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# Long-term effectiveness of a cognitive behavioural therapy (CBT) in the management of fatigue in patients with relapsing remitting multiple sclerosis (RRMS): a multicentre, randomised, open-label, controlled trial versus standard care

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## SUMMARY

**Background** Fatigue is a disabling symptom of multiple sclerosis (MS). The lack of effective therapeutics has promoted the development of cognitive behavioural therapy (CBT)-based fatigue management programmes. However, their efficacy does not sustain over time. We proposed to test the long-term effectiveness of a 6-week fatigue programme supplemented with four booster sessions ('FACETS+') in patients with relapsing remitting MS (RRMS) and fatigue.

**Methods** This multicentre, randomised, controlled, open-label, parallel-group trial versus standard care enrolled patients with RRMS and fatigue. Participants were randomised to either FACETS+ plus standard care or standard care alone. The primary outcome measure was fatigue impact (Modified Fatigue Impact Scale (MFIS) at 12 months) based on intention-to-treat analyses.

**Results** From May 2017 to September 2020, 162 patients were screened; 105 were randomly assigned to FACETS+ (n=57) or standard care (n=48) and 88 completed the primary outcome assessment for the MFIS. At month 12, participants showed improved MFIS compared with baseline in the intervention group (mean difference (MD)=14.0 points; (95% CI 6.45 to 21.5)) and the control group (MD=6.1 points; (95% CI −0.30 to 12.5)) with a significant between-group difference in favour of the intervention group (adjusted MD=7.89 points; (95% CI 1.26 to 14.52), standardised effect size=0.52, p=0.021). No trial-related serious adverse events were reported.

**Conclusions** A 6-week CBT-based programme with four booster sessions is superior to standard care alone to treat MS-related fatigue in the long term (12 months follow-up). The results support the use of the FACETS+ programme for the treatment of MS-related fatigue.

**Trial registration number** NCT03758820.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fatigue is described by many as one of the worst symptoms of multiple sclerosis (MS), and there is no conclusive evidence on pharmacological treatment effectiveness.

⇒ Cognitive behavioural therapy (CBT) and energy conservation programmes have shown effectiveness in the short to medium term but maintaining therapeutic benefits over time is a problem.

### WHAT THIS STUDY ADDS

⇒ Our results show for the first time that a 6-week CBT programme with four associated booster sessions resulted in a significant reduction of MS-related fatigue at 12 months and a trend in favour of a maintained effect at 18 months.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This programme can be delivered by a range of healthcare professionals and can also be easily implemented in current practice.

## INTRODUCTION

Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system. Fatigue is one of the most commonly reported symptoms affecting 75%–86% of people with MS.[1] In 80% of cases, fatigue is experienced during the first year following diagnosis.[2] It is considered by 65% of patients to be one of the three most disabling symptoms, before difficulties with walking, balance, bowel and bladder disorders.[3] It is described as the worst symptom of the disease by 50% of patients.[4] It is worsened by relapses and can lead to professional career changes, temporary work stoppages and early retirement.[5]

MS-related fatigue is different from the so-called 'normal' fatigue experienced by healthy people after physical or mental effort. It is defined as 'a subjective lack of physical or mental energy that is perceived by the individual or caregiver to interfere with usual and desired activities'(MS Council for Clinical Practice Guidelines, 1998).[6]

Two types of fatigue have been identified: primary fatigue and secondary fatigue.[7] 'Primary'

fatigue relates to aspects of fatigue deemed to be directly related to the disease process such as lassitude or asthenia (an overwhelming sense of tiredness not directly related to participation in activity or exercise) or heat-sensitive fatigue (where fatigue is triggered or worsened by heat). 'Secondary' fatigue refers to fatigue that is not unique to MS and is related to common factors (eg, sleep disturbance, medication side effects, anaemia, vitamin deficiency, endocrine diseases, infection, physical exertion). Anxiety/Depression and fatigue influence each other: anxiety and depression make fatigue worse and the effects of anxiety and depression are amplified by fatigue.[8]

Pharmacological treatments are available to treat MS-related fatigue but, in most cases, there is no conclusive evidence on their effectiveness. The recent study by Nourbakhsh *et al* failed to show superiority over placebo of the three main treatments (amantadine, modafinil and methylphenidate) commonly used to treat MS-related fatigue.[9]

