2006; **77**(3): 393-6.
35. Hammaren E, Kjellby-Wendt G, Lindberg C. Muscle force, balance and falls in muscular impaired individuals with myotonic dystrophy type 1: a five-year prospective cohort study. *Neuromuscular disorders : NMD* 2015; **25**(2): 141-8.
36. Baldanzi S, Bevilacqua F, Lorio R, et al. Disease awareness in myotonic dystrophy type 1: an observational cross-sectional study. *Orphanet journal of rare diseases* 2016; **11**: 34.
37. Lee IM, Shiroma EJ. Using accelerometers to measure physical activity in large-scale epidemiological studies: issues and challenges. *British journal of sports medicine* 2014; **48**(3): 197-201.
38. Matthews CE, Hagstromer M, Pober DM, Bowles HR. Best practices for using physical activity monitors in population-based research. *Med Sci Sports Exerc* 2012; **44**(1 Suppl 1): S68-76.

Web Extra Material - I

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List of protocol deviations

1. Primary outcome measure

We used the DM1-Activ-c, an updated version of the DM1-Activ scale as primary outcome measure. Whereas the original scale DM1-Activ was published in 2010, criticism led to its revision and publication of an updated version in 2015.[1,2] As DM1-Activ-c was available before inclusion of the first patient, this updated version was used in the trial.[2] Note that the power calculation was based on the DM1-Activ metric scale from 0 to 40, whereas the DM1-Activ-c metric scores range from 0 to 100. The University of Maastricht developer of DM1-Activ (both versions) considers a 1 point difference on the 0 to 40 scale to be equivalent to 2·5 points on the 0 to 100 scale. We think the power calculations would not have been affected by the choice of the 0-100 instead of the 0-40 scale, as the MCID would be expected to change accordingly.

2. Graded exercise

We planned to offer the graded exercise component of the program across all four clinical sites. However, due to preexisting regular weekly physiotherapy as part of national standard of care in Germany and France, the program was eventually offered in two out of four sites (Newcastle and Nijmegen). The graded exercise component commenced only once the patient successfully increased his or her level of physical activity (walking) during the graded activity program of the CBT and was interested in more vigorous activity. Our statistical analysis plan included a subgroup analysis to look at outcomes in those who did and did not have graded exercise, as well as investigating the effect of site.

3. Blinding

The original protocol stated that all study outcome measures would be collected by staff blind to allocation of patients.[3] Due to logistical and staffing constraints, this was not always possible in Newcastle. Our statistical analysis plan investigated the effect of site.

4. InQoL versions

The individualized neuromuscular quality of life questionnaire (InQoL) was a secondary outcome measure.[3] Due to a logistical error, the clinical site Nijmegen used a different version of the InQoL (that is, version 1.2 – Dutch translated version) than the other three clinical sites (that is, version 2.0). Both contain the items required to calculate the quality of life subscore of the InQoL.

5. ADL assessment

In our protocol paper, we listed activities of daily living (ADL) assessment as a secondary outcome measure (protocol paper, page 7/19). However, we did not include outcome measures that directly measured this (see Trial Measurement Outcome Schedule, protocol paper, page 17/19). In fact, we simply forgot to delete it from the list.

Table S1. Inclusion- and exclusion criteria

Table S1. Inclusion- and exclusion criteria
Inclusion criteria for patients 1) Able to provide informed consent 2) Genetically proven DM1, aged 18 years and older, suffering from severe fatigue (CIS-fatigue subscale score ≥35). The genetic diagnosis and level of fatigue were determined as part of the eligibility screening process 3) Ability to walk independently (ankle-foot orthoses and canes accepted)
Exclusion criteria for patients 1) Neurological or orthopedic co-morbidity interfering with the interventions or possibly influencing outcomes 2) Use of psychotropic drugs (except modafinil, methylphenidate and antidepressants where the dosing regimen has been stable for at least 12 months prior to screening). If the doses of modafinil or methylphenidate increase during the 10 months of intervention/non-intervention, then the patient will be excluded 3) Severe depression at screening as per clinical judgement 4) Participation in another clinical trial of an investigational medicinal product (CTIMP) or other interventional study considered to influence outcomes being evaluated in OPTIMISTIC concurrently or within 30 days prior to screening for entry into this study 5) Unable to complete study questionnaires
Inclusion criteria for caregivers 1. Ability to give informed consent 2. Ability to complete study questionnaires 3. Ability to attend CBT sessions with patients

