



## Improving fatigue in multiple sclerosis by smartphone-supported energy management: The MS TeleCoach feasibility study



Marie D'hooghe<sup>a,\*</sup>, Geert Van Gassen<sup>b,\*</sup>, Daphne Kos<sup>c,k</sup>, Olivier Bouquiaux<sup>d</sup>, Melissa Cambron<sup>e</sup>, Danny Decoo<sup>f</sup>, Andreas Lysandropoulos<sup>g</sup>, Bart Van Wijmeersch<sup>h</sup>, Barbara Willekens<sup>i</sup>, Iris-Katharina Penner<sup>j</sup>, Guy Nagels<sup>a</sup>

<sup>a</sup> National MS Center, Neurology, Vanheylenstraat 16, Melsbroek and Vrije Universiteit Brussel (VUB), Center for Neurosciences, Laarbeeklaan 103, 1090 Brussel, Belgium

<sup>b</sup> Teva Pharma Belgium NV, Medical Department, Laarstraat 16, 2610 Wilrijk, Belgium

<sup>c</sup> KU Leuven, Department of Rehabilitation Sciences, Tervuursevest 101, postbox 1501 - Gebouw De Nayer, Room 02.58 3001 Leuven, Belgium

<sup>d</sup> Centre Neurologique et de Readaptation Fonctionnelle, Neurologie, Champ des Alouettes 30, 4557 Fraiture, Belgium

<sup>e</sup> Universitair Ziekenhuis Brussel, Neurology, Laarbeeklaan 103, 1090 Brussel, Belgium

<sup>f</sup> AZ Alma, Neurologie, Ringlaan 15, 9900 Eeklo, Belgium

<sup>g</sup> Erasme Hospital, Neurology, Route de Lennik 808, 1070 Bruxelles, Belgium

<sup>h</sup> Hasselt University and Translational Universiteit Limburg, School of Life Sciences, Biomedical Research Institute; Rehabilitation & MS Center, Boemerangstraat 2, 3900 Overpelt, Belgium

<sup>i</sup> Universitair Ziekenhuis Antwerpen, Neurology, Wilrijkstraat 10, 2650 Edegem, Belgium

<sup>j</sup> Heinrich Heine University, Neurology, Medical Faculty; COGITO Center, Neurocognition and Neuropsychology, Merowingerplatz 1, 40225 Düsseldorf, Germany

<sup>k</sup> AP University College Antwerp, Occupational Therapy, Campus Spoor Noord, Noorderplaats 2, B 2000 Antwerpen, Belgium

### ARTICLE INFO

#### Keywords:

Multiple sclerosis  
Fatigue  
Telemedicine  
Physical activity  
Self-management

### ABSTRACT

**Background:** Fatigue is a frequently occurring, often disabling symptom in MS with no single effective treatment. In current fatigue management interventions, personalized, real-time follow-up is often lacking. The objective of the study is to assess the feasibility of the MS TeleCoach, a novel intervention offering telemonitoring of fatigue and telecoaching of physical activity and energy management in persons with MS (pwMS) over a 12-week period. The goal of the MS TeleCoach, conceived as a combination of monitoring, self-management and motivational messages, is to enhance levels of physical activity thereby improving fatigue in pwMS in an accessible and interactive way, reinforcing self-management of patients.

**Methods:** We conducted a prospective, open-label feasibility study of the MS TeleCoach in pwMS with Expanded Disability Status Scale  $\leq 4$  and moderate to severe fatigue as measured by the Fatigue Scale for Motor and Cognitive Functions (FSMC). Following a 2-week run-in period to assess the baseline activity level per patient, the target number of activity counts was gradually increased over the 12-week period through telecoaching. The primary efficacy outcome was change in FSMC total score from baseline to study end. A subset of patients was asked to fill in D-QUEST 2.0, a usability questionnaire, to evaluate the satisfaction with the MS TeleCoach device and the experienced service.

**Results:** Seventy-five patients were recruited from 16 centres in Belgium, of which 57 patients (76%) completed the study. FSMC total score ( $p = 0.009$ ) and motor and cognitive subscores ( $p = 0.007$  and  $p = 0.02$  respectively) decreased from baseline to week 12, indicating an improvement in fatigue. One third of participants with severe fatigue changed to a lower FSMC category for both FSMC total score and subscores. The post-study evaluation of patient satisfaction showed that the intervention was well accepted and that patients were very satisfied with the quality of the professional services.

**Conclusion:** Using MS TeleCoach as a self-management tool in pwMS suffering from mild disability and moderate to severe fatigue appeared to be feasible, both technically and from a content perspective. Its use was associated with improved fatigue levels in the participants who completed the study. The MS TeleCoach seems to meet the need for a low-cost, accessible and interactive self-management tool in MS.

\* Corresponding author.

E-mail addresses: [marie.dhooghe@mscenter.be](mailto:marie.dhooghe@mscenter.be) (M. D'hooghe), [geert.vangassen@tevelgium.be](mailto:geert.vangassen@tevelgium.be) (G. Van Gassen), [daphne.kos@kuleuven.be](mailto:daphne.kos@kuleuven.be) (D. Kos), [bouquiauxoli@me.com](mailto:bouquiauxoli@me.com) (O. Bouquiaux), [melissa.cambron@gmail.com](mailto:melissa.cambron@gmail.com) (M. Cambron), [dannydecoo@me.com](mailto:dannydecoo@me.com) (D. Decoo), [andreas.lys@hotmail.com](mailto:andreas.lys@hotmail.com) (A. Lysandropoulos), [bart.vanwijmeersch@uhasselt.be](mailto:bart.vanwijmeersch@uhasselt.be) (B. Van Wijmeersch), [Barbara.Willekens@uza.be](mailto:Barbara.Willekens@uza.be) (B. Willekens), [ik.penner@cogito-center.com](mailto:ik.penner@cogito-center.com) (I.-K. Penner), [guy.nagels@mscenter.be](mailto:guy.nagels@mscenter.be) (G. Nagels).

