

Testing non-inferiority of blended versus face-to-face Cognitive Behavioural Therapy for severe fatigue in patients with Multiple Sclerosis and the effectiveness of blended booster sessions aimed at improving long term outcome following both therapies: – study protocol for two observer-blinded randomized clinical trials

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Study protocol

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Abstract

Background: Cognitive behavioural therapy (CBT) has been found effective in reducing fatigue severity in MS patients directly following treatment. However, long-term effects are inconsistent leaving room for improvement. In addition, individual face-to-face CBT draws heavily on limited treatment capacity, and the travel distance to the treatment centre can be burdensome for patients. Therefore, we developed “MS Fit”, a blended CBT for MS-related fatigue, based on a face-to-face CBT protocol found effective in a previous study, and “MS Stay Fit”, internet-based booster sessions to improve long term effectiveness of CBT for MS-related fatigue. This paper presents the protocol of two Randomised Clinical Trials (RCTs) conducted within one study investigating 1) the non-inferiority of MS Fit compared to evidence-based face-to-face CBT for MS-related fatigue, and 2) the effectiveness of MS Stay Fit on the long-term outcome of fatigue compared to no booster sessions. Methods/design: The first part of this study is an observer-blinded non-inferiority multicentre RCT, in which 166 severely fatigued MS patients will be randomized (1:1 ratio, computer-generated sequence) to either face-to-face CBT or blended CBT (MS Fit) for fatigue. The primary endpoint is at 20 weeks after baseline. After this post-treatment assessment, patients will be randomized again (1:1 ratio, computer generated sequence) to either MS Stay Fit consisting of 2 booster sessions at 2 and 4 months after end of treatment, or no booster sessions. The primary endpoint of the second study is 52 weeks after baseline. Primary outcome measure in both studies is fatigue severity assessed with the fatigue severity subscale of the Checklist Individual Strength (CIS20r). Outcomes will be assessed at baseline (T0), end of treatment (T20), after 39 and 52 weeks (T39 and T52). Discussion: If MS Fit is found to be non-inferior to face-to-face CBT it will improve the accessibility of this treatment. In addition, the study aims to test if it is possible to improve long-term effectiveness of CBT for MS-related fatigue with MS Stay Fit.

Background

Multiple Sclerosis (MS) is a neurodegenerative disease characterized by demyelination, axonal loss and inflammation of the central nervous system that usually appears between the age of 20 and 40. MS can cause a variety of symptoms such as motor weakness, sensory deficits, impaired balance, fatigue, depression and pain. Fatigue is with 75-90% one of the most often reported symptoms in MS [1-4], and half of the MS patients even report it to be one of the most burdensome symptoms affecting their daily functioning and worsening other MS symptoms [5].

The etiology of MS-related fatigue is not clear and likely to be multifactorial. In a cognitive-behavioural model Van Kessel and Moss-Morris proposed that where disease-related factors, such as inflammation and neurodegeneration, may initially cause fatigue, psychological mechanisms play an important role in perpetuating and increasing fatigue [6]. These mechanisms consist of cognitive, emotional and behavioural responses to fatigue, for example catastrophizing cognitions, depression, helplessness, all-or-nothing behaviour, avoidance, and sleep problems. Based on this model a cognitive behavioural therapy was developed, aimed at decreasing fatigue, in which patients learn to change unhelpful beliefs and behaviours regarding fatigue [7, 8].

Although in clinical practice treatments for MS-related fatigue often include energy conservation management, exercise therapy, and multidisciplinary interventions, recent systematic reviews and meta-analyses of RCTs have shown cognitive behavioural therapy (CBT) to be an effective treatment for reducing fatigue. There is no evidence for effectiveness of pharmaceuticals or multidisciplinary rehabilitation treatment [9-12]. In the recent TREFAMS-ACE programme, TREFAMS being an acronym for TReating FAtigue in Multiple Sclerosis, three RCTs were conducted studying the effectiveness of respectively Aerobic Exercise Training (TREFAMS-AT), Cognitive Behavioural Therapy (TREFAMS-CBT) and individual Energy Conservation Management (TREFAMS-ECM), compared to MS nurse consultations on fatigue [13]. Results showed that aerobic exercise training and energy conservation management did not lead to a significant or clinically relevant reduction of fatigue [14, 15], whereas the TREFAMS-CBT trial, in contrast, showed that MS-related fatigue can be reduced significantly with individual face-to-face CBT carried out by trained psychologists [16], although one-year follow-up measurements showed that the effect of CBT had worn off over time. More studies have shown that fatigue in MS can be treated effectively with CBT [8, 17-19]. However, CBT was applied in different forms and protocols (individual and group formats, internet-based or face-to-face), and long-term effects differed between studies [20]. Analysis of cognitive-behavioural variables mediating the fatigue relapse in the TREFAMS-CBT study showed that increased daytime sleepiness, more problems in staying physically active and an increase of subjective cognitive problems (i.e. concentration) mediated the fatigue relapse after one year [7]. However, in these analyses only a limited number of possible mediating factors were included. More research is needed to determine which other factors are responsible for the increase in fatigue at long-term follow-up .

Face-to-face CBT draws heavily on limited treatment capacity and requires patients to travel and schedule appointments which is burdensome for fatigued patients. Therefore, blended CBT, in which online treatment is combined with limited face-to-face contacts or video consultations with the CBT-therapist, might be an attractive treatment option for severely fatigued patients with MS. Several studies have been conducted on the effectiveness of internet-based CBT for MS-related fatigue, showing positive results [17, 18, 21]. However, it remains unclear whether the effectiveness of blended-CBT is comparable to that of face-to-face CBT in treating primary MS-related fatigue.

In the proposed study two RCTs will be conducted to answer the following two research questions:

1. Is blended CBT (MS Fit) non-inferior with respect to its effect on fatigue severity compared to evidence-based face-to-face CBT in severely fatigued patients with MS?
2. Do blended CBT booster sessions (MS Stay Fit) improve long-term outcome with respect to fatigue severity at 1-year follow-up compared to no booster sessions?