Lack of effective pharmacological treatments and the contribution of psychological factors to the experience of fatigue have led to the development of non-pharmacological approaches to manage fatigue. Approaches involving therapeutic education or exercise have proved to be more effective in reducing fatigue than pharmacological treatments.[10]

The cognitive behavioural therapy (CBT)-based psychological interventions are robust.[11 12] Seven randomised controlled trials (RCTs) demonstrated the effectiveness of psychological interventions for managing fatigue with significantly reduced fatigue scores following CBT treatment.[13–20]

The effectiveness of CBT is related to its action on cognition and emotions, in particular challenging and modifying dysfunctional beliefs and thoughts related to fatigue that can contribute to its onset, maintenance and amplification.[21] Several studies have shown that the most important variables are: having a negative view of fatigue, focusing on fatigue and believing that fatigue reflects a worsening of the disease.[8 22 23]

However, this effect does not last >6 months after the end of the sessions even if the effect on quality of life is maintained for a longer period of time.[11 12] Two factors, that likely interact, may explain why benefits are not maintained over time: (1) sudden ending of the programme with loss of therapist and/or group support and (2) lack of consolidation of skills making it difficult to deal with new challenges that arise. The long-term impact of these programmes is a real issue as they are intended for people living with a life-long condition. Such an investment in a fatigue management programme, both in relation to the patients and staff involved in the programme and the costs incurred, is justified if we can make these programmes effective for a longer period of time.

The addition of booster sessions after the end of self-management programmes has been shown to result in long-term benefits for various conditions such as insomnia,[24] chronic fatigue,[25] weight-loss maintenance,[26] mood disorders in children[27] and obsessive compulsive disorder.[28] However, the addition of booster sessions has never been tested in MS-related fatigue management programmes.

The aim of this randomised controlled, open-label trial was to assess the effectiveness and safety of a 6-week CBT programme with four booster sessions compared with standard care on fatigue severity and impact at 12 months in a population of patients with RRMS with fatigue.

## METHODS

### Trial design and participants

This is a multicentre, randomised controlled, parallel-group, open-label trial versus standard care that was conducted from May 2017 to September 2020 in three MS centres in France.

Potentially eligible participants were identified by neurologists during patients' medical visits. Awareness of the trial was promoted by patient associations (Réseau SEP IDF Ouest, Ligue Française contre la SEP). Key inclusion criteria were a clinically confirmed diagnosis of RRMS (according to the 2010 McDonald criteria), aged 18 years and older, with fatigue at screening visit (Modified Fatigue Impact Scale (MFIS) score >45), able to walk without aid (Expanded Disability Status Scale (EDSS) score ≤5.5). Those with cognitive deficits such that they would not be able to engage and benefit from a group-based programme, or who had a relapse within the past 3 months, were not eligible. The full list of inclusion/exclusion criteria can be found in online supplemental annex 1.

### Randomisation and masking

An independent statistician used R software V.3.0.1 to produce a randomisation list stratified by centre. As the programme was designed for groups of at least six people, the randomisation was performed with random permuted blocks of variable size inside sets of 12, with a ratio of 1:1. The list was used to prepare randomisation cards, which were placed in sequentially numbered opaque sealed envelopes. Once 12 participants had been recruited at the screening visit, they were invited to attend a baseline visit. Randomisation took place once baseline measures had been completed using the appropriate set of 12 envelopes. Envelopes were opened in the presence of participants with neither the researchers nor medical staff enrolling participants aware of the allocation for each potential participant. In the case of withdrawal between screening and the baseline visit, unused envelopes among the set of 12 were archived. It was not possible to mask participants or facilitators because of the nature of the intervention.

### Procedures

All participants continued to receive local standard care comprising general advice and information about MS-related fatigue (including its characteristics, contributory factors and ways to reduce its impact). This would typically take the form of provision of information leaflets alongside tips for fatigue management (such as keeping active, keeping cool, conserving energy) from a member of the clinical team. A small number of individuals may have been prescribed pharmacological treatments for fatigue. Inevitably, there will have been some minor variations between-centres and within-centres, depending on available local resources and clinical need. Collecting individually detailed information on the type and quantity of advice received as part of standard care was outside the scope of this study.

Patients randomised to the intervention group received FACETS+. FACETS+ is based on the original face-to-face FACETS group programme[29] developed in the UK but with the addition of four booster sessions delivered over a 12-month timeframe at the end of the programme.