<https://doi.org/10.1016/j.msard.2018.03.020>

Received 3 January 2018; Received in revised form 21 March 2018; Accepted 26 March 2018

2211-0348/© 2018 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

## 1. Introduction

Fatigue is the most commonly reported symptom among persons with multiple sclerosis (pwMS), affecting 75–95% of patients. The underlying mechanisms are unknown and may be multiple: more than 30 primary and secondary pathological fatigue pathways were identified (Langeskov-Christensen et al., 2017). In 50–60% of patients, fatigue substantially interferes with the activities of daily living and negatively affects quality of life (QoL) (Lerdal et al., 2007; Finlayson et al., 2013; Penner, 2016). Fatigue is one of the main reasons for the inability to work and early retirement requests in MS (Schiavolin et al., 2013).

Current fatigue management interventions include aerobic exercise, energy conservation strategies and cooling devices (Davis et al., 2010; Khan et al., 2014). A full spectrum of fatigue management approaches has been proposed, from exercise to educational interventions in conjunction with medication (Asano and Finlayson, 2014). A recent review suggested that one of the limitations to promote exercise through the patient–clinician interaction in MS is the absence of a conceptual framework and toolkit for translating the evidence into practice (Motl et al., 2017). What is often lacking in current fatigue management interventions is personalized, real-time follow-up.

Looking at the effect of such interventions, group-based energy conservation strategies showed mainly short-term effects on fatigue and QoL (Asano and Finlayson, 2014; Blikman et al., 2013), as did studies on exercise training (Motl and Pilutti, 2012; Pilutti et al., 2013). It was reported recently that exercise might repair or improve connectivity in the brain of MS patients (Stellmann, 2017).

Taking into account the need for effective and convenient fatigue management approaches that can be easily built in the daily lives of pwMS, a multidisciplinary team of MS experts developed a tele-rehabilitation intervention, called MS TeleCoach. Complementary to existing fatigue management approaches, the intervention aims at enhancing physical activity and thereby improving fatigue in pwMS in an accessible and interactive way, reinforcing self-management of the pwMS.

A multidisciplinary team of MS experts was involved in the development of the intervention. The starting point of the development process was the vision of creating a tool to target physical activity and fatigue in pwMS, based on positive reinforcement. To the best of our knowledge, no such interventions are currently available.

The potential benefit of MS TeleCoach would be to reduce fatigue in pwMS substantially. A clinically relevant improvement in fatigue would be a decrease of 10 points and/or a change in category on the Fatigue Scale for Motor and Cognitive Functions (FMSC) (Penner et al., 2009). Our intervention meets the need for a low-cost, accessible and convenient way for pwMS to increase their physical activity. Our longer-term vision for the intervention would be a wide-spread use of it by MS patients.

The primary objective of the study was to explore the feasibility and usefulness of MS TeleCoach in MS patients during a 12-week period. Furthermore, we also evaluated the effectiveness of the MS TeleCoach in improving fatigue.

## 2. Materials and methods

### 2.1. MS TeleCoach

MS TeleCoach was conceived by an international group of MS experts to be a combination of monitoring, self-management and motivational messages, focusing on energy management and enhancement of physical activity with the goal of improving fatigue levels in pwMS. The expert group consisted of neurologists, occupational therapists, neuroscientists and neuropsychologists with a focus on MS.

MS TeleCoach is a telerehabilitation intervention developed as a smartphone application consisting of two main components: tele-monitoring and telecoaching. Telemonitoring refers to the

measurement of the individual's physical activity through the device's integrated accelerometers and self-reported fatigue impact levels. Three times daily (morning, noon and evening), participants were asked to assess the degree of impact of fatigue using the Visual Analogue Scale (VAS) (Kos et al., 2006) on the MS TeleCoach. Telecoaching refers to the set of motivational messages and advices on the one hand, and the goal setting towards increasing physical activity on the other hand, that were presented to the patients through the application. Three times a week, patients received encouraging messages to increase their physical activity. In addition, standardized advice and coaching on energy management was provided throughout the 12-week evaluation period on a daily basis, aiming at reminding subjects of their activity goals, providing suggestions on energy management and motivational messages to stimulate patients in performing extra physical activity and to follow the energy management advice. The treating neurologist had the possibility to consult the patients' data through a web interface.

During the 2-week run-in period, the mean daily number of activity counts was determined per patient. This was then considered to be the baseline activity level for that particular patient. Every three weeks, the target number of activity counts increased to levels that were respectively 5%, 10%, 15%, and 20% higher compared to the individual's baseline level. Three times a week, the MS TeleCoach reminded the patient of the current motor activity goal. The type of physical activity was individually adapted according to the patients' usual daily activity.

A 3-axis accelerometer in the MSteleCoach with a signal sampled at a frequency of 50 Hz provided a continuous and reproducible recording of physical activity levels. To do this in a reliable way, only the MS TeleCoach application was active on the device that was provided to the participants during the trial. All other functionalities were switched off. The device was placed horizontally in a belt-pouch tied around the waist. Actigraphic telemetric data measuring the activity count from pwMS were used when data from at least one week per period (week –2 to 0, week 0–6, week 6–12) were available. All data were captured on a secured server on a daily basis.