To this purpose “MS Fit” was developed, an internet-based version of the CBT intervention used in the TREFAMS study [16]. In the MS Fit study group, patients will receive two face-to-face sessions with a CBT-therapist, and will be supported during their online treatment by video-consultations and email contact. The online sessions of MS Fit are also based on the previously found effective online CBT used for

treating severe fatigue in patients with Type 1 Diabetes Mellitus [22], breast cancer survivors [23] and patients with chronic fatigue syndrome [24]

In addition, “MS Stay Fit” has been developed, a blended booster programme consisting of several optional online booster modules and two video-consultations with the therapist two and four months after finishing the initial CBT. To our knowledge this will be the first study testing the effectiveness of booster sessions in sustaining the effects of CBT for chronic fatigue. In this paper, the SPIRIT reporting guideline is used [25]

Method/design

The first part of the study is an observer-blinded non-inferiority multicentre RCT, in which patients who are eligible to participate will be randomly allocated to either the face-to-face CBT intervention, or MS Fit [26, 27]. Both groups will receive CBT for 20 weeks, and after a post-treatment assessment, patients who complete the second assessment will be randomized again to MS Stay Fit or receiving no booster sessions. Patients who drop-out of the initial treatment or study will not be randomized for the second RCT. All patients will be assessed at baseline (T0), post-treatment (T20), after 9 months (T39) and after one year (T52) (see Figure 1).

Randomisation

Randomisation with concealed treatment allocation will be carried out using a web-based randomisation facility. The randomisation scheme is computer-generated with stratification for treatment centre, and using random variable block sizes (range 2-6). Using the same software, patients will be randomized again (R2) at the end of the initial treatment, either to MS Stay Fit or no booster sessions. Patients will be stratified according to previous CBT study group (Figure 1). Randomisation will be done by one of the project members (HB) who is not involved in the enrolment process, treatments, or assessments.

Participants

The 166 patients required for the non-inferiority RCT will have to meet the same inclusion criteria as in the TREFAMS-CBT study [13, 26, 27]: (a) definitive diagnosis of MS, (b) severely fatigued, (c) aged between 18 and 70 (d) ambulatory; (e) no evident signs of an exacerbation and no corticosteroid treatment in the past three months; (f) no current infections; (g) no anaemia; (h) a normal thyroid function. The exclusion criteria are (a) depression; (b) primary sleep disorders; (c) other severe somatic or psychiatric co-morbidity; (d) current pregnancy or having given birth in the past three months; (e) pharmacological treatment for fatigue that was started in the past three months; (f) non-pharmacological therapies for fatigue that took place in the last three months (g) having received CBT in the TREFAMS trial. This last exclusion criterion is added for this study. See Table 1 for the operationalization of the inclusion and exclusion criteria.

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
a. Definitive diagnosis of MS confirmed by a neurologist	a. Depression (BDI > 4 and meeting criteria of depression as assessed by M.I.N.I.)
b. Severely fatigued (CIS20r-fatigue \geq 35)	b. Primary sleep disorders (anamnesis)
c. Aged between 18 and 70	c. Severe co-morbidity (CIRS item \geq 3)
d. Ambulatory patients (EDSS \leq 6)	d. Current pregnancy or having given birth in the past three months
e. No evident signs of an exacerbation, or corticosteroid treatment in the past three months	e. Pharmacological treatment for fatigue that was started in the past three months
f. No current infections (anamnesis)	f. Non-pharmacological therapies for fatigue that took place in the last three months
g. No anaemia (anamnesis)	g. Receiving CBT in the TREFAMS-CBT trial
h. A normal thyroid function (anamnesis)	

As effectiveness of the booster programme can only be measured if patients have completed the initial treatment, the following additional inclusion criteria were defined for participation in the second RCT testing the effectiveness of MS Stay Fit: (a) having started treatment, i.e. formulated treatment goals after the first session of CBT or MS Fit; (b) having finished the initial treatment period with a face-to-face session and assessment at T20.

Sample size calculation

Non-inferiority trial (RCT 1): If there is truly no difference between the face-to-face CBT and blended CBT, then 150 patients are required to be 80% sure that the lower limit of a one-sided 95% confidence interval will be above the non-inferiority margin of -5.3 points on the Checklist Individual Strength (CIS20r) fatigue severity subscale. Adjusting for a drop-out of 10%, 166 participants need to be included (2 groups of 83) [26-28]. The non-inferiority margin was defined on the basis of statistical reasoning (i.e. by using the TREFAMS-CBT results), and clinical judgment [16]. In the TREFAMS-CBT trial the difference in the change score between CBT and MS nurse consultations for fatigue was 6.67 points (95% CI: 2.70 - 10.68) on the CIS20r fatigue [16]. In accordance with the recommendations of the Food and Drug Administration [26], the mean effect 6.67 was used as criterion - 50% of the lower limit (i.e. 2.7) of the 95% CI of the

TREFAMS-CBT effect at week 16, that is $6.67 - 1.35 = 5.32$, and the 1.35 point is considered as a clinically acceptable loss in effectiveness of blended CBT compared to TREFAMS-CBT [16]. Tummers et al. [28] derived the same non-inferiority margin of 5.3 points on the CIS20r fatigue severity subscale through post hoc analysis of the course in the waiting list of an RCT testing the efficacy of CBT in patients with chronic fatigue syndrome. The margin of 5.3 points reflects the largest loss of effect in the blended CBT group that would be clinically acceptable.

Booster trial (RCT 2): This RCT concerns a superiority between-group comparison at 1-year follow-up of MS Stay Fit, i.e. web-based booster sessions combined with email contact and video-consultations vs. no booster sessions. Treatment effects on fatigue are assumed to be maintained with additional booster sessions but to gradually wear off to the fatigue level at baseline in the study group without additional booster therapy sessions. In the TREFAMS-CBT study the treatment effects gradually wore off directly post-treatment until 1 year after the start of treatment [16]. At one-year follow-up, fatigue levels in the CBT group were comparable with level of fatigue at baseline. A between-group difference of 6.7 points on CIS20r fatigue is expected. Two-sided significance testing with an α of 5%, two study groups of 75 participants at 1-year, will result in a power of 98%. Therefore, the total number of enrolled patients (2 groups of 83, i.e. 75 patients plus a 10% attrition rate) yields sufficient power in RCT 2 to address the second research question.