The FACETS programme focuses on the management of MS-related fatigue and is based on a conceptual framework that incorporates elements of cognitive-behavioural, energy effectiveness, self-management and self-efficacy theories. It aims to help people normalise their experience of fatigue, learn to change

the way they think about fatigue to a more adaptive perspective and make more effective use of their energy. It consists of six, once-weekly sessions of 90 min (with a break) that include facilitator presentations, group discussions using a flipchart, group activities and between-session 'homework' tasks. It is designed for groups of 6–10 people and in the UK is delivered by two facilitators (usually occupational therapists, physiotherapists and MS nurses). In the French delivery model, unlike the original UK programme, FACETS is delivered by two psychologists.

The programme is fully manualised, helping to ensure consistency in delivery and facilitating transadaptations. Sessions are supported by PowerPoint presentations as well as a facilitator manual providing detailed session content, guidance on the preparation and presentation of each session with a suggested script, notes and guidance on timings and a fidelity checklist. There is a companion participant workbook for each session that includes a recap of session content and descriptions of the homework tasks with instructions. During sessions, activities done as part of group discussions and homework enable content to be adapted to individual circumstances and to the goals/priorities of group members.

To become familiar with the programme, a clinical psychologist (one of the authors), travelled to the UK to observe a FACETS programme being delivered in a National Health Service setting by a clinical specialist research physiotherapist who was involved in the FACETS UK multicentre trial and delivers FACETS facilitator training to healthcare professionals for the UK MS Society. While in the UK, the French clinical psychologist received training from the original FACETS programme creator. She then trained the four assistant psychologists involved in the delivery of FACETS+ as part of the current study.

All FACETS materials, including the facilitator manual, participant handbooks and handouts and PowerPoint slides were forward translated by a native-speaking bilingual clinical psychologist (over 45 000 words in total). All translated materials were read by a second native-speaking bilingual clinical psychologist. Time and resource constraints precluded back translation. Minor changes were made to ensure cultural and linguistic relevance in French while remaining faithful to the original programme.

FACETS+ incorporates four face-to-face booster sessions (at weeks 6, 12, 18 and 36) drawing on Schwarzer's Health Action Process Approach[30 31] in order to activate and reinforce the cognitive and behavioural processes initiated during the intervention. These sessions involve reviewing the concepts and behaviours learnt during the programme via rehearsal exercises and action plans to maintain goal setting and planning. They also incorporate specific exercises to highlight successes to promote feelings of self-efficacy and to maintain new behaviours (see online supplemental annex 2).

Assessment of outcomes took place in the MS centres. For those in the intervention group, the timings were after session 6 and at 6, 12 and 18 months following the 6-week intervention (with equivalent timings in the control arm). Self-report measures were completed by participants in a separate room. Because of COVID-19, some patients were followed up remotely rather than in person at 12 months (n=21) and 18 months (n=51) via videoconference or telephone interviews with the questionnaires being sent in advance via email.

## Outcomes

The primary outcome measure was the comparison between both arms based on fatigue change scores between baseline and 12 months assessed via the MFIS. The MFIS is a self-report questionnaire that measures the impact of MS-related fatigue. It is a shortened version of the FIS and includes 21 items scored from 0 to 4 with a possible total score ranging from 0 to 84. There are three subscales (i) cognitive (10 items), (ii) physical (9 items) and (iii) psychosocial (2 items). This scale is recommended by the American Multiple Sclerosis Council for Clinical Practice Guidelines[32] and is widely used in therapeutic trials.

Secondary primary outcome domains included: (1) anxiety and depression (Hospital Anxiety and Depression Scale (HADS)), (2) fatigue severity (Fatigue Severity Scale (FSS)),[42] (3) sleep quality (Pittsburgh Sleep Quality Index (PSQI 1.0)), (4) daytime sleepiness (Epworth Sleepiness Scale (ESS)), (5) MS-specific quality of life (Multiple Sclerosis Impact Scale (MSIS-29)) and finally (6) generic quality of life (EuroQol-5 Dimensions (three levels) (EQ-5D-3L)).

Adverse events (AEs) were recorded by the local study team by asking the participants during the assessment visits.

## Statistical analysis

The target sample size was based on the results of a study by Stankoff *et al* in which the change in MFIS score from week 0 to week 35 showed an SD between 16.6 and 18.5 depending on the arm.[33] The detection of a 9.5 absolute difference between the mean change scores required follow-up data from 55 patients per group with 80% power and at 5% significance level using a two-tailed method. Allowing for 10% loss to follow-up or non-completion of primary outcome, we aimed to recruit 120 participants.