Table S2. Description of standard care in the four different clinical sites

Brief name	Standard care
Why	**Regular follow-up** Every patient received standard care as to local neuromuscular care practice prior, during and after conduct of the study. Standard care aims to monitor disease progression, ameliorate symptoms and prevent or treat DM1 related complications. Here we provide an overview of what constitutes standard care in these four countries, and highlight differences in practice between them. **Physiotherapy** Assessment of patients by physiotherapists is common in all countries, but significant between country differences exists. Physiotherapy addresses functional deficits, fall prevention, orthotics, respiratory problems and pain in DM1 patients. Its goals are to maintain functionality and participation. The intensity (number and duration of contact moments) of physiotherapy vary between countries.
What (materials)	**Treatment guidelines** All centers provide standard care as per local protocols and guidelines. *Munich Germany:* Local care protocol; no national guideline available *Nijmegen, the Netherlands:* Local care protocol, based on multidisciplinary treatment guideline, which is available from: https://richtlijnendatabase.nl/richtlijn/myotone_dystrogie_type1/myotone_dystrofie_type1_-_korte_beschrijving.html. *Paris, France:* Local care protocol; no national guideline available *United Kingdom:* Local care protocol, no national guideline available **Information for patients** Patient education and information is digitally provided by patient groups at all four sites. These sites also provide information for the physiotherapists. France: https://www.afm-telethon.fr/maladie-steinert-1175 *Germany:* https://www.dgm.org/muskelerkrankungen/myotone-dystrophie-typ-1 *the Netherlands:* https://www.spierziekten.nl/overzicht/myotone-dystrofie *UK:* http://www.myotonicdystrophysupportgroup.org/ **Screening questionnaires might include** • Fatigue and daytime sleepiness Fatigue and daytime sleepiness scale (FDSS), Epworth sleepiness scale (ESS), Checklist individual strength-subscale fatigue (CIS-fatigue). • Mood disorders Beck depression inventory (BDI)
What (procedures)	All participating centers offer specialized multidisciplinary neuromuscular care. This involves regular follow-up for every patient at the outpatient clinic in the specialized neuromuscular center. For each patient, a neurologist and/or rehabilitation specialist, specialized nurse and research physiotherapist is involved. Assessments are organized on the same day if feasible. Involvement of other care professionals is dependent upon the needs of the patient. Coordination of care is the responsibility of the neurologist or rehabilitation specialist. Cardiac care involves annual or bi-annual cardiac consultation and yearly ECG control with additional diagnostics as needed. Pulmonary care involves yearly respiratory function tests in all patients, with referral to a pulmonary specialist if indicated.
Who provided	**Regular follow-up** Multidisciplinary care is usually coordinated by a neurologist or rehabilitation specialist who is supported by a specialist nurse. The different aspects of multidisciplinary care are provided by the respective care professionals: • Medical specialty care: cardiology, respiratory, gynecology, gastro-enterology and medical genetics • Paramedical care: physiotherapy, speech therapy, occupational therapy • Psychological and other care: occupational attention and social support, (medical) psychology All professionals involved have experience in caring for patients with neuromuscular disorders and are connected within the network that the specialized neuromuscular center provides. **Physiotherapy** *Munich, Germany:* Physiotherapists of occupational therapists at hospital or in local settings. *Nijmegen, the Netherlands:* Physiotherapists of neuromuscular care unit or locally working physiotherapists *Paris, France:* Occupational therapists of neuromuscular care unit and locally working physiotherapists *Newcastle, UK:* Physiotherapists or physiotherapist assistants of the neuromuscular care unit
How	**Regular follow-up** Annual neurologic or rehabilitation visits are usually in a face-to-face format. Follow-up appointments may be via telephone or internet. **Physiotherapy**

	Physiotherapy is provided face-to-face, normally in single person sessions and rarely in group therapy. It is often provided by a local physiotherapist (*e.g.* working in the vicinity of the patient's home)
Where	**Regular follow-up** Regular follow-up is in the setting of the specialized neuromuscular care unit of the hospital. **Physiotherapy** *Munich, Germany:* Physiotherapy is provided at the hospitals or at local physiotherapy and occupational therapist centers. *Newcastle, UK:* Physiotherapy is provided at neuromuscular care units in hospital settings throughout the UK *Nijmegen, the Netherlands:* Physiotherapy is provided at the neuromuscular care unit or at a local center for physiotherapy. *Paris, France:* Occupational therapy is provided at the neuromuscular care unit and physiotherapy at local physiotherapist centers.
When and how much	**Regular follow-up** Annual control visits that last 30 to 90 minutes constitute the minimum intensity of standard care. Additional or more frequent visits are planned if required, such as in the case of complications or progressive disease. Cardiac follow-up is annual at minimum. **Physiotherapy** *Munich, Germany:* Physiotherapy is provided at least once a week, twice a week for most patients for 20 minutes each session. *Newcastle, United Kingdom:* Visits are scheduled annually as standard and last for approximately 30 minutes. When required, additional visits may be scheduled. *Nijmegen, Netherlands:* Physiotherapy is provided once a week at minimum for 20 to 30 minutes per session. *Paris, France:* Physiotherapy is provided once a week or twice a week for most patients for 20 minutes per session.
Tailoring	**Regular follow-up** An individual care plan is made for every patient on the basis of screening for symptoms, signs and complications known to occur in DM1. Screening is based on nurse and physician anamnesis, sometimes supported with patient reported questionnaires. Particular attention is given to the presence of cardiac or respiratory complications. **Physiotherapy** Physiotherapy recommendations are tailored to the individual according to specific needs and functional deficits. In addition, the physiotherapy may vary as consequence of local variations in physiotherapy practice.
Modifications	Local protocol and guidelines for standard care may be updated upon availability of new evidence on interventions. No relevant changes or updates were made during the conduct of the trial.
How well	At every study assessment, it was recorded whether concomitant therapies were given as part of standard care.

Table S2. Table describing standard care according to TIDieR checklist and guide.[4]

Table S3. Description of Cognitive behavioural therapy (CBT)