Recruitment strategy

Patients will be recruited in 11 participating rehabilitation centres and hospitals in the Netherlands and 1 in Belgium (Table 2). More treatment sites can be added during the study if not enough eligible patients are available. Rehabilitation physicians will hand over the information letter to patients who are eligible for the study. When interested, patients will be contacted by phone by the research assistant, to further inform them about the study. When willing to participate, they will be sent the Informed Consent Form (ICF) in two-fold to their home address, and asked to return the signed ICF. Subsequently patients are invited by email, sent by the research assistant, to complete the subscale fatigue of the CIS20r and the Beck Depression Inventory-Primary Care version (BDI-PC) online, after which all in- and exclusion criteria will be assessed in a phone-call with the patient by the researcher. This includes assessment of the EDSS and CIRS.

If patients contact the researcher directly and not via the rehabilitation physician, e.g. after reading about the study online, they will be referred for screening to a rehabilitation physician participating in this study before final inclusion and referral can take place.

Table 2. Participating treatment centres.

Amsterdam University Medical Centers, location VU University Medical Center in Amsterdam
Expert Center for Chronic Fatigue, Amsterdam University Medical Centers
Maasstad Hospital in Rotterdam
Rijndam rehabilitation center in Rotterdam
Basalt rehabilitation center in Leiden
Sint Maartenskliniek in Nijmegen
Roessingh rehabilitation center in Enschede
Klimmendaal rehabilitation center in Zutphen
Canisius Wilhelmina hospital in Nijmegen
Rehabilitation center Friesland in Sneek
National MS center in Melsbroek (Belgium)
Bravis hospital in Roosendaal and Bergen op Zoom

Interventions

Face-to-face cognitive behavioural therapy (CBT)

In the face-to-face-CBT study arm, patients receive twelve individual, face-to-face, 45-minute therapy sessions distributed over a 20-weeks period according to the protocol tested in the TREFAMS-CBT study [16]. CBT will be provided by certified health care psychologists, most of them licensed cognitive behavioural therapists, who will be trained to deliver (blended) CBT for MS-related fatigue and receive supervision every two-weeks.

Patient-tailoring of (blended) CBT

CBT for MS-related fatigue is directed at the fatigue maintaining behaviours and beliefs of the patient. The general aim of the CBT is to lessen the fatigue by changing fatigue-maintaining cognitions and behaviours and improve daily functioning. As the individual differences in the maintaining factors are substantial, first the relevant fatigue-maintaining factors for the individual patient are assessed using specific screening instruments (see Table 3). The patient is treated with the CBT modules aimed at the factors maintaining the fatigue of the individual patient. There are ten treatment modules: (1) formulation and attainment of treatment goals; (2) sleep and rest; (3) unhelpful beliefs about MS; (4) beliefs about fatigue; (5) focusing on fatigue; (6) physical activity regulation; (7) regulation of social activity; (8) regulation of mental activity; (9) social support; (10) unhelpful beliefs about pain. Therapists will get the results of the assessment to determine which CBT treatment modules are indicated for the individual

patient. The following instruments are used for tailoring the CBT-modules: Impact of Event Scale [29], Illness Cognition Questionnaire [30], Cognitive-Behavioural Responses to Symptoms [31, 32], Beck Depression Inventory – primary care version [33], Fear of Disease Progression-Short Form [34, 35], Self-Efficacy Scale [36], Jacobsen Fatigue Catastrophizing Scale [37], Illness Management Questionnaire [38], Social Support List (SSI & SSL D) [39] and Pain Catastrophizing Scale [40].

Table 3. CBT modules and assessment tools used for patient tailoring of fatigue treatment

Treatment modules	Questionnaires and instruments
<p><i>1. Treatment goals.</i></p> <p>Positive and concrete goals of the fatigue treatment are formulated by each patient. The goals consist of activities they would do when no longer severely fatigued.</p>	All patients
<p><i>2. Sleep and rest.</i></p> <p>The importance of a regular sleep-wake cycle and a good sleep hygiene are discussed, and instructions are given how to improve this.</p>	<p>Sickness Impact Profile subscale sleep and rest (scores ≥ 60)[46, 47]</p> <p>Sleep log during one week</p>
<p><i>3. Uncertainty about the (consequences of the) illness and appraisal of MS as threatening.</i></p> <p>In case of non-accepting cognitions of having MS and extreme fear of the future, the patient will be helped to gather realistic information about MS, to develop helping cognitions about MS and the personal future and to develop and maintain a more accepting attitude towards the illness and its consequences.</p>	<p>Impact Event Scale (IES ≥ 20) [29],</p> <p>subscale Acceptance of the Illness Cognition Questionnaire (ICQ-acceptance ≤ 12) [30],</p> <p>Beck Depression Inventory-PC (>4) [33],</p> <p>Fear of Disease progression Questionnaire- short form (FoP-Q-SF ≥ 34)[34, 35],</p> <p>The Cognitive behavioural Responses to Symptoms Questionnaire (CBRSQ) [31, 32]:</p>

- Resting behaviour > 14.3,
- all-or-nothing behaviour > 12.9,
- symptom focusing > 15.5,
- Embarrassment > 16.4,
- Damage > 20.5,
- Fear avoidance > 15.3

4. *Fatigue-related cognitions.*

Sense of control over fatigue symptoms (self-efficacy), fatigue catastrophizing, somatic attributions and other dysfunctional thoughts are assessed [67, 68][42, 43][65, 66]. Patients are helped to change these cognitions in daily life.

modified Self Efficacy Scale for fatigue (≤ 19), Jacobson-Fatigue Catastrophizing Scale (≥ 16) [37]

5. *Focusing on fatigue.*

Information about and consequences of focusing on fatigue will be discussed. Patients will practice with redirecting the focus of attention (away from the fatigue toward activity and other sensations)

Illness Management Questionnaire (≥ 4) [38]

6. *Physical activity regulation.*

Depending on the activity pattern patients will learn to spread activities more evenly, sometimes to lower activities and followed by a systematical increase of regular physical activity. After patients have increased their

Activity Pattern Interview

physical activity level they increase other activities in order to reach the goals step by step.

