THE LANCET
Neurology

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Okkersen K, Jimenez-Moreno C, Wenninger S, et al, for the OPTIMISTIC consortium. Cognitive behavioural therapy with optional graded exercise therapy in patients with severe fatigue with myotonic dystrophy type 1: a multicentre, single-blind, randomised trial. *Lancet Neurol* 2018; published online June 19. http://dx.doi.org/10.1016/S1474-4422(18)30203-5.

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 S6a. 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 S6a. **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 S6b. Subgroup analyses for all (primary and secondary) outcome measures

Table S6b. **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 S6b. **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 S7. Repeated measures analysis for primary and secondary outcomes

Table S7. 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 S7. **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

S8. 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.

S9. 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.

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