Brief name	Cognitive behavioural therapy (CBT)
Why	CBT was based on a model of determinants of disease burden in DM1. This model predicted that to improve patient reported health status and thus reduce disease burden, treatment should aim to compensate for a reduced initiative, alleviate experienced fatigue, optimize the interaction with caregivers, and increase activity and social participation. CBT has been shown to be effective to improve health status in other chronic diseases.
What	All patients started with psycho-education and goal formulation. Patients were then offered a tailored CBT intervention consisting of a maximum of six modules: 1) Learning to compensate for a reduced initiative; 2) Optimize social interactions with caregivers;3) Regulation of sleep-wake pattern; 4) Reformulation of dysfunctional beliefs with respect to fatigue or DM1; 5) Activity regulation and graded activity; 6) Coping with pain. Which modules were administered was decided on the basis of an assessment and intake. During every session, one or several treatment modules were discussed. At the end of every session, 'homework' exercises were discussed with the patient. During the first CBT session ('intake') therapist and patient decided if exercise therapy would be added to the graded activity of CBT. Graded exercise commenced if patients successfully increased their level of physical activity during the graded activity module. Only two sites provide graded exercise. All patients completed CBT with step by step realization of treatment goals. Therapists delivered the CBT according to a detailed manual (available on request from H Knoop: hans.knoop@amc.uva.nl), which was specifically designed for this study. The intervention was delivered in face-to-face sessions or sessions via telephone of skype. Patients could also correspond via email with their therapist. The exercise module of the intervention was delivered by a physical therapist in cooperation with the CBT therapist. Patients were provided with a workbook that provided information on the disease and CBT. In addition, the workbook was used to document treatment goals, record progression and identify potential problems. If possible, CBT also involved the caregiver of the patient to help the patient in achieving the treatment goals.
	Essential in CBT was that by interaction with the patient, his/her thoughts were changed and behaviour was altered in such a way that health status was improved. CBT focused mainly on three common and debilitating symptoms in DM1: (1) chronic fatigue, (2) reduced initiative and (3) lack of and/or negative social interactions. It was assumed that the level of physical activity and social participation could be increased if the afore mentioned problems were addressed. A graded activity program, with exercise added if appropriate, was thought to be an important element of the intervention in order to reduce fatigue and increase activity and participation.
Who provided	Over the four participating centers, 10 cognitive behavioural therapists delivered the intervention. They received a three day training program prior to the start of the trial with weekly or biweekly supervision during the trial.
How	CBT sessions were delivered to the individual patients. We aimed for a minimum of five face-to-face sessions. Other communication formats, such as telephone, or video-conferencing were acceptable. Appointments for the next session were made at the end of the session.
Where	In some clinical sites, CBT was delivered in the same location where the assessment took place. In other centers, delivery was in a different location remote from the clinical site. If sessions were delivered remotely, the patients could stay at home or alternatively be at work or elsewhere.
When and how much	CBT was started immediately after randomization and baseline assessment. CBT session were divided into 1 to 3 week windows, with a maximum of 14 sessions over a 10-month period, with the majority of sessions delivered in the initial four months. There was no minimum duration of sessions, but anticipated duration was between 15 and 75 minutes depending on the communication format.
Tailoring	CBT was tailored to the individual patient. At the start of therapy, each patient underwent baseline CBT screening with self-reported questionnaires. On the basis of cut-off scores, it was then determined which CBT modules were indicated and these were planned to be delivered during therapy.[3] Additional modules could be added by the therapist on the basis of the intake session if deemed necessary. The duration of therapy and communication format were determined by shared decision making between therapist and patient.
Modifications	No modifications to CBT were made during the conduct of the trial.
How well	Throughout the period in which CBT was given, there was remote supervision for all therapists by two experienced CBT therapists who had been involved in the design of the manual. Any difficulties or problems were discussed. At the end of every session, the therapist recorded the number, duration, communication format, whether the caregiver attended and which modules had been addressed during the session on a predesigned CBT case report form (CRF). This information was later used by independent assessors to determine whether the delivered CBT was in accordance with the protocol and the scheduled contents of therapy as determined by the baseline CBT screening. In addition, a proportion of the sessions were recorded for purpose of later assessment of treatment integrity. These sessions were rated by independent assessors with the help of a previously designed, piloted and adjusted rating form.
	Participants received an average of 9.0 (SD 3.2) hours of CBT divided over an average of 10·7 (SD 3.3) sessions. For patients allocated to CBT for which the information was available (N = 119), the different modules were given in the following numbers: (1) regulating sleep wake rhytm: 116 (97.5%), (2) compensating for reduced initiative: 109 (91.6%), (3) activity regulation and graded activity: 112 (94.1%), (4) reformulation of dysfunctional beliefs with respect to fatigue or DM1: 98 (82.4%), (5) optimize social interactions with caregivers: 79 (66.4%), (6) coping with pain 19 (16.0%). 73 (61.3%) participants had their caregiver involved in the study. An average of 6.3 (SD 4.0) sessions was given in face-to-face communication format. 70 participants (58.8%) had at least 5 face-to-face sessions.

	For an extended analysis of CBT treatment integrity, we refer to supplement S8.

Table S3. Table describing cognitive behavioural therapy according to TIDieR checklist and guide.[4] A more detailed description has been published previously.[3]

Table S4. Description of graded exercise

Brief name	Graded exercise
Why	To increase patient's activity levels on a graded, structured and guided manner. In DM1, exercise therapy has been shown to be feasible and safe, and suggestions of impact on disease burden have been made, although efficacy remains to be demonstrated.
What	The need for an exercise program was defined through the CBT therapist counseling and aimed to incorporate moderate intensity exercises such as walking, cycling, jogging or dancing.
	In both Newcastle and Nijmegen, main activities of GET were outdoor or indoor cycling, outdoor walking, swimming and cardio fitness at a fitness center.
Who provided	Physiotherapists with experience in DM1.
How	First visit aimed to define: 1) exercise concept, 2) graded exercise goals, 3) graded exercise program and 4) identification of any possible barriers. It was always face-to-face with a minimum duration of one hour. Follow-up assessments were allowed to be performed by phone, or video-conferencing or face-to-face. Each patient received a graded exercise diary to record: 1) form of exercise recommended and practiced, 2) duration and frequency of training, 3) sessions per week and, 4) either heart rate measurement or the score of perceived exertion (BORG scale) after each training session, and, 5) any comments on their experience with the program. These diaries were part of the CBT workbooks. These were reviewed and discussed with the physiotherapist in charge at every follow-up assessment and appropriate modifications were made.
Where	Graded exercise were only implemented in Newcastle (UK) and Nijmegen (Netherlands). The first graded exercise session was delivered at clinical site/hospital in both Nijmegen and Newcastle. In Nijmegen, follow-up appointments were held primordially by telephone, whereas in Newcastle, some participants preferred face-to-face sessions. Participants were free to choose the locations for them to exercise, including but not limited to: their homes, local fitness centers, dancing schools or hospital physiotherapy facilities.
When and how much	The graded exercise module was incorporated within the months of the CBT intervention (i.e. 10 months after randomization). This module was offered after patients had increased their activity levels as part of the standard graded activity module and had reached the established goals for this module. The option for further activity increment was either expressed by the participant or suggested by the CBT therapist. Exercise was recommended for at least half an hour, three times a week with the maximum dose based on the physiotherapists' clinical judgment.
Tailoring	Exercise type and recommendations were tailored to each patient's disease and demographic characteristics. The program could change or increase at every follow-up assessment as a shared-decision process between patient and physiotherapist.
Modifications	No modifications to the protocol for the graded exercise module were made during the conduct of the trial.
How well	There was no pre-defined number of sessions for the graded exercise module; however, compliance was considered when a minimum of one baseline session plus a follow-up verifying patient's involvement was completed.
	Together, 58 patients at Newcastle and Nijmegen were randomized to the intervention, of whom 33 were recommended for the graded exercise program. There were two losses in follow-up from this module due to lack of compliance with the program. The median [IQR] duration of exercise practice was 127 [79] minutes a week per patient.