Means, SD, numbers and percentages were used to present descriptive statistics. Participants with missing data at 12 months were compared with those with 12-month follow-up data. No difference was found between both groups in terms of sociodemographic data, clinical data at baseline and score results at 6 weeks and 6 months. We thus assumed data were missing at random and multiple imputation was performed for missing follow-up data using 10 iterations. Imputations for the outcome measures were undertaken at a scale rather than item level using the following variables: age, age at disease onset, gender, EDSS score, group and score values available at other timepoints. Baseline variables, for which a correlation test with the score value to be imputed had a p value <0.2, were also used for imputation.

For each outcome measure score, the comparison of both treatment groups for changes from baseline values was performed using a multiple linear regression model with the respective baseline score, EDSS baseline score, baseline age at trial enrolment, age at diagnosis, gender, centre and whether or not taking beta-interferon, as covariates. The time since disease diagnosis was not included in the multivariate model as there was multicollinearity with age at trial enrolment and age at diagnosis. As the imputation of missing data led to 10 datasets, the result of the comparison was obtained by pooling the 10 models from the 10 datasets. Additional analyses adjusting for any clustering effect arising from the group-based nature of FACETS+ were performed.

Statistical analyses were carried out in the intention-to-treat (ITT) population. Then, a per-protocol analysis was also performed (population receiving at least four sessions with available follow-up values). Two-sided tests were conducted. The significance level was 5%. All statistical analyses were performed using software R (V.4.0.2).

There were no data monitoring committee. This study was prospectively registered at *clinicaltrials.gov* (NCT03758820).