### 2.2. Study design

This is a one-armed, open-label, multicentre prospective feasibility study to evaluate the effect of using MS TeleCoach on fatigue severity in pwMS that are moderately to severely fatigued. A 2-week run-in period was followed by a 12-week evaluation period. The primary outcome measure was the change in total score on the Fatigue Scale for Motor and Cognitive Functions (FMSC) from baseline to study end.

### 2.3. Patients

Relapsing-remitting MS (RRMS) patients between 18 and 60 years old with moderate to severe fatigue and EDSS  $\leq$  4 were recruited from 16 centres in Belgium. Inclusion and exclusion criteria are listed in Table 1. The study was conducted in compliance with Good Clinical

**Table 1**  
Patient inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
$\geq$ 18 years and $\leq$ 60 years old	MDD diagnosis according to DSM-IV
RRMS diagnosis	SPMS diagnosis
3 months MS exacerbation free	Severe cognitive impairment
EDSS $\leq$ 4	Co-morbidities that prevent patients to perform normal physical activity (e.g. to walk)
On Glatiramer Acetate, for at least 6 weeks	Injuries that prevent patients to perform normal physical activity (e.g. to walk)
FSMCTotal $\geq$ 53 (moderate to severe fatigued)	Pregnancy

Abbreviations: RRMS: Relapsing-remitting multiple sclerosis; MDD: Major depressive disorder; EDSS: Expanded disability status scale; SPMS: Secondary progressive MS; FSMC: Fatigue scale for motor and cognitive function.

**Table 2**  
Visit schema and assessed parameters.

	Run-in (– 2 weeks)	Baseline (0 weeks)	6 weeks	12 weeks
Informed Consent	X			
Assessed parameters				
Sociodemographic data	X			
Clinical characteristics	X			
Clinical status		X	X	X
EDSS	X			
FSMC	X	X	X	X
MFIS	X	X	X	X
SF–36	X	X	X	X
VAS_1 fatigue	X	X	X	X
HADS	X	X	X	X
Physical activity (activity count)	X	X	X	X

**Abbreviations:** FSMC: Fatigue Scale for Motor and Cognitive Function, MFIS: Modified Fatigue Impact Scale, EDSS: Expanded Disability Status Scale, SF-36: Short-Form-36, VAS: Visual Analogue Scale, HADS: Hospital Anxiety Depression Scale.

Practice and the study protocol was approved by the leading ethical committee (UZ Brussel, Vrije Universiteit Brussel) and the ethical committees of all participating centres.

#### 2.4. Assessments

Participants meeting the inclusion criteria underwent a complete neurological evaluation by the principal investigator of the participating centre during the first visit at run-in, including Expanded Disability Status Scale (EDSS), sociodemographic data and other clinical MS characteristics. During the visits scheduled at baseline, week 6 and week 12, the clinical MS status and questionnaires were completed (Table 2). The primary outcome measure was the change in FSMC total score from baseline to study end. The FSMC is a well-defined and validated instrument for assessing cognitive and motor fatigue in pwMS (Penner et al., 2009). Clinical staging cut-off values were defined as mild, moderate or severe fatigue when FSMC total score values were  $\geq 43$ ,  $\geq 53$ , or  $\geq 63$  respectively (Penner et al., 2009). Secondary outcomes were the FSMC cognitive and FSMC motor subscales, Modified Fatigue Impact Scale (MFIS) (Kos et al., 2003), Short Form-36 (SF-36) (Stewart et al., 1988), Hospital Anxiety Depression Scale (HADS) - depression subscale (Zigmond and Snaith, 1983). Cut-off values for the FSMC cognitive subscale were  $\geq 22$  for mild,  $\geq 28$  for moderate, and  $\geq 34$  for severe cognitive fatigue. Cut-off values for the FSMC motor subscale were  $\geq 22$  for mild,  $\geq 27$  for moderate, and  $\geq 32$  for severe motor fatigue (Penner et al., 2009).

#### 2.5. Post-study evaluation of patient satisfaction

To evaluate the subject's satisfaction level with regard to the MS TeleCoach intervention, 23 patients from two centres were asked to complete the D-QUEST 2.0 (Wessel et al., 2000). The D-Quest 2.0 is a usability questionnaire consisting of 12 questions related to comfort, durability and ease of use. Each question was rated on a five point scale, ranging from "not satisfied at all" to "very satisfied".

#### 2.6. Statistical analyses

To get an indication of how many patients should be included in this study, statistical power analysis was done using the R statistical package. Assumptions were a power of 90% (beta = 10%), alpha = 1%, SD = 17.91 and an expected difference between measurements of ten

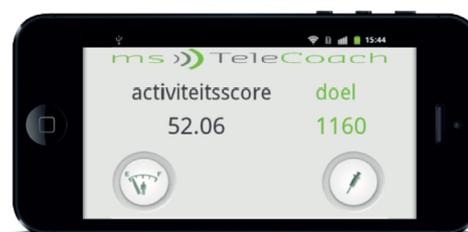


Fig. 1. Home screen of the MS TeleCoach.

points on the FSMC, a clinically meaningful difference, as communicated by Dr. Penner. Since we wanted to examine whether there would be a significant difference in the mean score of a group of individuals at two time points, a paired *t*-test was chosen. This resulted in a required sample size of 51 subjects. We anticipated a substantial dropout, as we were going to ask pwMS with moderate to severe fatigue to increase their physical activities. With an estimated dropout rate of 30%, the target minimum number of inclusions was increased to 72 pwMS.

Statistical analysis of the study results was carried out with SAS Software 9.3 (Cary, NC, USA) and R3.1.3. Normality was checked graphically using qqplots. Changes over time in primary and secondary outcomes were analysed using paired Student *t*-tests for normally distributed data or the non-parametric Wilcoxon Signed Rank test in case the data had a non-Gaussian distribution. For the analysis of the success-rate, generalized mixed models with random intercept were used. No corrections were made for multiple testing, instead exact p-values were used (Fig. 1).