Table S4. Table describing graded exercise therapy according to TIDieR checklist and guide.[4] A more detailed description has been published previously.[3].

Table S5. Overview of primary and secondary outcome Measures

Table S5. Overview of primary and secondary outcome measures				
Name and Reference (abbreviation)	**Score range**	**What is measured**	**Direction of Score**	**Notes**
Primary Outcome				
DM1-Activ-c[1,2] (DM1-Activ-c)	0 to 100	capacity for activity and participation	higher scores are beneficial	Independent conversion of raw data at Maastricht University Medical Centre, Maastricht, the Netherlands
Secondary Outcomes				No conversion was done, analysis of raw data
Six-minute walk test[5,6] (6MWT) BORG scale	0 to ∞ 0 to 10	exercise capacity perceived exertion	higher scores are beneficial lower scores are beneficial	 Taken after completion of the 6MWT
Myotonic Dystrophy Health Index[7,8] (MDHI)	0 to 100	impact of disease	lower scores are beneficial	Independent conversion of raw data at Rochester University, Rochester, USA
Fatigue and Daytime Sleepiness Scale[9] (FDSS)	0 to 100	experienced fatigue and sleepiness	lower scores are beneficial	Independent conversion of raw data at Maastricht University Medical Centre, Maastricht, the Netherlands
Checklist Individual Strength – subscale - fatigue[10] (CIS – fatigue)	8 to 56	experienced fatigue	lower scores are beneficial	No conversion was done, analysis of raw data
Accelerometry	0 to ∞	activity	higher scores are beneficial/indicate higher activity levels	No conversion was done, analysis of raw data
Individualized Neuromuscular Quality of Life Questionnaire – domain quality of life[11] (INQoL)	0 to100%	quality of life/ health status	lower scores are beneficial	No conversion was done, analysis of raw data
Beck Depression Inventory – fast screen[12,13] (BDI – FS)	0 to 21	depression	lower scores are beneficial	No conversion was done, analysis of raw data
Apathy Evaluation Scale – clinical version[14] (AES – c)	18 to 72	apathy	lower scores are beneficial	No conversion was done, analysis of raw data
Stroop color-word interference score (Stroop interference)	0 to ∞	executive cognitive functioning	lower scores are beneficial	No conversion was done, analysis of raw data

Table S5a. Mixed model primary analysis and tests of pre-specified subgroup differences for primary outcome DM1-Activ-c

Primary Analysis	**Adjusted* Regression Coefficient (95% CI)**	**p-value**
Behavioural Intervention vs Standard Care	3·27 (0·93 to 5·62)	0·007
Intervention (Behavioural intervention vs Standard care) by Subgroup Analyses	**Adjusted* Regression Coefficient (95% CI)**	**p-value**
Intervention x age	-0·166 (-0·373 to 0·041)	0·117
Intervention x gender (female/male)	5·996 (1·592 to 10·399)	0·014
Intervention x site	Overall†	0·330
Intervention x site (Paris as comparator)	Individual Sites	
Intervention Munich (vs. Paris)^	-0·065 (-4·738 to 4·608)	0·978
Intervention Newcastle (vs. Paris)^	3·212 (-1·808 to 8·231)	0·212
Intervention Nijmegen (vs. Paris)^	-0·773 (-5·599 to 4·054)	0·754
Standard Care Munich (vs. Paris)^	-1·895 (-6·567 to 2·777)	0·428
Standard Care Newcastle (vs. Paris)^	-1·087 (-6·106 to 3·933)	0·672
Standard Care Nijmegen (vs. Paris) ^	-4·807 (-9·524 to -0·090)	0·047
Intervention by MIRS	0·404 (-2·341 to 3·149)	0·773
Intervention x Caregiver (Y/N)	2·114 (-2·651 to 6·878)	0·385
Intervention x (CBT alone / CBT +graded exercise)	1·5100 (-1·904 to 4·924)	0·388
Intervention x No. of CBT sessions	0·1172 (-0·275 to 0·509)	0·559

Table S5a. **Mixed model primary analysis and tests of pre-specified subgroup differences for primary outcome DM1-Activ-c**

Since none of interactions was significant at the level corrected for multiple testing of $p<0·004$ ($p = 0·05/ 13$), the presented regression coefficients should be considered resulting from 'post-hoc' analyses.

*Adjusted for Baseline value, MIRS, Site, Carer (Yes, No) and Age.