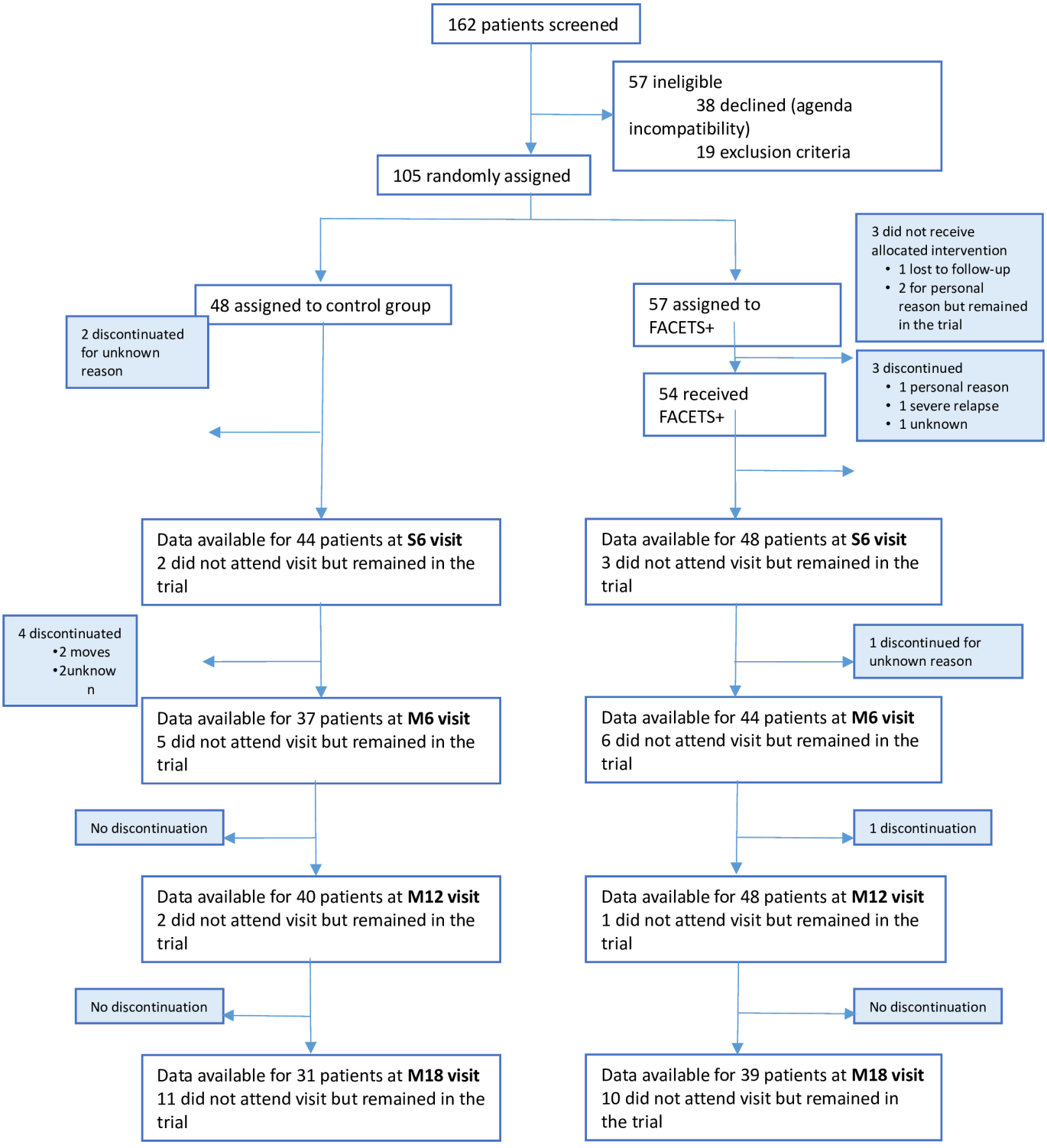


**Figure 1** Trial profile.

## RESULTS

From 31 May 2017 to 28 March 2019, 162 patients were screened. Of these, 105 were randomised with 57 patients allocated to FACETS+ and 48 to the control group (figure 1). Baseline demographic characteristics of randomised patients are presented in table 1. The percentage of non-attending patients at each session is reported in online supplemental annex 3.

Baseline characteristics were similar in both groups, with the exception of age being higher in control group participants. Of the 57 patients randomised to FACETS+, 54 commenced the programme. Three patients withdrew from the trial in the first 6 weeks (one due to a severe relapse, one for personal reasons and one for unknown reasons) and two others in the first year (for unknown reasons). At 12 months, of the 49 patients still in the trial, 48 were assessed for primary outcome measures.

In the control group, at 12 months, of the 42 patients still in the trial (4 discontinued for unknown reasons and 2 because they were moving), 40 patients were assessed for primary outcome measures. In total, 88 (84%) patients were assessed for primary outcome measures at 12 months.

**Table 1** Baseline characteristics

| | FACETS+ group (n=57) | Control group (n=48) |
|---|---|---|
| Age (years) | 43.2 (9.4) | 47.4 (10.0) |
| Sex | | |
| Male | 7 (12.3%) | 9 (18.8%) |
| Female | 50 (87.7%) | 39 (81.2%) |
| Education | | |
| <Bachelor degree | 26 (45.7%) | 29 (60.4%) |
| ≥Bachelor degree | 31 (54.4%) | 19 (39.6%) |
| Age at MS onset (years) | 31.1 (9.5) | 35.8 (8.8) |
| Duration of disease (years) | 12.1 (9.2) | 11.6 (7.7) |
| EDSS score | 2.5 (0–5.5) | 2.5 (0–5.5) |
| MS treatment | 53 (93%) | 44 (91.7%) |
| Medication | | |
| Interferon | 9 (15.8%) | 17 (35.4%) |
| Antidepressants | 14 (24.6%) | 15 (31.2%) |
| Amantadine | 2 (3.5%) | 2 (4.2%) |
| Modafinil | 1 (1.8%) | 0 (0%) |
| Last relapse | | |
| <6 months | 9/43 (20.9%) | 5/35 (14.3%) |
| ≥6 months | 34/43 (79.1%) | 30/35 (85.7%) |

Data are mean (SD), n (%), median (range) or n/N (%).
EDSS, Expanded Disability Status Scale; MS, multiple sclerosis.

Among the patients in the intervention group, 50/57 attended at least four of the six FACETS sessions. Of these, 48/50 received at least one booster session and 19/50 received the four booster sessions planned in the protocol.

According to the primary outcome analysis, at 12 months, patients had improved MFIS scores compared with baseline in the intervention group (14.0 points; (95% CI 6.45 to 21.5)) and the control group (6.1 points; (95% CI −0.30 to 12.5)). There was a significant between-group difference in favour of the intervention group (7.89 points; (95% CI 1.26 to 14.52); standardised effect size (SES=0.52, p=0.021) (table 2, figure 2).