7. Regulation of social activity.

The relationship with reduction in social activities as well as the cognitions about these activities and fatigue will be assessed in relation to the set goals. Suggestions how to increase social activities and how to handle the problems that are experienced during social interactions (as a consequence of cognitive impairments or intolerance of noise) are given.

Sickness Impact Profile
(≥ 100)[46]
subscale social
functioning of the SF36
(≤ 65)[49]

8. Regulation of mental activity.

Patients are supported with regards to practicing and expanding mental activities such as computer use or reading. They learn how to deal with possible cognitive deficits such as concentration and memory problems.

CIS20r-concentration
subscale (score ≥ 18)[42]

9. Social support.

Goal of this module is to support emotional independence of others, as far as fatigue is concerned. Unrealistic expectations of others and expressing boundaries are discussed.

The Sonderen Social
Support Inventory:
subscale discrepancy
(score ≥ 50)
subscale negative
interactions (score ≥ 14)
[39]

10. Unhelpful thoughts about pain.

Dysfunctional pain cognitions are challenged and more helpful pain cognitions will be installed.

SF36 bodily pain
subscale (score ≤ 40)
Pain Catastrophizing
Scale (score ≥ 16)[40]

Blended CBT (MS Fit) consists of 2 face-to-face contacts, respectively one at the beginning and one at the end of the initial 20-week treatment period, 3 video-consultations, and 7 web-based therapy sessions with information and assignments delivered via an internet portal and supported by email contact with the therapist who provides feedback on the progress made by the patient. The blended CBT will also be patient-tailored based on the same 10 treatment modules as described earlier (Table 3). The therapists who deliver the face-to-face CBT will also deliver MS Fit and the treatments are supervised once every two weeks.

Development of MS Fit and usability testing

The information and assignments provided in the internet portal are developed by experts on CBT for MS-related fatigue and are based on “Dia-Fit”, an evidence-based blended CBT intervention for severely fatigued patients with Diabetes type 1 [22] and “On the road to recovery”, an evidence-based intervention for cancer related fatigue in breast cancer survivors [23]. The interventions were adapted for MS. Comparable treatment modules are formulation of treatment goals, sleep and rest, beliefs about fatigue, focusing on fatigue, and regulation of activity (table 3). Two specific modules about MS namely unhelpful beliefs about MS, and pain were developed by experts on chronic fatigue and MS. Two patients with MS, who already had received face-to-face CBT for fatigue, and one patient with MS who participates in the Trial Steering Committee on behalf of the Dutch patient organisation MSVN, were asked for usability testing of the portal. Their feedback was used to improve parts of the intervention.

MS Stay Fit

The booster programme MS Stay Fit consists of two patient-therapist booster consults with the same therapist who delivered the first part of the intervention, scheduled at 2 and 4 months following end of initial treatment. Booster sessions will be delivered via the internet via a secured video connection and combined with email contact and web-based CBT assignments on prevention of fatigue relapses. Five optional “booster modules” are aimed at the factors that mediated the relapse in fatigue following the intervention in the original trial: sleep-wake pattern and activity regulation (both physical and mental) [7], but also at cognitions about fatigue, coping with “normal fatigue” and continuing reaching the set goals.

Therapist training and supervision

All involved therapists received a 3-day training course in the face-to-face CBT protocol for MS-related fatigue, and a 1-day training course in delivering the e-health intervention. The CBT training course consists of training the content and indication of each treatment module, and practicing the intervention techniques in role-playing, with help of professional actors who simulate patients. The e-health training course consists of an introduction to the online platform, practicing in delivering MS Fit, and skills in writing e-mails. All therapists will provide both face-to-face and blended CBT, to make sure that any between-group differences found are not contributable to specific therapist-factors or treatment centres. All therapists will receive two-weekly supervision via the telephone by a psychologist with extensive experience in the treatment of chronic fatigue (MG and HK).

Modification of allocated intervention

Reasons for discontinuing the allocated intervention can be new health problems or life events hindering patients to continue the treatment, or patient's decision to withdraw from the treatment.

After eight months a small adjustment was made in the introduction page of MS Fit, after receiving feedback of two patients who found the description not applicable to them, demotivating them to continue treatment. These sentences were adjusted, and an example was added, in order to clarify the purpose of the blended CBT.

Concomitant care

Patients are instructed not to follow or use any other therapies or medication aimed at fatigue during the one-year study period. Multidisciplinary rehabilitation treatments aimed at other health problems should be phased before or postponed after the 20-week CBT intervention. All other medical interventions are allowed. Use of additional fatigue management is not systematically registered, since it would be difficult to reliably assess this during the course of one year, and the assumption is made that this will be comparable between all groups.

Outcome measures

Outcome measures consist of validated self-reported questionnaires, which will be assessed at baseline (T0), end of initial treatment (T20) which is equal to the end of the non-inferiority RCT 1, and at 39 and 52 weeks (end of RCT 2). See figure 2 for measurements at all time points. Patients can complete these questionnaires online from their home. At all these time points patients will also keep an online sleep log during one week, which is sent to them daily for seven consecutive days. Completing the questionnaires online requires filling in every item, which prevents occurrence of missing item values. The research assistant checks for possible missing sleep logs, and, if needed, sends as a reminder additional sleep logs to the patient.