† Test of Intervention effect by site over all sites

^ Test for interaction of site with treatment allocation (intervention versus standard care) on outcome, with Paris as arbitrarily chosen comparator

Table S5b. Subgroup analyses for all (primary and secondary) outcome measures

Table S5b. **Pre-specified subgroup analysis at 10-month follow-up.**								
		Treatment by subgroup interaction					**Intervention Alone^**	
Outcome	**Adjusted* model-Treatment**	**Age**	**Sex**	**Site**	**MIRS**	**Caregiver**	**CBT alone vs CBT +graded exercise**	**Number of CBT sessions**
	p-value	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**	**p-value**
Primary outcome								
DM1-activ	0·007	0·117	0·014	0·330	0·773	0·385	0·388	0·559
Secondary outcomes								
Total distance (m) in 6 MWT	0·0009	0·221	0·784	0·026	0·074	0·622	0·298	0·092
MDHI	0·144	0·795	0·376	0·014	0·169	0·733	-	-
Acceler.† (mean activity)	0·0005	0·056	0·681	0·408	0·026	0·582	0·273	0·454
Acceler.† (5 hours of highest activity)	0·005	0·091	0·888	0·138	0·039	0·485	0·271	0·494
Acceler.† (5 hours of lowest activity)	0·141	0·342	0·673	0·695	0·511	0·188	0·980	0·268
FDSS	0·0002	0·277	0·730	**0·0002**	0·412	0·237	-	-
CIS – fatigue	0·001	0·859	0·432	0·011	0·375	0·709	0·003	0·170
INQOL– QOL domain	0·196	0·037	0·639	0·038	0·220	0·880	0·254	0·133
BDI-FS, log transformed	0·859	0·769	0·494	0·039	0·876	0·140	0·715	0·088
AES-c	0·444	0·470	0·429	0·002	0·064	0·618	0·004	0·003
Stroop Score (log transformed)	0·389	0·021	0·851	**0·006**	0·858	0·087	0·421	0·958

Table S5b. **Pre-specified subgroup analysis at 10-month follow-up.**

*adjusted for baseline value, MIRS, site, cares (yes/no) and age

† N=143 who completed accelerometry.

For 84 tests in total, p<0·0006 indicates corrected statistical significance; one of the statistical tests reached significance: values indicated in **bold** are significant.

^ In case of empty cells, the model was unable to calculate the estimates. This could be due to lack of data or small numbers in cells.

Abbreviations: 6MWT: six-minute walk test; AES apathy evaluation scale; BDS-FS: Beck depression inventory – fast screen; CIS-fatigue: checklist individual strength – subscale fatigue; InQoL: individualized neuromuscular quality of life; MDHI: myotonic dystrophy health index; MIRS: muscular impairment rating scale; Stroop: Stroop color-word interference test.

Table S6. Repeated measures analysis for primary and secondary outcomes

Table S6. Repeated measures analysis for primary and secondary outcomes										
Outcome	**Treatment arm**	**Baseline**		**5 months**		**10 months**		**16 months**		**Repeated measures***
Primary outcome		**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**N**	**Mean (SD)**	**Overall difference (se)**
DM1-activ-c	Intervention group	128	61·22 (17·35)	120	63·50 (19·30)	115	63·92 (17·41)	107	62·57 (18·18)	2·87 (0·99), p = 0·004
	Standard care group	127	63·00 (17·35)	104	62·75 (17·74)	116	60·79 (18·49)	105	62·31 (17·30)	
Secondary outcomes										
Total distance (m) in 6MWT	Intervention group	128	389·3 (123·2)	113	419·35 (124·1)	111	420·65 (134·8)	97	413·10 (131·0)	25·9 (6·4), p < 0·001
	Standard care group	127	400·7 (119·7)	101	397·54 (122·6)	99	401·10 (133·5)	94	400·78 (131·7)	
MDHI	Intervention group	128	37·49 (18·33)	117	31·46 (20·25)	112	31·78 (19·35)	103	33·28 (19·42)	-2·32 (1·37), p = 0·090
	Standard care group	127	35·64 (16·08)	103	32·63 (17·67)	106	33·05 (17·72)	104	31·54 (17·15)	
FDSS	Intervention group	128	45·9 (9·7)	115	39·4 (10·8)	110	38·4 (10·3)	105	39·8 (11·6)	-3·50 (0·99), p < 0·001
	Standard care group	127	46·6 (11·5)	110	43·9 (10·7)	104	43·2 (10·8)	102	42·7 (10·1)	
CIS – Fatigue	Intervention group	128	44·89 (5·92)	120	36·73 (10·03)	113	36·27 (10·91)	107	38·59 (11·22)	-3·46 (0·99), p < 0·001
	Standard care group	127	44·88 (6·34)	104	41·23 (8·64)	106	40·62 (8·46)	105	40·29 (8·75)	
Acceler.† (Mean activity)	Intervention group	128	19·92 (9·53)	77	21·27 (9·61)	88	21·22 (9·91)	63	20·28 (9·41)	1·87 (0·73), p = 0·011
	Standard care group	127	21·33 (12·72)	77	19·19 (9·88)	76	19·32 (8·85)	76	19·02 (10·72)	
Acceler.† (5 hours of highest activity)	Intervention group	128	48·80 (26·19)	77	53·57 (27·63)	88	53·60 (29·93)	63	49·77 (26·91)	5·20 (2·08), p = 0·013
	Standard care group	127	51·01 (34·56)	77	46·42 (28·53)	76	47·21 (24·93)	76	46·56 (30·53)	
Acceler.† (5 hours of lowest activity)	Intervention group	128	3·86 (0·79)	77	3·96 (1·08)	88	3·88 (0·78)	63	3·80 (0·68)	0·10 (0·10), p = 0·297
	Standard care group	127	4·29 (2·38)	77	3·89 (1·06)	76	3·80 (0·66)	76	3·73 (0·65)	
BDI-FS	Intervention group	128	4·31 (3·10)	117	3·88 (3·42)	110	4·06 (3·44)	104	3·96 (3·11)	0·003 (0·020), p = 0·888
	Standard care group	127	4·03 (3·15)	103	3·33 (2·91)	105	3·60 (3·14)	103	3·33 (3·03)	
AES-c	Intervention group	128	38·87 (9·07)	111	36·94 (8·51)	109	36·31 (8·47)	105	38·08 (8·91)	-1·31 (0·70), p = 0·061

	Standard care group	127	37·33 (8·65)	101	37·80 (9·42)	103	37·24 (9·84)	101	36·72 (8·65)	
Stroop Score	Intervention group	128	92·19 (72·26)	117	77·96 (41·57)	115	73·95 (40·15)	106	71·98 (37·49)	-0·0002 (0·04), p = 0·996
	Standard care group	127	90·27 (51·99)	99	77·09 (39·82)	105	77·75 (51·41)	104	68·15 (34·48)	
INQOL– QoL domain	Intervention group	128	78·14 (31·94)	119	70·17 (36·93)	113	69·21 (35·95)	104	72·03 (37·66)	-3·62 (2·90), p = 0·212
	Standard care group	127	72·72 (34·82)	103	68·50 (33·78)	105	70·26 (34·80)	104	69·32 (34·20)	

Table S6. **Overview of raw scores per allocation group for all primary and secondary outcomes at all timepoints**

The numbers indicate the number of participants available analysis at each time point for the outcome measure.