### 3. Results

#### 3.1. Study participants

Seventy-five RRMS patients were recruited from 16 centres in Belgium, of which 57 patients (76%) completed the study (Fig. 2). The most frequently reported reasons for drop out were having a relapse, technical problems with the device or lack of motivation.

Demographic and baseline characteristics of the sample are summarized in Table 3. The gender distribution was in line with the overall distribution in the MS population. With a median value of less than 1 h/week, the number of hours per week spent on rehabilitation, physiotherapy or fitness was rather low in our group of patients. The mean FSMC total score at inclusion was 72.51, indicating severe fatigue.

Comparing the profiles of patients completing the study versus patients dropping-out, no apparent differences were seen in demographic or baseline characteristics, such as the median baseline values of FSMC Total and EDSS. Only the median MFIS Total score was slightly higher in patients dropping out than in patients completing the study (56 vs. 48 respectively;  $p = 0.15$ , data not shown).

#### 3.2. Primary and secondary efficacy endpoints

FSMC total, cognitive and motor scores changed significantly between baseline and study end (Table 4). The change in FSMC total score was  $-3.76$  (95% CI  $-6.55; -0.97$ ) ( $p = 0.009$ ). About one third of the initially severely fatigued patients changed to a lower FSMC category for both FSMC total and FSMC subscores (Fig. 3). During the two-week run-in period, in which there was no active telecoaching, the mean total FSMC score decreased by 2.0 points (95% CI  $-3.9; 0.0$ ).

The mean change in MFIS total score between baseline and study end was  $-3.96$  (95% CI  $-7.92; -0.01$ ) ( $p = 0.03$ ). The MFIS total, physical and psychosocial subscale scores showed similar significant reductions between baseline and study end. Only the cognitive subscale of the MFIS did not change significantly (Table 4).

The SF-36 subscale related to physical health limits showed a

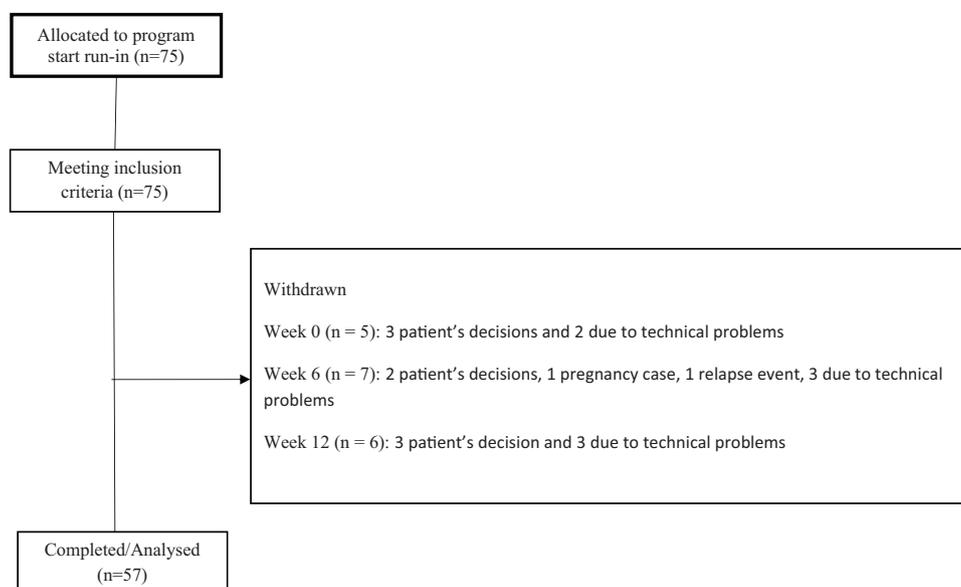


Fig. 2. : Distribution of patients completing and withdrawing from the study.

significant improvement of 10.7 points between baseline and study end. No other SF-36 subscales, nor the HADS-depression subscore showed a significant change (data not shown).

### 3.3. Feasibility

While in general the transfer of data between the patient and the MS TeleCoach application was successful, a problem with the logging of the accelerometry data occurred in eight patients, most probably caused by 3 G connectivity problems, as these few patients lived in a remote area in Belgium with a limited cellular communications network. The connectivity problem did not interfere with the information that the MS TeleCoach delivered to the individual patients on a daily basis. These missing data did not affect the analysis of the primary endpoint of our study. It did however impact the retrospective assessment of the percentage of patients that successfully attained the requested increase in physical activity. The exploratory analysis in 67 of the 75 patients who started the study showed that increasing the motor activity target goals (from +5% to +10%, from +10% to +15% and from +15% to +20% additional to the baseline physical activity count) resulted in significantly lower odds to reach the higher physical activity targets (Table 5). Reaching the target goals of 5%, 10%, 15% and 20% was not influenced by “daily variance in fatigue” and “mean daily fatigue”, as measured by the VAS on the MS TeleCoach (data not shown).

### 3.4. Post-study evaluation of patient satisfaction

Of 23 completers being asked to participate in the post-study evaluation, 21 (91,3%) completed the D-QUEST 2.0. Overall, 4,8% of the subjects in this subsample scored “more or less satisfied”, 85,7% scored “quite satisfied” and 9,5% scored “very satisfied”. Each of the 12 questions resulted in a median of “quite satisfied” with the exception of the quality of the professional services (information, attention) with a median score of “very satisfied” (see supplementary data).