Primary outcome measure

In both RCTs the primary outcome measure will be fatigue severity, as measured by the CIS20r fatigue severity subscale, at either the end of initial treatment (RCT 1: T20) or at one year (RCT 2: T52). At these time points the differences in fatigue severity between both groups will be assessed. The same primary outcome measure is used as in the TREFAMS-CBT trial. The CIS20r is a 20-item self-reported questionnaire consisting of 4 subscales: (a) fatigue severity (8 items); (b) reduction in motivation (4 items); (c) reduction in physical activity (3 items) and (d) concentration problems (5 items) [41, 42]. Items are answered on a 7-point Likert scale and added to a total score. The total score of the fatigue severity subscale can vary between 8 and 56 points. The CIS20r is a reliable and valid instrument for measuring

fatigue in various study populations [43]. A cut-off score of 35 or higher is used to discriminate between severe fatigue and fatigue levels within the normal range.

Secondary outcome measures

Clinical significant improvement assessed with the CIS20r is a secondary outcome measure. Clinical significant improvement is defined as either a score of < 35 on the CIS20r subscale fatigue severity, or an improvement of ≥ 8 points on this subscale [16]. As the CIS20r is also used as a screening tool thereby limiting the variance in the outcome measure, we decided to use the following additional fatigue measures as secondary outcome measures. The Fatigue Severity Scale (FSS) is used to measure the severity and impact of fatigue in patients with MS [44]. The FSS consists of 9 items to be rated on a scale from 1 (strongly disagree) to 7 (strongly agree). The final score is the mean of all item-scores. Also, the PROMIS-Fatigue Short Form 8a [45] is used to measure fatigue in addition to the CIS20r. This questionnaire consists of 8 items to be rated on a scale from 1 (not at all / never) to 5 (very much / always). The final score is the sum score of all items.

The Sickness Impact Profile (SIP) [46, 47] will be used to measure limitations of daily functioning in 8 different domains of functioning. The eight subscale scores are summed to provide one weighted score of disability (SIP8 total score). The SIP was used in several intervention studies with chronically fatigued patients. The Work and Social Adjustment Scale (WSAS) [48] is used to measure restrictions in participation. The WSAS is a 5-item scale rating impairment on 5 different domains of functioning on a scale from 1 (not at all impaired) to 8 (severely impaired). The final score is the sum of all items. Health-related quality of life will be assessed by the SF36 [49], consisting of 36 items and 8 subscales. Raw scores on each scale are converted to a score on a scale of 0 to 100, with a higher score indicating a higher level of well-being.

For these secondary outcome measures, no margins of non-inferiority have been defined. The course of the scores on these secondary outcome measures during the whole study year will be plotted for the various subgroups of participants.

See online supplementary Table 2 for specifications of the primary and secondary outcome measures.

Demographic and disease characteristics

The demographic characteristics that will be assessed are age, gender, ethnicity, level of education and employment. Disease-related determinants which are assessed include self-reported type of MS, date of diagnosis, date of onset of MS, use of disease modifying drugs, and the score on the Expanded Disability Status Scale (EDSS) [50] and comorbidities using the Cumulative Illness Rating Scale (CIRS) [51] both assessed by the researcher at baseline.

Moderators and mediators

Since various factors may play a moderating or perpetuating role in fatigue and since CBT consists of multiple modules which intervene on different aspects of fatigue, it is interesting to measure variables that 1) may moderate the effect of blended CBT in comparison to face-to-face CBT and/or 2) moderate or mediate the effects of the booster sessions of CBT on long term outcome [7, 32]. In addition to the measurement instruments used to tailor the CBT modules, the following factors will be assessed at several time points for the analysis of moderation and mediation. Psychological distress will be assessed using the total score on the Symptom Check List (SCL-90) [52, 53]. Daytime sleepiness will be assessed by the Epworth Sleepiness Scale [54]. Sleep dysfunction is assessed by the Pittsburg Sleep Quality Index [55]. A sleep log of 1 week will be used to assess sleep parameters. Self-management will be measured with The Multiple Sclerosis Self-Management Scale [56].

Attentional and Interpretative Bias

To measure the tendency of patients to direct their attention to illness-related information, a Visual Probe Task (VPT) is used. This task was developed by Hughes et al [57] to measure an attentional bias for illness-related information in patients who are chronically fatigued. As this computer task is programmed using e-Prime, it needs to be performed on a computer under controlled conditions. Therefore, only participants living in the Amsterdam area will be asked to complete this task. The VPT will be assessed prior to the first and last treatment session at the treatment centre by a research assistant. Furthermore, an interpretive bias task will be used to assess the tendency of patients to interpret bodily sensations in a negative, threatening way [57]. We aim to assess patients before and after treatment (T20) and to determine if a change in the tendency of patients to focus on symptoms is related to the reduction in fatigue brought on by CBT.

Treatment preference, outcome expectation and treatment satisfaction

Patient-therapist factors will be taken into account by assessing treatment preference (online vs face-to-face CBT), and patients expectations of treatment outcome using the Treatment Outcome Expectations Questionnaire (TOEQ) [58] at baseline. At the end of treatment (T20) and one year after the start of treatment (T52), therapeutic alliance will be assessed using the Working Alliance Inventory (WAI-SR) [59, 60]. Also, patients satisfaction with treatment and satisfaction with the platform will be assessed using the System Usability Scale (SUS) [61, 62].

Participant retention

Participants receive the questionnaires online. For optimal retention, participants will be contacted by email or phone by the research assistant, when they have not started the completion of the questionnaires within one week. Randomization is done after completing all questionnaires at T0 (R1) or T20 (R2), preventing missing data at these important moments. When participants are not willing to complete all measurements at T20, T39 or T52, they are asked to at least fill in the subscale fatigue of the CIS20r, being the primary outcome measure.

Participant withdrawal

Patients can leave the study at any time for any reason if they wish to do so without any consequences. Nevertheless, these patients are requested to fill in a final CIS20r fatigue. The researcher can withdraw a patient from the study in case of incorrect enrolment of the participant. Withdrawing from the study, does not necessarily mean the patients has to stop treatment. The treating physician, or the treating psychologist can decide to withdraw a patient from the study for urgent (medical) reasons. These reasons will be documented.

Serious adverse events

Any spontaneously by patient or therapist reported adverse events will be recorded.