At the end of the six sessions of the FACETS programme, there was a significant difference in favour of the intervention group for the MFIS total score (11.40 points; (95% CI 5.10 to 17.69), SES=0.78, p<0.001). A significant difference in favour of the intervention group was also found at 6 months (9·94 points; (95% CI 3.92 to 15.96), SES=0.55, p=0.002). At 18 months, 9 months after the last booster session, 70 (67%) patients were assessed. The maintenance of therapeutic effect was no longer statistically significant in the intervention group (possibly due to diminution of statistical power), although the SES was still medium (6.51 points; (95% CI 1.10 to 14.11), SES=0.43, p=0.092) (table 2). The results for the primary outcome analysis were unaltered when we adjusted for clustering effects.

Regarding secondary outcomes, differences in favour of the intervention group were found at 12 months for the following outcome measures: FSS (0.80 points; (95% CI 0.32 to 1.28), SES=0.87, p=0.001), MSIS physical subscale (6.14 points; (95% CI 2.20 to 10.08), SES=0.49, p=0.003). However, there were no significant differences between groups for the following secondary outcome measures: ESS, MSIS psychological subscale, HADS, EQ-5D-3L and PSQI (table 2).

The per-protocol analysis, that is, in patients who attended at least four FACETS sessions and who provided outcomes on the MFIS at 12 months (n=37 in the intervention group and n=31 in the control group), showed effectiveness on the primary outcome measure (MFIS) from 6 weeks with a trend towards maintenance of effectiveness at 18 months with a between-group difference of 8.92 points ((95% CI −0.03 to 17.88), p=0.051).

Twenty-three AEs were recorded (including 15 (non-COVID-19) infections) in 20 patients (online supplemental annex 4). Only one patient in the intervention group was infected with COVID-19. Eleven patients experienced serious adverse events (SAEs). The frequency of AEs and SAEs was similar in both groups. There were no AEs attributable to the FACETS+ programme.

## DISCUSSION

To our knowledge, this is the first RCT to use booster sessions to evaluate the maintenance of CBT effectiveness in the treatment of fatigue in patients with MS. A statistically significant difference was observed at 12 months in fatigue scores (MFIS) in favour of the patients with MS who received FACETS+ compared with controls. A significant difference was also found on a second fatigue scale (FSS). Both differences exceeded the minimally important difference reported in the literature for the respective scale (≥0.45 points for the FSS and ≥4 points for the MFIS)[34] and thus constitute clinically significant differences in fatigue.

In the current trial, the effect on fatigue was observed at the end of the intervention (at 6 weeks), thus confirming existing findings in the literature[16 21] and was maintained at 6 and 12 months after the end of the intervention. To date, significant improvements in fatigue have seldom been demonstrated at 6 months and never at 12 months.

We hypothesise that the addition of booster sessions to the FACETS programme enabled the maintenance of benefits in the longer term. Programmes that have used booster sessions in other long-term conditions have also demonstrated long-term maintenance of benefits.[24–28]

We propose two possible explanations for the effectiveness of booster sessions in the maintenance of therapeutic effects at 12 months: on the one hand, tapered booster sessions facilitate participants' progressive withdrawal from the group and on the other hand, they encourage working on one's own with increasingly spaced support and monitoring, thus reinforcing self-efficacy and contributing to the integration of achievements with increasingly autonomous practice.[8 21]

The ITT analyses of the primary outcome at 18 months were not significant. This could be related to the 37% missing data and to a lack of power. A per-protocol analysis however, showed a positive trend (with medium SES), thus indicating that patients who followed the programme and who were assessed maintained their improvements.

No difference was found between patients lost to follow-up at 18 months and those who remained in the trial, for baseline characteristics or for scores obtained at 12 months. As the last booster session took place 9 months before the final assessment at 18 months, this may have led to decreased motivation or withdrawal from the programme. The issue of maintaining booster sessions or some form of support in the longer term thus warrants further consideration.

COVID-19 did not impact on the schedule of the FACETS+ programme sessions and only necessitated some minor changes in the assessments at 12 months and 18 months with the outcome measures completed online. Scores completed online did not differ from those completed following the standard procedure, either on the primary or secondary outcomes.