## 4. Discussion & conclusion

The primary objective of the study was to explore the feasibility and usefulness of MS TeleCoach - a novel intervention designed to enhance physical activity levels to improve fatigue in MS patients - in MS patients during a 12-week period. This study included a rather homogeneous group of MS patients with limited to mild disability and

moderate to severe fatigue, all treated with the same immunomodulatory drug.

The number of study completers (76%) suggests that the use of the MS TeleCoach was considered as an added value, or at least not as a burden. Indeed, appreciation of the MS TeleCoach by its users was confirmed by a post-study evaluation of patient satisfaction in a subset of study completers. As a comparison, a teleconference-delivered fatigue management program for pwMS (Finlayson et al., 2011) reported more than 90% of completers and an internet-supported physical exercise training for pwMS (Tallner et al., 2016) had a completer rate of 61%. With 76% completers, our study had an intermediate percentage of completers. As shown above, reasons for drop-out were mainly due to technical problems and patient's decisions. The technical problems were nearly all related to 3 G connectivity issues. In the meantime, 3 and 4 G coverage has improved in Belgium and the rest of Europe. This could potentially increase the completer rate in the future. Among the drop-outs related to patient's decisions, lack of motivation was often reported, indicating that a telerehabilitation program might not suitable for every person with MS-related fatigue.

Telerehabilitation in general has the potential of delivering an intervention in remote areas, be complementary to existing rehabilitation, allow rehabilitation outside normal working hours and stimulate self-management of patients. Limitations for telerehabilitation are high developmental costs, the balance between technicity and user friendliness of the intervention, possible data privacy issues, difficulties in getting reimbursement, challenges in personalizing individual patient needs and the use of Patient-Reported Outcomes measures rather than objective measures.

In this feasibility study, we demonstrated significant improvements in total, cognitive and motor fatigue scores after 12 weeks of use by moderately to severely fatigued MS patients. While not being the main objective of this study, a clinically meaningful decrease of 10 points on the mean FSMC total score was not reached in the overall population (Penner et al., 2009). Nevertheless, a statistically significant improvement in mean FSMC scores from baseline to study end was observed and in a subset of 16 subjects (28%), a decrease of 10 points on the FSMC total score between baseline and study end was observed. In addition, one third of the initially severely fatigued pwMS changed to a lower fatigue category over the 12 week study period, which is also interpreted as clinically meaningful. The improvement in fatigue observed with the FSMC was confirmed by an improvement in MFIS. There may be multiple reasons why we did not obtain a clinically

**Table 3**  
Characteristics of the study population (n = 75).

Sociodemographics	Frequency
<b>Gender</b>	
Male	26.7%
Female	66.7%
Missing	6.7%
<b>Marital status</b>	
Married or living with a partner	64.0%
Living alone	25.3%
Widow(er)	2.7%
Missing	8.0%
<b>Highest education level</b>	
Primary school	9.3%
Secondary school	36.0%
Bachelor	32.0%
Master	9.3%
Master after Master	4.0%
Ph.D.	1.3%
Missing	8.0%
<b>Work status</b>	
Professionally active	53.3%
Retired	1.3%
Disablement (inability to work)	24.0%
Unemployed	4.0%
Sick leave	8.0%
Missing	9.3%
<b>Profession</b>	
Blue-collar worker	14.7%
White-collar worker	40.0%
Self-employed	5.3%
Unemployed	29.3%
Blue-collar worker / Self-employed	1.3%
White-collar worker / Self-employed	1.3%
Missing	8.0%
<b>Sociodemographics</b>	<b>Mean (SD)</b>
Age (year)	39.19 (10.1)
Length (cm)	169.7 (9.10)
Weight (kg)	75.89 (17.6)
<b>Clinical characteristics</b>	<b>Mean (SD) or Median (Q1-Q3)</b>
Number of MS exacerbations last year	0 (0 – 1)
Number of MS exacerbations last 2 years	1 (0 – 2)
Time since RRMS diagnosis (years)	5.08 (2.52 – 10.83)
EDSS (run-in)	2 (1.5 – 3)
FSMCTotal (run-in)	72.51 (11.0)
MFIS (run-in)	48.76 (13.7)
SF – 36 (run-in)	496 (405 – 562)
HADS-Dep (run-in)	6 (4 – 8)
<b>Physical training</b>	<b>Median (Q1-Q3)</b>
Multidisciplinary rehabilitation (hours/week)	0 (0 – 0)
(hours/week)	
Physiotherapy (hours/week)	0 (0 – 1)
Fitness (hours/week)	0 (0 – 0)

\*If data were normally distributed mean and SD are given, otherwise median with Q1-Q3 were given.

meaningful change for all of the participants, including a too short evaluation period, a heterogeneous patient group of responders and non-responders to physical activity, the limitation of the MS TeleCoach to differentiate the type of physical activity performed, and finally the fact that the odds to reach the higher physical targets dropped substantially with higher targets.

A recently published Cochrane review on the effect of exercise therapy on fatigue in MS (Heine et al., 2015) described significant effects on fatigue in favor of exercise therapy for endurance training, mixed training, and 'other' training, compared to no exercise. However, it was also suggested that the effects of exercise therapy on fatigue may not be of the same magnitude for each person and may, in part, depend on the type of exercise stimulus.