CBT, both face-to-face and blended, are expected to be safe treatment methods. However, all serious adverse events (SAEs) will be reported according to the Dutch Act on Medical Research Involving Human Subjects. An SAE is defined as any untoward medical occurrence or effect that is lethal and/or life threatening, requires hospitalisation or prolongation of existing inpatients' hospitalization, results in persistent or significant disability or incapacity. SAEs will be reported to the researcher by the therapists, during by-weekly supervision or by email. All SAEs need to be timely reported to the Medical Ethics Review Committee. When adverse events occur appropriate diagnostic procedures and medical treatment will be undertaken as needed. The Ethical Committee has granted dispensation for insurance for damage to research participants through injury or death caused by the study, as participation in this study is without risks.

Treatment fidelity and compliance

After the first therapy session, each therapist registers which modules are indicated based on the patient-reported questionnaires, and which modules are indicated based on their interview. With regard to the process, they will register each provided therapy session or patient contact (face-to-face, video, phone, email), the duration of the contact and which of the indicated treatment modules were delivered in that session. Patient therapy adherence in MS Fit will be assessed via log data provided by the online platform.

All therapists will be supervised bi-weekly by an experienced clinical psychologist (HK or MH) to ensure patient-specific treatment integrity.

Blinding of outcome measurements and data analysis

In this study, mainly patient-reported outcomes will be gathered. Patients and therapists cannot be blinded for the type of treatment. A research assistant, who will be blinded with respect to treatment allocation, will send out the internet questionnaires and will monitor the timely completion of filling in the questionnaires. The statistical analyses will be carried out by an independent researcher on an encrypted data file, blinded for treatment allocation.

Handling and storage of data and documents

Data, other than the questionnaires, are entered in an electronic Case Report File (eCRF), which includes an audit trail. Personal data will be handled confidentially and in a coded way, and comply with the Dutch Personal Data Protection Act. Patient identification will be coded for all study procedures. Only the project leader and primary researcher have access to the codes and participant data. Codes and participant data will be stored in password-protected files. After finishing the study, the key to the code will be safeguarded by the coordinating investigator. Data will be stored by the Department of Rehabilitation Medicine of the Amsterdam University Medical Centers for 15 years following completion of the project.

Therapist secrecy and confidentiality will be maintained at all times. Patient correspondence by e-mails will be encrypted and securely stored to guarantee privacy and confidentiality. An email-account of the university hospital will be used for correspondence by emails. Participant information will not be disclosed to third parties.

Only the Trial Steering Committee will have access to the full dataset.

Biological specimens

No biological specimens will be collected in the study.

Monitoring and auditing

This study will be subject to on-site monitoring in accordance with the quality assurance advice of the The Dutch Federation of University Medical Centres regarding research involving human subjects [63]. On-site monitoring will be based on the risk-classification (negligible).

The sponsor/investigator will submit a summary of the progress of the trial to the Ethical Committee once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

Statistical analyses

Non-inferiority of blended CBT compared to face-to-face CBT at 20 weeks

Primary analyses will be on the basis of intention-to-treat (ITT) and per protocol using Mixed Model Analysis, in order to reduce the risk of falsely claiming non-inferiority of blended CBT [26, 27], with the CIS20r fatigue severity score at the end of treatment (T20) as dependent and study group (blended vs f2f CBT) as fixed factor. A graph showing CIS20r fatigue confidence intervals and margins of non-inferiority will be used, see figure 3 [26, 27]. When blended care is found non-inferior, a sensitivity analysis will be performed on the basis of different assumptions about the values of missing data.

To compare the effect of blended care and face-to-face CBT on the secondary outcome measures the ITT mixed model analysis will be repeated with the secondary outcomes at the end of treatment (T20) as dependent variable and study group as fixed factor.

H0: blended CBT is inferior to face-to-face CBT, meaning that face-to-face CBT – blended CBT \geq M. M is the non-inferiority margin (6.67 – 5.32 = 1.35)

H1: blended CBT is non-inferior to face-to-face CBT, meaning face-to-face CBT – blended CBT < M

Effectiveness of CBT booster sessions at 52 weeks

Primary analysis of long-term effects of additional booster sessions will be based on ITT using Mixed Model Analysis with CIS20r fatigue severity one year after the start of treatment (T52) as dependent measure and condition (booster session vs no booster sessions) as fixed factor. In case of a large attrition rate, a per protocol analysis will be added.

To compare the effect of booster sessions on the secondary outcome measures the ITT mixed model analysis will be repeated with the secondary outcomes at T52 as dependent variable and study group as fixed factor.

In a separate analysis we will additionally investigate the differential effect of the booster sessions in patients who are no longer severely fatigued at T20 compared to those who are still fatigued at T20.

Analyses of factors mediating long-term effectiveness will be conducted. In addition, analyses will be done to identify possible moderators of the response to the booster sessions and response to face-to-face or blended CBT.

Discussion

A study protocol was presented of two RCTs combined in one study testing respectively non-inferiority with respect to the effect of MS Fit (blended CBT) on fatigue severity compared to face-to-face CBT in severely fatigued patients with MS [13, 16], and the effectiveness of MS Stay Fit, i.e. additional internet-based booster sessions following MS Fit or face-to-face CBT, compared to no booster sessions on fatigue severity up to one year after randomisation.

By combining two RCTs this study is able to address two important research questions. The non-inferiority trial aims to give more insight in whether the CBT protocol applied in a blended form is non-inferior as to when applied face-to-face. If MS Fit is indeed non-inferior to face-to-face CBT, it probably will be a more time-efficient but also a more accessible treatment option, enhancing implementation of this intervention. Since long-term effects of CBT vary between studies with some showing considerable

fatigue relapse [20], and little is known about the underlying mechanisms of fatigue relapses after successful treatment [7], testing the effect of booster sessions, and testing possible mediators and moderators of the response to treatment, may contribute to better understanding of these mechanisms and most importantly improving long-term effects. To our knowledge, this is the first study testing the effectiveness of booster sessions in treating chronic severe fatigue. In addition, by training psychologists of 12 participating rehabilitation centres and hospitals, this study aids in implementation of CBT for MS-related fatigue in the Netherlands and Belgium, making effective fatigue treatment more accessible to MS patients.