*Repeated measures for overall difference are adjusted for age, baseline, MIRS, involvement of a caregiver, clinical site and visit.

Abbreviations: 6MWT: six-minute walk test, FDSS: fatigue and daytime sleepiness scale; CIS-fatigue: checklist individual strength, subscale fatigue, Accel: accelerometry, BDI-FS: Beck depression inventory, fast screen; AES-c: apathy evaluation scale, clinician version; Stroop: Stroop interference score; InQoL: individualized neuromuscular quality of life questionnaire – quality of life domain

S7. Analysis of treatment integrity

Methods

Description of the intervention

In OPTIMISTIC, 128 out of the recruited 255 severely fatigued DM1 patients were randomised to receive a behavioural intervention from April 2014 to May 2015. There were four treatment sites: Nijmegen, the Netherlands (n=33); Munich, Germany (n=33); Paris, France (n=37) and Newcastle, UK (n=25). All patients allocated to intervention received CBT with added GET in a subset of patients (33 out of 128, 26%). We here outline the general structure of CBT, a more detailed description is available in the published protocol paper of the OPTIMISTIC study. CBT focused on three common and debilitating problems in DM1: chronic fatigue (1), reduced initiative (2) and a lack in social interactions and negative interactions (3). All patients started with psycho-education and goal setting. There were 6 treatment modules: regulating sleep-wake pattern (1), compensating for a reduced initiative (2), graded activity with an optional graded exercise therapy (GET) add-on (3), formulating helpful beliefs about fatigue and MD (4), optimizing social interactions (5) and coping with pain (6). The contents (modules) of CBT were individualised on the basis of the baseline assessment consisting of questionnaires, actigraphy and a clinical interview at the start of CBT. At baseline it was determined which modules were indicated. The questionnaires and their cut-off scores used to tailor therapy to the individual patient are listed below.

Module	**Module**	**Instrument**	**Score whereby specified module is selected**
	Psychoeducation and goal setting	None	Always indicated
1.	Regular sleep-wake rhythm	- Registration: overview of sleep/wake rhythm over 12 days - Sickness Impact Profile (SIP) subscale sleep & rest	Visual inspection by therapist Score ≥ 60
2.	Compensating for reduced initiative	- Apathy evaluation Scale – clinician version (AES-c)	Score >38
3.	Activity	None	Always indicated
4.	Helpful thoughts about fatigue and DM	<u>Cognitions about fatigue</u> - Jacobsen Fatigue Catastrophing scale (FCS) - SES-28 fatigue - IMQ-focus on fatigue <u>Cognitions about DM1</u> - Pictorial Representation of Self and Illness measure (PRISM) - Beck Depression Inventory (BDI-II-PC) - Illness Cognition List subscale acceptance	 Score ≥ 16 Score ≤ 19 Score ≥ 30 The DM causes more suffering than the fatigue, measured in lower distance in cm from the person Score ≥ 4 Score ≤ 12

5.	Optimising the interactions with direct environment	<u>Interaction with close others</u> - Caregiver strain index (CSI) - Marital satisfaction VAS <u>Experienced social support</u> Social Support Inventory - Subscale Discrepancy (SSL-D) - Subcale Negative Interactions (SSL-N)	 Score ≥ 7 One of partners ≤ 60 mm Score ≥ 53 Score ≥ 11
6.	Managing pain	McGill Pain Questionnaire (MPQ) SF-36 Pain	Score ≥ 44 Score ≤ 60

Supplementary table S8-1: Treatment modules and their indication according to baseline quantitative questionnaires

Participants could opt for the GET module, a structured exercise program aimed at further gradually increasing physical activity levels and fitness goals from those set and already reached as part of the graded activity module. This module would be offered when a participant formulated goals that asked for a more structured exercise program and when they reached a satisfactory activity performance on their graded activity module that could allow the implementation of an exercise routine (i.e. already walking or cycling a minimum total of 30 minutes 3 to 5 times per week). The overall intervention (*i.e.* CBT and GET when applicable) had a duration of 10 months. The treatment protocol described that the majority of CBT sessions should be delivered in the first 4-5 months, with a total maximum of 14 sessions. There was no pre-defined number of sessions for the GET module; however, compliance was considered when a minimum of one baseline session plus a follow-up verifying patient's involvement was completed.

CBT therapists and training

Ten licensed CBT therapists, all but one also psychologists, delivered the intervention in the 4 treatment centres. None of them had prior experience with delivering CBT in patients with DM1 and most of them had also no experience with treating patients with a somatic illness. Prior to start of the study, 12 therapists were given a 3-day training followed by a skills test. Eleven of them passed the test. Therapists were given weekly or biweekly supervision by telephone delivered by HK, SB and SvL. One therapist left the study before the end of CBT.

Analysis of treatment delivery for CBT and GET

At each CBT session, the therapist filled out a case rerport form (CRF) from which the following variables were calculated for each participant: total number of CBT sessions, total session time in minutes, number of sessions delivered in face-to-face communication format, number of sessions in which the caregiver attended, which

modules were delivered during treatment, and the number of sessions that were given within the first four months of treatment. Patients randomized to treatment who never started therapy or had ≤2 sessions were considered drop-outs and excluded.