In the MS TeleCoach intervention, no specific requirements were made related to the nature of the physical activity. The idea was to keep the participation threshold deliberately as low as possible, and motivate

**Table 4**  
Changes in FSMC and MFIS scores between end of the study (12 weeks) and baseline or run-in.

	Mean change between baseline and study end (95% CI)	Mean change between run-in and study end (95% CI)
<b>FSMC</b>		
FSMCTot	– 3.76 (–6.55 to –0.97)**	– 6.3 (–9.27 to –2.88)***
FSMCCog	– 1.73 (–3.22 to –0.23)*	– 2.86 (–4.41 to –1.31)***
FSMCMot	– 2.02 (–3.38 to –0.58)**	– 3.21 (–4.99 to –1.43)***
<b>MFIS</b>		
MFISTot	– 3.96 (–7.92 to –0.01)*	– 4.91 (–9.20 to –0.63)*
MFISCog	– 1.51 (–3.33 to 0.31)	– 1.70 (–3.50 to 0.21)
MFISPsy	– 0.48	– 0.70**
MFISPhys	– 2 (–3.98 to –0.03)*	– 2.59 (–4.80 to –0.38)*

Paired *t*-test, assumption of normality was checked. If not valid, a Wilcoxon signed-Rank test was performed.

\* *p* < 0.05.

\*\* *p* < 0.01.

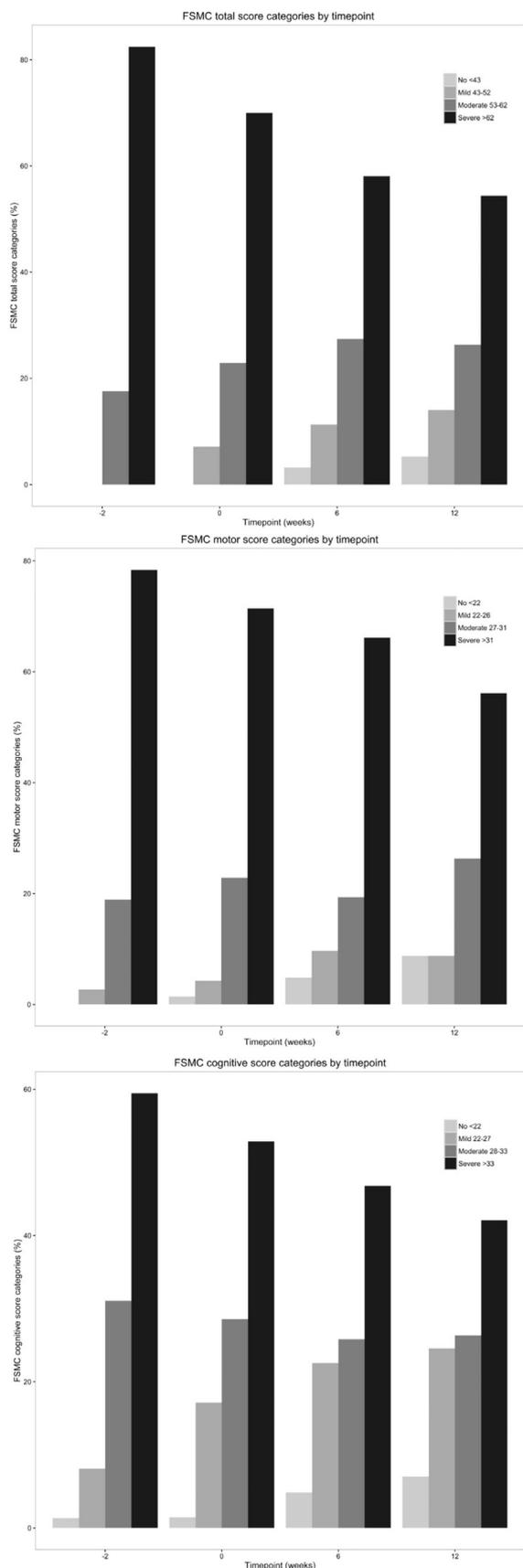
\*\*\* *p* < 0.001.

the pwMS to do more of the physical activities they were used to do on a daily basis, e.g. walking, biking. A limitation of this approach is that we don't know which physical activity stimulus gave rise to the observed improvement in fatigue, and that it may be different from participant to participant. On the other hand, as has been previously proposed, just decreasing the level of sedentary behavior in pwMS could already potentially be beneficial (Veldhuijzen van Zanten et al., 2016). Heterogeneous levels of physical activity intensity among participants might therefore potentially explain why clinically relevant improvements were not found in all patients. Furthermore, as demonstrated in this feasibility study, the odds to reach higher physical activity targets dropped substantially with higher physical targets. The higher targets of a 15% and 20% increase in physical activity above baseline may be have been too demanding and ambitious for pwMS, since only few patients in the study were able to reach them within the timeframe of 12 weeks. Therefore we recommend that future coaching programs lower the physical activity targets to realistic and achievable levels. Finally, on a methodological level, we addressed two of the 3 major limitations that were found in similar studies by Heine and colleagues, namely we explicitly included a rather homogenous moderate to severe fatigued pwMS and used a validated outcome measure for fatigue in MS, the FSMC, as the primary endpoint.

To our surprise, the FSMC scores already substantially decreased during the 2 week run-in period, when the subjects carried the MS TeleCoach device to measure activity levels, without receiving any feedback or coaching. This suggests that the mere fact of measuring physical activity levels and monitoring fatigue may have a positive effect on perceived fatigue. A similar effect was seen in a study where the use of activity diaries was shown to be a contributor to the self-management of fatigue (Jongen et al., 2015b), and in studies of self-management programs using an interactive web-based program (Jongen et al., 2015a).

Regarding the QoL endpoints, the significant increase for the physical limitation score is equivalent to an improvement of perceived physical health limits. PwMS experienced significantly fewer limitations at work or other daily activities at 12 weeks compared to baseline. This suggests that telecoaching lowers the perception of having physical barriers in work and daily life.