In this trial inclusion criteria and the face-to-face CBT protocol used are similar as in the TREFAMS-CBT study. However, in our study more rehabilitation centres are including and treating patients, and, even with the same set of enrolment criteria, this may lead to a more varied patient sample. Considering the number of therapists (currently 20 therapists are involved) in the study, it is also plausible that there is more variance in therapist-related factors, for example familiarity with providing e-health interventions such as blended CBT. Providing an extensive manual, intensive training and supervision of all therapists, intends to limit these variance and optimize treatment integrity as much as possible [64], respecting the consistency rules of non-inferiority trials [26, 27]. Taking this into account, these aspects may also well increase generalizability of the results of this pragmatic trial to clinical practice. In addition, in this trial, treatment duration is set at 20 weeks instead of 16 weeks, since this is expected to increase opportunity for patients to reach treatment goals and cognitive and behavioural changes.

Non-inferiority of blended-CBT is measured by means of fatigue severity as the primary outcome measure, but benefits of treatment may regard other aspects as well, for example accessibility, time-efficiency or adherence. Being effective, but having a high drop-out rate for example, can also have implications for implementation. These factors will be measured and might help in interpreting the primary trial results.

Even though the content of treatment is similar in both treatments, differences in form of treatment may affect several factors possibly influencing effectiveness. It is known that factors in the therapy relationship, e.g. outcome expectations and working-alliance, can contribute to treatment outcome in general [65], but also more specific in treating fatigue [58]. In general, working-alliance is found to be related to self-efficacy, outcome expectancies, treatment adherence and satisfaction [66]. Since in the blended-CBT group therapist contact is more distant and less frequent, this might influence treatment adherence, satisfaction and outcome effects. For that reason, patients' evaluation of the working-alliance, treatment satisfaction and usability of the platform will be taken into account in secondary trial analyses. Outcome expectations are also measured at baseline, but at time of measurement, patients will not be randomized yet, so these expectations will not apply to the form of treatment that they will adhere. It could be argued that treatment expectations may be higher in the present study than in the TREFAMS-CBT study, since CBT for MS-related fatigue is proven effective now.

In conclusion, this paper presents the study protocol of two combined RCTs testing non-inferiority of blended CBT compared to face-to-face CBT for MS-related fatigue, and the effect of booster sessions on long-term outcome. This study aims to provide more insight in effectiveness of CBT in various applied forms, and in possibilities for improving long-term effectiveness of the treatment. In addition, by conducting the study and training of psychologists in 12 rehabilitation centres in the Netherlands and Belgium, this study is a first step in implementation of CBT in clinical practice.

Trials' status

Patient recruitment started in April 2018 and is expected to end in March 2021. At time of submission 64 patients have been randomized. The trial is being conducted according to the protocol version 7, dated 4-7-2019.

Abbreviations

AT: Aerobic Training; BDI-PC: Beck Depression Inventory-Primary Care; CBT: Cognitive Behavioural Therapy; CI: confidence interval; CIRS: Cumulative Illness rating Scale; CIS20r: Checklist Individual Strength; ECM: Energy Conservation Management; eCRF: electronic Case Report File; EDSS: Expanded Disability Status Scale; MS: Multiple Sclerosis; RCT: Randomized Clinical Trial; SAE: Serious Adverse Event; TREFAMS: TREating FATigue in MS; VPT: Visual Probe Task

Declarations

Competing interests

The authors declare that they have no competing interests.

Consent for publication

The results of this study will be submitted for publication as scientific articles in peer-reviewed, open access journals. The results will also be presented at national and international conferences for clinicians, researchers and patients. Publication is not restricted to the outcome of the study, all results (positive and negative) will be incorporated in the paper.

Availability of data and material

Any request to share the data of these RCTs will be considered by the Trial Steering Committee, and will need to be approved by the ethical committee of the Amsterdam University Medical Centers, location VU university medical center, before granted.

Informed consent form in Dutch is available as supplement.

Author's contributions

The steering committee of the trials consists of the authors of this paper and a member of the Dutch patient organisation MSVN.