**Table 2** Changes in outcomes from baseline

| | FACETS+ group (n=57) | | | Control group (n=48) | | | Mean (95% CI) difference between groups | P value |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) Unadjusted | Mean change (95% CI) From baseline adjusted | N | Mean (SD) Unadjusted | Mean change (95% CI) From baseline adjusted | Adjusted | |
| **Primary outcome** | | | | | | | | |
| MFIS score | | | | | | | | |
| Baseline | 57 | 55.44 (11.53) | – | 48 | 55.77 (13.00) | – | – | |
| 6 weeks | 50 | 42.92 (15.82) | 11.01 (3.70 to 18.32) | 44 | 55.48 (15.54) | -0.39 (-6.86 to 6.08) | 11.4 (5.10 to 17.69) | <0.001 |
| 6 months | 47 | 43.60 (14.76) | 13.20 (6.33 to 20.15) | 37 | 54.46 (15.20) | 3.30 (-2.94 to 9.54) | 9.94 (3.92 to 15.96) | 0.002 |
| 12 months | 49 | 41.20 (15.73) | 14.00 (6.45 to 21.5) | 40 | 50.23 (13.39) | 6.1 (-0.30 to 12.5) | 7.89 (1.26 to 14.52) | 0.021 |
| 18 months | 40 | 41.88 (17.38) | 16.03 (8.11 to 23.9) | 31 | 50.55 (18.31) | 9.52 (2.02 to 17.0) | 6.51 (-1.10 to 14.11) | 0.092 |
| **Secondary outcomes** | | | | | | | | |
| MSIS-29 physical score | | | | | | | | |
| Baseline | 57 | 42.40 (14.51) | – | 48 | 44.67 (10.23) | – | – | |
| 12 months | 49 | 33.55 (8.32) | 7.19 (2.49 to 11.1) | 40 | 41.40 (12.99) | 1.05 (-3.18 to 5.28) | 6.14 (2.20 to 10.08) | 0.003 |
| MSIS-29 psychological score | | | | | | | | |
| Baseline | 57 | 26.96 (7.74) | – | 48 | 27.08 (7.66) | – | – | |
| 12 months | 49 | 22.37 (7.64) | 4.03 (0.71 to 7.35) | 40 | 23.90 (7.97) | 3.03 (-0.04 to 6.10) | 1.00 (-2.14 to 4.13) | 0.53 |
| FSS score | | | | | | | | |
| Baseline | 57 | 47.67 (7.84) | – | 48 | 44.85 (10.03) | – | – | |
| 12 months | 49 | 39.49 (10.18) | 0.78 (0.27 to 1.29) | 40 | 47.20 (9.59) | -0.02 (-0.49 to 0.46) | 0.80 (0.32 to 1.28) | 0.001 |
| ESS score | | | | | | | | |
| Baseline | 57 | 10.82 (5.19) | – | 48 | 9.77 (4.94) | – | – | |
| 12 months | 49 | 9.92 (5.67) | 0.57 (-1.37 to 2.51) | 40 | 10.53 (4.42) | -0.69 (-2.36 to 0.98) | 1.26 (-0.46 to 2.98) | 0.15 |
| HADS score | | | | | | | | |
| Baseline | 57 | 15.89 (6.65) | – | 48 | 17.35 (6.70) | – | – | |
| 12 months | 48 | 13.55 (5.87) | 1.72 (-0.97 to 4.40) | 40 | 15.43 (8.03) | 1.03 (-1.45 to 3.55) | 0.69 (-1.79 to 3.17) | 0.58 |
| HADS anxiety score | | | | | | | | |
| Baseline | 57 | 6.00 (3.73) | – | 48 | 6.96 (3.83) | – | – | |
| 12 months | 48 | 5.08 (3.5) | 0.26 (-1.45 to 1.98) | 40 | 6.35 (5.01) | -0.31 (-1.85 to 1.24) | 0.57 (-0.95 to 2.10) | 0.46 |
| HADS depression score | | | | | | | | |
| Baseline | 57 | 9.89 (4.15) | – | 48 | 10.40 (4.07) | – | – | |
| 12 months | 48 | 8.47 (3.41) | 1.05 (-0.46 to 2.56) | 40 | 9.07 (4.15) | 0.98 (-0.36 to 2.48) | 0.07 (-1.24 to 1.38) | 0.75 |
| EQ-5D-5L | | | | | | | | |
| Baseline | 56 | 0.60 (0.26) | – | 47 | 0.59 (0.21) | – | – | |
| 12 months | 49 | 0.69 (0.22) | -0.09 (-0.19 to -0.002) | 40 | 0.69 (0.19) | -0.07 (-0.15 to 0.02) | -0.03 (-0.11 to 0.06) | 0.52 |
| EQ-5D VAS | | | | | | | | |
| Baseline | 57 | 6.95 (1.67) | – | 48 | 6.42 (1.47) | – | – | |
| 12 months | 49 | 7.14 (1.22) | -0.60 (-1.20 to 0.004) | 40 | 6.60 (1.48) | -0.19 (-0.74 to 0.37) | -0.41 (-0.93 to 0.11) | 0.12 |