The goal of this one-arm, 12-week feasibility study of the MS TeleCoach device as a self-management tool in pwMS suffering with mild disability and moderate to severe fatigue was reached. We saw a confirmation of the feasibility of the intervention, both technically and from a content perspective. This means that the MS TeleCoach is now ready to be tested in a larger, randomized and controlled study, over a longer period of time. This will allow a quantification of the effect of the MS TeleCoach on the lives of pwMS and an assessment of any long-



**Fig. 3.** Percentage of patients per FSMC fatigue category at each study visit, a) FSMC total score; b) FSMC motor score and c) FSMC cognitive score. FSMC cut-off scores for no fatigue (< 43), mild fatigue (between 43 and 52), moderate fatigue (53–62) and severe fatigue (> 62) are used.

**Table 5**

Model: Evolution of the target success rate with the extra expected activity percentage using the 5% extra work level as a reference.

		Estimate	95% CI LL	95% CI UL
<b>Odds</b>	5% extra work	1.19	0.91	1.57
<b>Odds ratio compared to 5% level</b>	10% extra work	0.61	0.51	0.73
<b>Odds ratio compared to 5% level</b>	15% extra work	0.51	0.42	0.61
<b>Odds ratio compared to 5% level</b>	20% extra work	0.47	0.38	0.58

term effects on fatigue and QoL.

Overall, we conclude that the MS TeleCoach was appreciated by the participants taking part in the feasibility study. It helped pwMS to increase their physical activity during their normal daily activities, without the need to go to a fitness centre or another sports facility, thereby meeting the demand for a low-cost, accessible and realistic way for MS patients to increase physical activity. The MS TeleCoach has the potential to grow out to a proper self-management tool for pwMS, that is complementary to existing treatment and care programs in MS, allowing pwMS to play an active role in the management of their disease.

**Acknowledgements**

First of all authors and MS TeleCoach investigators like to thank the PwMS that have participated. The MS TeleCoach investigators and study nurses were: NMSC Melsbroek (M. D'hooghe, G. Nagels, P. Eelen, A. Van Remoortel), MS & Revalidatiecentrum Overpelt (B. Van Wijmeersch, R. Jansen, A. Bogaers), UZBrussel (J. De Keyser, M. Cambron, A. Van Merhaegen), Antwerp University Hospital (B.Willekens, L. Wagemakers, D. Mahieu), AZ Alma (D.Decoo, M. De Sutter), AZ Groeninge (P. Vanderdonckt, S. Willaert), UZGent (, J. Debruyne, L. Van Hijfte), ZNA Middelheim (R. Crols, P. Ongena), Erasme (A. Lysandropoulos, A. Fadel, N. Alaerts), Saint-Luc (S. Elsankari, A. De Haan, G. Landenne), CHU Charleroi (P.Seeldrayers, R. Iqbal), CHR Saint-Joseph (A. Mélin, G. Tincani), CHU Mont Godinne (P.Laloux, K. de Fays); Vivalia (O. Bouquiaux), CNRF (R. Reznik, MF. Maréchal). A special thanks goes to Piet Eelen and Ann Van Remoortel who were the enthusiastic drivers of the study in Melsbroek. Further acknowledgment goes to Lizzy De Lobel and Dries Reynders from STAT-Gent for all statistical analyses and to Ingrid Nobels from Archemin and Sofie Van Gestel for support in medical writing. Finally, we like to thank Chris Loos from TASS for the development of the embedded software on the smartphone.

**Conflicts of interests**

Dr. D'hooghe has received consultancy fees, travel and research grants from Teva Pharma, Biogen, Novartis, Roche, Sanofi-Genzyme, Bayer-Schering, Merck-Serono and Allergan. Dr. Van Gassen reports I am a full-time employee of Teva Pharma Belgium. Dr. Kos has nothing to disclose. Dr. Bouquiaux reports grants from Teva, during the conduct of the study; personal fees from Teva, outside the submitted work. Dr. Cambron reports grants from Teva (recruitment of patients and study visits), during the conduct of the study. Dr. Lysandropoulos reports grants and personal fees from Biogen, grants and personal fees from Teva, grants and personal fees from Novartis, grants and personal fees from Merck, grants and personal fees from Sanofi Genzyme, personal fees from Roche, outside the submitted work. Dr. Van Wijmeersch has received Research and Travel Grants, Honoraria for MS-Expert Advice and Speakers Fees from: Bayer-Schering, Biogen Idec, Sanofi Genzyme, Merck-Serono, Novartis, Roche and Teva. Dr. Willekens reports grants

from Teva (recruitment of patients and study visits), during the conduct of the study and travel support from Biogen, Genzyme, Merck-Serono, Novartis and Teva. The institution (UZA) received fees for consultancy and lectures from Teva, Biogen, Genzyme, Merck-Serono, Novartis, Roche. Dr. Penner has nothing to disclose. Dr. Nagels reports grants and personal fees from Biogen, Teva, Novartis, Merck and Sanofi Genzyme and holding stock in Icometrix (neuroimaging spinoff) and Zebra Academy (telemedicine spinoff) outside the submitted work.