Principal investigators: VG, HK, HB

Design study: HB, VG, HK, MH

Design interventions: HK and MH

Recruitment of participating centers: VG and MH

Training and supervising therapists: HK and MH

Recruitment and inclusion of patients: MH and KV

Drafting manuscript: MH, HB, KV, HK, VG

Overall project coordination: HB and MH

Data management: HB and MH

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Figures

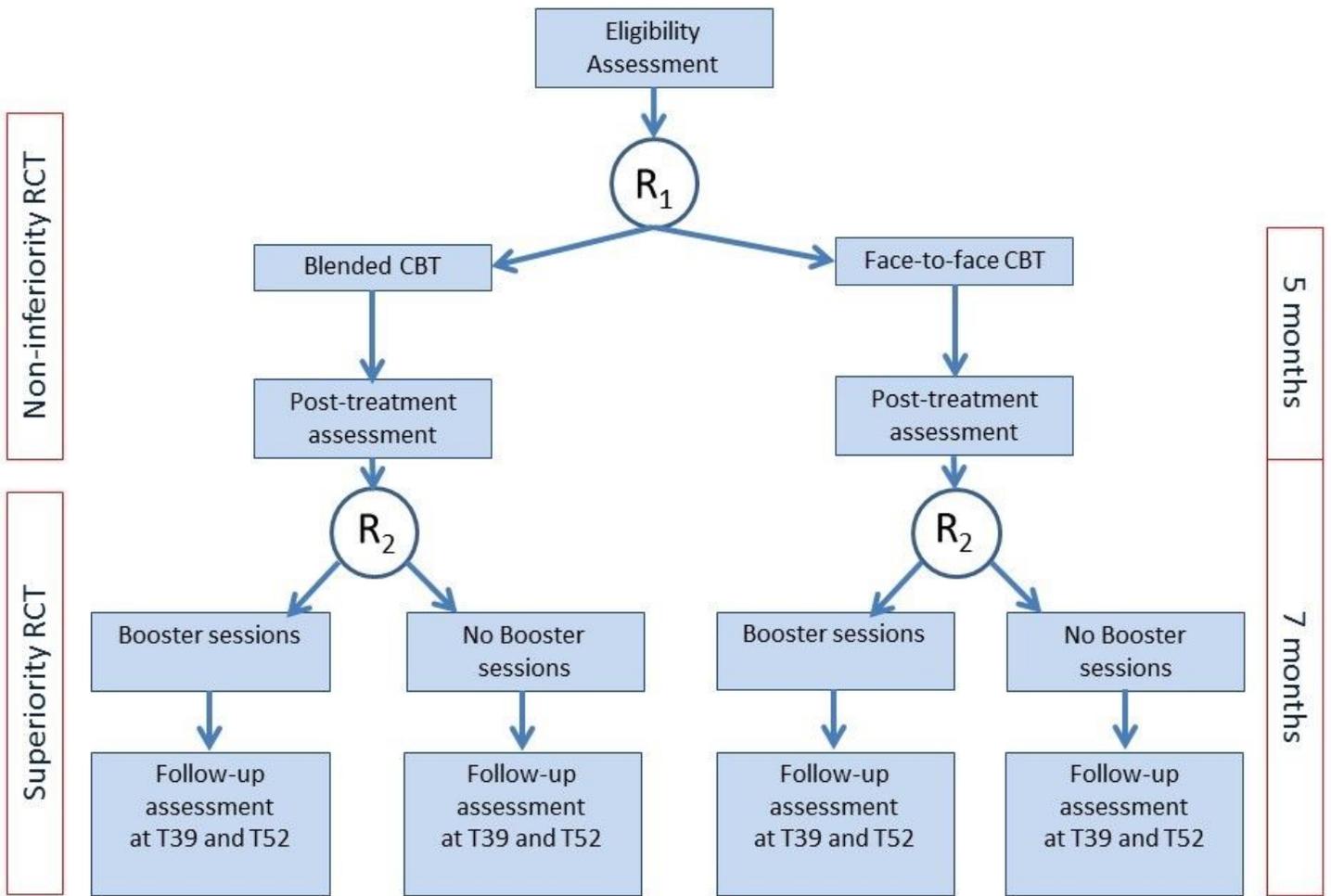


Figure 1

Study design

TIMEPOINT**	Enrolment	Allocation	Time-points			
	-t ₁	0	T ₀	T ₂₀	T ₃₉	T ₅₂
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
INTERVENTIONS:						
Face-to-face CBT			—————			
Blended CBT			—————			
Booster sessions					—————	
ASSESSMENTS:						
<i>Primary Outcome</i>						
Fatigue: CIS20r subscale fatigue			X	X	X	X
<i>Secondary Outcome</i>						
CIS20r subscales Motivation, Physical activity, Concentration problems			X	X	X	X
PROMIS fatigue 8a			X	X	X	X
Fatigue Severity Scale (FSS)			X	X	X	X
Sickness Impact Profile (SIP8)			X	X	X	X
Work and Social Adjustment Scale (WSAS)			X	X	X	X
SF36			X	X	X	X
Other determinants						
Symptom Checklist (SCL-90)			X	X	X	X
Multiple Sclerosis Self-management Scale			X	X	X	X
Pittsburg Sleep Quality Index (PSQI)			X	X	X	X
Sleeplog			X	X	X	X
Epworth Sleepiness Scale (ESS)			X	X	X	X
Interpretive bias task			X	X		
Visual Probe Task			X	X		
Treatment Preference			X			
Treatment Outcome Expectations Questionnaire (TOEQ)			X			
Working Alliance Inventory (WAI-SI)				X		X
Treatment Satisfaction				X		X
System Usability Scale (SUS)				X		X
Impact of Event Scale (IES)			X	X		X
Fear of disease progression-short form (FoPQ-SF)			X	X		X
Cognitive Behavioral Responses to Symptoms (CBRSQ)			X	X	X	X
Jacobson Fatigue Catastrophizing Scale			X	X	X	X
Pain Catastrophizing Scale (PCS)			X			
Illness Cognitions Questionnaire (ICQ)			X	X	X	X
Social Support List (SSL)			X			
Self-Efficacy Scale (SES-28)			X	X	X	X
Illness Management Questionnaire (IMQ)			X	X		X

T₀ = baseline; T₂₀ = end of initial treatment; T₃₉ = 39 weeks after start treatment; T₅₂ = 52 weeks after start treatment
 ↓ = Allocation to boosters or no boosters

Figure 2

Time points of all measurements T₀ = baseline; T₂₀ = end of initial treatment; T₃₉ = 39 weeks after start treatment; T₅₂ = 52 weeks after start treatment

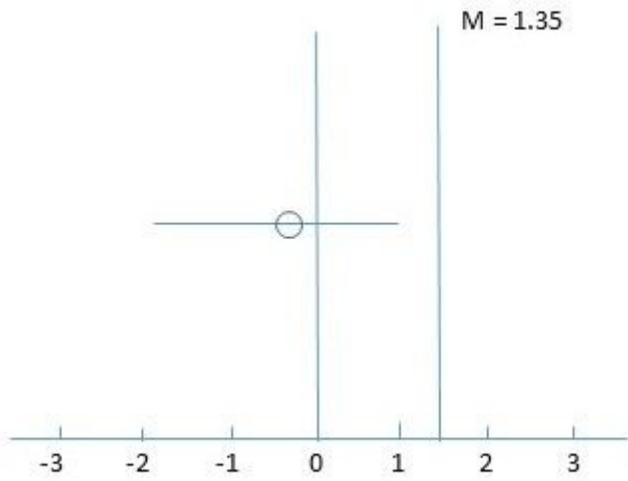


Figure 3

Illustration of a possible result of the non-inferiority trial

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [OnlineSupplementaryTable2.pdf](#)
- [OnlineSupplement3.pdf](#)
- [OnlinesupplementaryTable1.pdf](#)
- [SPIRITchecklist.pdf](#)