Continued

**Table 2** Continued

| | FACETS+ group (n=57) | | | Control group (n=48) | | | Mean (95% CI) difference between groups | P value |
|---|---|---|---|---|---|---|---|---|
| | N | Mean (SD) Unadjusted | Mean change (95% CI) From baseline adjusted | N | Mean (SD) Unadjusted | Mean change (95% CI) From baseline adjusted | Adjusted | |
| PSQI score | | | | | | | | |
| Baseline | 56 | 15.09 (3.02) | – | 48 | 14.65 (3.25) | – | – | |
| 12 months | 47 | 13.81 (2.43) | -0.31 (-1.54 to 0.93) | 40 | 14.55 (3.22) | -0.77 (-1.88 to 0.34) | 0.47 (-0.42 to 1.35) | 0.30 |

HADS depression, HADS depression subscale score; EQ-5D-5L, EuroQol-5 Dimensions (five levels); EQ-5D VAS, EuroQol-5 Dimensions Visual Analogue Scale; ESS, Epworth Sleepiness Scale; FSS, Fatigue Scale Severity; HADS, Hospital Anxiety and Depression Scale; MFIS, Modified Fatigue Impact Scale; MSIS-29, Multiple Sclerosis Impact Scale; PSQI, Pittsburg Sleep Quality Index.




**Figure 2** Primary outcome in the intention-to-treat population: comparison between both arms based on fatigue change scores assessed via the Modified Fatigue Impact Scale (MFIS) from M0. Error bars show the SE.

We did not find any significant effects of the FACETS+ programme on sleep or depression. These results were not unexpected as participants did not, for the most part, suffer from depression and sleep disturbance and sleepiness could have been caused by multiple factors (eg, bladder control, neurological disorders) not targeted by the programme. Thus, the decrease in fatigue is more likely attributable to changes in fatigue-related representations and behavioural/lifestyle adjustments than indirect effects of the programme on sleep/sleepiness or depressive symptoms.

We did not find a significant effect on quality of life, unlike what has been found for other fatigue interventions.[12 14 15] We also did not find a significant effect on the psychological subscale of the MSIS. However, this may be due to the relatively low functional impact of MS on our trial sample (low EDSS scores) along with relatively low anxiety and depression scores and relatively good quality of life scores. Additionally, it has been suggested that the EQ-5D, a generic quality of life scale, may lack relevance and sensitivity in assessing quality of life in MS.[35] Notably, it neither includes any fatigue items (a known key driver of quality of life[36–38]) nor does it capture fluctuations in symptoms and functioning.[39] The recent EuroQol Health and Well-being-shortform does include a fatigue item but is still in development and yet to be fully validated.[32]

Randomisation was not stratified on the presence or absence of depression due to the difficulty in constituting patient groups. Finally, few depressed patients were included and there was no difference in baseline depression scores between groups.

Our results apply to relapsing forms of MS and cannot be generalised to progressive forms. We did not assess cognitive disorders which can limit the effectiveness of this type of programme.

FACETS+ was well tolerated, AEs were rare and minor. Thus, the relative benefit-risk profile is supportive of the programme, unlike pharmacological treatments for which AEs are common with no therapeutic effects.[18] Furthermore, FACETS+ was well-accepted by participants which should facilitate its implementation in routine care. Due to the nature of the intervention, it was not possible to mask participants, personnel or therapists. Consideration of the optimal interval between booster sessions and the duration and format of this support over time should be explored further. Online

delivery may increase uptake of the booster sessions and we note that in the UK, in response to the COVID-19 pandemic, some healthcare professionals have been delivering the FACETS programme via videoconferencing with initial participant feedback promising. Finally, FACETS+ should be tested for individuals with progressive forms of MS.

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