## Funding

This study (TV44400-CNS-40005) is a Company Sponsored Study of Teva Pharma Belgium

## References

- Asano, M., Finlayson, M.L., 2014. Meta-analysis of three different types of fatigue management interventions for people with multiple sclerosis: exercise, education, and medication. *Mult. Scler. Int.*, 798285. <http://dx.doi.org/10.1155/2014/798285>.
- Blikman, L.J., Huisstede, B.M., Kooijmans, H., Stam, H.J., Bussmann, J.B., van Meeteren, J., 2013. Effectiveness of energy conservation treatment in reducing fatigue in multiple sclerosis: a systematic review and meta-analysis. *Arch. Phys. Med. Rehabil.* 94 (7), 1360–1376.
- Davis, S.L., Wilson, T.E., White, A.T., Frohman, E.M., 2010. Thermoregulation in multiple sclerosis. *J. Appl. Physiol.* 109, 1531–1537.
- Finlayson, M., Preissner, K., Cho, C., Plow, M., 2011. Randomized trial of a tele-conference-delivered fatigue management program for people with MS. *Mult. Scler. J.* 17 (9), 1130–1140.
- Finlayson, M., Johansson, S., Kos, D., 2013. Fatigue. In: Finlayson, M. (Ed.), *Multiple Sclerosis Rehabilitation: from Impairment to Participation*. CRC Press., Boca Raton, FL, pp. 69–99.
- Heine, M., van de Port, I., Rietberg, M.B., van Wegen, E.E., Kwakkel, G., 2015. Exercise therapy for fatigue in multiple sclerosis. *Cochrane Database Syst. Rev.* 11 (9), CD009956. <http://dx.doi.org/10.1002/14651858.CD009956.pub2>.
- Jongen, P.J., Heerings, M., Lemmens, W.A., Donders, R., van der Zande, A., van Noort, E., et al., 2015a. A prospective web-based patient-centred interactive study of long-term disabilities, disabilities perception and health-related quality of life in patients with multiple sclerosis in The Netherlands: the Dutch multiple sclerosis study protocol. *BMC Neurol.* 15, 128.
- Jongen, P.J., Sinnige, L.G., van Geel, B.M., Verheul, F., Verhagen, W.L., van der Kruijk, R.A., et al., 2015b. The interactive web-based program MSmonitor for self-management and multidisciplinary care in multiple sclerosis: concept, content, and pilot results. *Patient Prefer Adherence* 9, 1741–1750.
- Khan, F., Amatyia, B., Galea, M., 2014. Management of fatigue in persons with multiple sclerosis. *Front. Neurol.* 5, 177.
- Kos, D., Kerckhofs, E., Nagels, G., D'Hooghe, B.D., Duquet, W., Duportail, M., et al., 2003. Assessing fatigue in multiple sclerosis: dutch modified fatigue impact scale. *Acta Neurol. Belg.* 103 (4), 185–191.
- Kos, D., Nagels, G., D'Hooghe, M.B., Duportail, M., Kerckhofs, E., 2006. A rapid screening tool for fatigue impact in multiple sclerosis. *BMC Neurol.* 6, 27. <http://dx.doi.org/10.1186/1471-2377-6-27>.
- Langeskov-Christensen, M., Bisson, E.J., Finlayson, M.L., Dalgas, U., 2017. Potential pathophysiological pathways that can explain the positive effects of exercise on fatigue in multiple sclerosis: A scoping review. *J. Neurol. Sci.* 373, 307–320.
- Lerdal, A., Celius, E.G., Krupp, L., Dahl, A.A., 2007. A prospective study of patterns of fatigue in multiple sclerosis. *Eur. J. Neurol.* 14 (12), 1338–1343.
- Motl, R.W., Pilutti, L.A., 2012. The benefits of exercise training in multiple sclerosis. *Nat. Rev. Neurol.* 8 (9), 487–497.
- Motl, R.W., Sandroff, B.M., Kwakkel, G., Dalgas, U., Feinstein, A., Heesen, C., et al., 2017. Exercise in patients with multiple sclerosis. *Lancet Neurol.* 16 (10), 848–856.
- Penner, I.K., 2016. Evaluation of cognition and fatigue in multiple sclerosis: daily practice and future directions. *Acta Neurol. Scand.* 134 (200), 19–23.
- Penner, I.K., Raselli, C., Stocklin, M., Opwis, K., Kappos, L., Calabrese, P., 2009. The fatigue scale for motor and cognitive functions (FSMC): validation of a new instrument to assess multiple sclerosis-related fatigue. *Mult. Scler.* 15 (12), 1509–1517.
- Pilutti, L.A., Greenlee, T.A., Motl, R.W., Nickrent, M.S., Petruzzello, S.J., 2013. Effects of exercise training on fatigue in multiple sclerosis: a meta-analysis. *Psychosom. Med.* 75 (6), 575–580.
- Schiavolin, S., Leonardi, M., Giovannetti, A.M., Antozzi, C., Brambilla, L., Confalonieri, P., et al., 2013. Factors related to difficulties with employment in patients with multiple sclerosis: a review of 2002–2011 literature. *Int. J. Rehabil. Res.* 36 (2), 105–111.
- Stellmann J.P. Aerobic exercise induces functional and structural reorganisation of the brain network: Results from a randomized controlled trial in relapsing-remitting multiple sclerosis. In: *Proceedings of the 7th Joint ECTRIMS-ACRIMS Meeting, Paris, France, Oral presentation, 25–28 October 2017, 234.*
- Stewart, A.L., Hays, R.D., Ware Jr., J.E., 1988. The MOS short-form general health survey. Reliability and validity in a patient population. *Med. Care* 26 (7), 724–735.
- Tallner, A., Streber, R., Hentschke, C., Morgott, M., Geidl, W., Mürer, M., Pfeifer, K., 2016. Internet-supported physical exercise training for persons with MS - a randomised, controlled study. *Int. J. Mol. Sci.* 17, 1667–1678.
- Veldhuijzen van Zanten, J., Pilutti, L., Duda, J., Motl, R., 2016. Sedentary behaviour in people with MS: is it time to stand up against MS? *Mult. Scler. J.* 22 (10), 1250–1256.
- Wessel R., Knops H., De Witte L., 2000. D-Quest meetinstrument voor de tevredenheid over een hulpmiddel verstrekking, Hoensbroek.
- Zigmond, A.S., Snaith, R.P., 1983. The hospital anxiety and depression scale. *Acta Psychiatr. Scand.* 67 (6), 361–370.