In addition to the CRFs recorded by the therapists information on treatment delivery was provided by, a proportion of CBT sessions that had face-to-face or Skype communication format and were audio recorded. Three assessors involved in the study but not with intervention delivery, were trained to rate CBT sessions by an experienced CBT therapist who was involved in the design of the treatment manual. A subset (11%) of randomly selected audio recorded sessions were rated, after stratification to obtain a representative sample of tapes based on treatment centre, sessions number and sessions given early versus late during the trial. We evaluated for each session the behaviour of the therapists, if the workbook was used and if homework assignments were discussed. On a Likert scale therapist behaviour was scored if the therapist had discussed the modules as indicated on the CRF. Scores could range from 'not dealt with'(score 0) to 'excellent concordance with treatment manual' (score 5), for which evidence of changed patient cognitions and concrete behavioural goals had to be demonstrated. We considered a score of ≥ 3 'adequate' for the module that was evaluated. The first eight Dutch sessions to be analysed were double-rated in order to assess the interrater reliability by means of intraclass correlation coefficients (ICCs). The module with the lowest ICC still had a moderate interrater-reliability (ICC equal to or higher than .50) and the mean was .83 which is a good interrater-reliability.[16] All remaining sessions were rated by one rater.

Criteria for CBT treatment integrity

We predefined a set of criteria for treatment integrity based on the treatment manual: (1) Was CBT delivered according to protocol in terms of frequency of contact and communication format? (2) Are the CBT treatment modules as given? (3) Was treatment content accoding to protocol? Regarding the first criterion, the required minimum of sessions was 10, with a minimum of 5 face-to-face sessions For the second criterion, the modules delivered by the therapist according to the CRFs were compared with the indicated modules at baseline screening, requiring a 100% overlap (100% of indicated sessions given). For the third criterion, we calculated the number of CBT modules that were scored ≥3 in the audio recorded sessions.

Results

Cognitive behavioural therapy: case report form analysis

Treatment delivery in OPTIMISTIC	
Criterion 1 (CRF)	
Number of participants randomised for intervention	128
Number of participants in CBT analysis	119
Average number of sessions of CBT per participant; - mean (SD)	10·7 (3·3)
Average total duration of CBT per participant in hours - mean (SD)	9·0 (3·2)
Average number of face-to-face sessions - mean (SD)	6·3 (4·0)
Number of participants with ≥ 10 sessions (% of participants)	82 (69)
Number of participants with ≥5 face-to-face sessions (% of participants)	70 (60)
Number of sessions with 'face-to-face' or Skype communication format (% of total)	837 (65·9)
Criterion 2 (CRF)	
Number (%) of participants for whom *psychoeducation* and *goal setting*) was indicated/given	119 (100) / 117 (98)
Number (%) of participants for whom module 1 (*sleep-wake rhythm*) was indicated/given	85 (71) / 116 (97)
Number (%) of participants for whom module 2 (*compensating for reduced initiative*) was indicated/given	73 (61) / 109 (92)
Number (%) of participants for whom module 3 (*activity*) was indicated/given	119 (100) / 112 (94)
Number (%) of participants for whom module 4 (*helpful beliefs*) was indicated/given	105 (88) / 98 (82)
Number (%) of participants for whom module 5 (*social interactions*) was indicated/given	97 (82) / 79 (66)
Number (%) of participants for whom module 6 (*pain*) was indicated/given	56 (47) / 19 (16)
Criterion 3 (audio recorded sessions)	
Number of taped sessions (as % of total number of sessions)	479/1270 (37·7)
Number of rated sessions (as % of total numer of taped sessions)	55 (11·5)
Number of modules dealt with in rated sessions	181
Module rating – mean (SD) / median [IQR]	3.6 (1.1) / 4 [1]
Number of modules rated ≥ 3 (% of total number of rated modules)	159 (87·8%)

Supplementary Table S8-2 Summary of CRF recorded treatment delivery parameters. CBT cognitive behavioural therapy, GET graded exercise therapy.

Results for the analysis of the treatment delivery analysis are shown in table S8-2. For 119 out of 128 participants, case report forms were available. For criterion 1, 82 (69%) of patients had ≥ 10 sessions, and 70 (60%) had ≥5 face-to-face sessions. With regards to the individual treatment modules, modules 1 (sleep-wake rhythm) and 2 (compensating for reduced initiative), were both less often indicated than given, 71·4 and 61·3 percent versus 97·5 and 91·6 percent respectively (see table S8-2). In contrast, modules 4 (helpful beliefs), 5 (social interactions) and especially 6 (pain) were more often indicated on the basis of intake than given during cognitive behavioural therapy: 88, 82 and 47 versus 82, 66 and 16 percent, respectively. We rated a total of 55 sessions, 11·5 percent of the 479 taped sessions (table S8-2). In those 55 sessions, there were 181 modules that were dealt with. Of these, 159 modules (87.8%) were rated ≥ 3.

Graded exercise therapy

GET was only implemented two out of four treatment sites (Nijmegen and Newcastle). Forty-two participants considered suitable for the GET program were referred by CBT therapist to physical therapists. Nine patients were unable to comply with the program requirements, due to insufficient motivation or inability to satisfy the aerobic exercise criterion (Appendix 2). Thirty-three participants officially started the GET program, of which 31 were able to complete the program. One participant lost contact with the physical therapist during GET, another participant withdrew from the study because of malignancy. In the first session, explanation of GET and its differentiation from graded activity was given to all patients. Also, SMART defined goals were set and barriers for exercising identified. All but two patients started GET with a face-to-face intake sessions, after which there was either face-to-face or telephone follow-up. In both Newcastle and Nijmegen, main activities of GET were outdoor biking, outdoor walking, swimming and cardio fitness in a fitness center. Median duration of aerobic exercise per week was 126 minutes in Nijmegen and 170 minutes in Newcastle.

S8. Accelerometry

Methods

GENEActiv tri-axial accelerometers (ActivInsights Ltd, United Kingdom) were worn on the non-dominant ankle for 14 consecutive days at each visit. Accelerometer data was processed in R (www.cran.r-project.org) using R-package GGIR (R Foundation for Statistical Computing, Vienna, Austria; available from http://www.R-project.org/.https://cran.r-project.org/web/packages/GGIR/index.html).[17,18] Default parameters with respect to the measures generates (ENMO, L5, M5), except where specified. Daily estimates of physical activity were calculated midnight to midnight. Signals were inspected and corrected for calibration error.[19] Only days with at least 23 hours of valid data were included for data analysis. No imputation for missing values was used. The first and last day of the raw accelerometer measurement were excluded to avoid cofounding factors related to distribution or delivery procedures. Accelerometer data was only included in analysis if 7 days of valid data was available. The average magnitude of ankle acceleration was calculated via metric Euclidian Norm Minus One (ENMO) (millig, where 1mg = 0.001g = 0.001 x 9.8 m/s2 = 0.001 x gravitational acceleration). The average acceleration during the most active and least active 5 hour period of each day were also included for analysis (M5, L5). The difference between M5 and L5 provided a simple indicator of the level of circadian variability.[20]

Table S9. **Missing accelerometry data, non-compliance and device losses for each visit over the course of the study (%)**

	Baseline			***5 months***			***10 months***			***16 months***		
	Devices Received^	Missing data	Non-compliance	Devices Received^	Missing data	Non-compliance	Devices Received^	Missing data	Non-compliance	Devices Received^	Missing data	Non-compliance
%	84	10.7	2.3	86	9.8	4.7	82	9	4.2	83	4.5	4

Table S8. Data reflects the % of patient data that was not available for accelerometry analysis from those devices registered as received or returned to the site (^); Missing data: Inadequate data capture (data too small/not available); < 7 days of < 23 hours; Non-compliance: declined to wear device; device location misplacement (not worn on the ankle); daytime recording only.

Web Extra references

1. Hermans MC, Faber CG, De Baets MH, de Die-Smulders CE, Merkies IS. Rasch-built myotonic dystrophy type 1 activity and participation scale (DM1-Activ). *Neuromuscular disorders : NMD* 2010; **20**(5): 310-8.
2. Hermans MC, Hoeijmakers JG, Faber CG, Merkies IS. Reconstructing the Rasch-Built Myotonic Dystrophy Type 1 Activity and Participation Scale. *PloS one* 2015; **10**(10): e0139944.
3. van Engelen B, Consortium O. Cognitive behaviour therapy plus aerobic exercise training to increase activity in participants with myotonic dystrophy type 1 (DM1) compared to usual care (OPTIMISTIC): study protocol for randomised controlled trial. *Trials* 2015; **16**(1): 224.
4. Hoffmann TC, Glasziou PP, Boutron I, et al. Better reporting of interventions: template for intervention description and replication (TIDieR) checklist and guide. *Bmj* 2014; **348**: g1687.
5. Kierkegaard M, Tollback A. Reliability and feasibility of the six minute walk test in subjects with myotonic dystrophy. *Neuromuscular disorders : NMD* 2007; **17**(11-12): 943-9.
6. Prahm KP, Witting N, Vissing J. Decreased variability of the 6-minute walk test by heart rate correction in participants with neuromuscular disease. *PloS one* 2014; **9**(12): e114273.
7. Heatwole C, Bode R, Johnson N, et al. Myotonic Dystrophy Health Index: initial evaluation of a disease-specific outcome measure. *Muscle & nerve* 2014; **49**(6): 906-14.
8. Heatwole C, Bode R, Nicholas J, et al. The myotonic dystrophy health index: Correlations with clinical tests and patient function. *Muscle & nerve* 2015.
9. Hermans MC, Merkies IS, Laberge L, Blom EW, Tennant A, Faber CG. Fatigue and daytime sleepiness scale in myotonic dystrophy type 1. *Muscle & nerve* 2013; **47**(1): 89-95.
10. Worm-Smeitink M, Gielissen M, Bloot L, et al. The assessment of fatigue: Psychometric qualities and norms for the Checklist individual strength. *Journal of psychosomatic research* 2017; **98**: 40-6.
11. Vincent KA, Carr AJ, Walburn J, Scott DL, Rose MR. Construction and validation of a quality of life questionnaire for neuromuscular disease (INQoL). *Neurology* 2007; **68**(13): 1051-7.
12. Benedict RH, Fishman I, McClellan MM, Bakshi R, Weinstock-Guttman B. Validity of the Beck Depression Inventory-Fast Screen in multiple sclerosis. *Multiple sclerosis* 2003; **9**(4): 393-6.
13. Poole H, Bramwell R, Murphy P. The utility of the Beck Depression Inventory Fast Screen (BDI-FS) in a pain clinic population. *European journal of pain* 2009; **13**(8): 865-9.
14. Marin RS, Biedrzycki RC, Firinciogullari S. Reliability and validity of the Apathy Evaluation Scale. *Psychiatry research* 1991; **38**(2): 143-62.
15. Brown EG, Wood L, Wood S. The medical dictionary for regulatory activities (MedDRA). *Drug Saf* 1999; **20**(2): 109-17.
16. Portney LG, Watkins MP. Foundations of clinical research : applications to practice. 3rd ed. ed. Upper Saddle River, N.J.: Pearson Prentice Hall; 2009.
17. RCoreTeam. R: A language and environment for statistical computing. R Foundation for Statistical Computing. 2013. http://www.R-project.org/.
18. van Hees VT, Gorzelniak L, Leon ECD, et al. Separating Movement and Gravity Components in an Acceleration Signal and Implications for the Assessment of Human Daily Physical Activity. Public Library of Science; 2013. p. e61691.
19. van Hees VT, Fang Z, Langford J, et al. Autocalibration of accelerometer data for free-living physical activity assessment using local gravity and temperature: an evaluation on four continents. *J Appl Physiol (1985)* 2014; **117**(7): 738-44.
20. Anderson KN, Catt M, Collerton J, et al. Assessment of sleep and circadian rhythm disorders in the very old: the Newcastle 85+ Cohort Study. *Age Ageing* 2014; **43**(1): 57-63.