

STUDY PROTOCOL

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The effectiveness of aerobic training, cognitive behavioural therapy, and energy conservation management in treating MS-related fatigue: the design of the TREFAMS-ACE programme

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Abstract

Background: TREFAMS is an acronym for TReating FATigue in Multiple Sclerosis, while ACE refers to the rehabilitation treatment methods under study, that is, Aerobic training, Cognitive behavioural therapy, and Energy conservation management. The TREFAMS-ACE research programme consists of four studies and has two main objectives: (1) to assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and improving societal participation in patients with MS; and (2) to study the neurobiological mechanisms of action that underlie treatment effects and MS-related fatigue in general.

Methods/Design: Ambulatory patients ($n = 270$) suffering from MS-related fatigue will be recruited to three single-blinded randomised clinical trials (RCTs). In each RCT, 90 patients will be randomly allocated to the trial-specific intervention or to a low-intensity intervention that is the same for all RCTs. This low-intensity intervention consists of three individual consultations with a specialised MS-nurse. The trial-specific interventions are Aerobic Training, Cognitive Behavioural Therapy, and Energy Conservation Management. These interventions consist of 12 individual therapist-supervised sessions with additional intervention-specific home exercises. The therapy period lasts 16 weeks. All RCTs have the same design and the same primary outcome measures: fatigue - measured with the Checklist Individual Strength, and participation - measured with the Impact on Participation and Autonomy questionnaire. Outcomes will be assessed 1 week prior to, and at 0, 8, 16, 26 and 52 weeks after randomisation. The assessors will be blinded to allocation. Pro- and anti-inflammatory cytokines in serum, salivary cortisol, physical fitness, physical activity, coping, self-efficacy, illness cognitions and other determinants will be longitudinally measured in order to study the neurobiological mechanisms of action.

(Continued on next page)

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(Continued from previous page)

Discussion: The TREFAMS-ACE programme is unique in its aim to assess the effectiveness of three rehabilitation treatments. The programme will provide important insights regarding the most effective treatment for MS-related fatigue and the mechanisms that underlie treatment response. A major strength of the programme is that the design involves three almost identical RCTs, enabling a close comparison of the treatment strategies and a strong overall meta-analysis. The results will also support clinical practice guidelines for the treatment of MS-related fatigue.

Trial registrations: Current Controlled Trials ISRCTN69520623, ISRCTN58583714, and ISRCTN82353628

Keywords: Multiple sclerosis, Fatigue, Aerobic training, Energy conservation management, Cognitive behavioural therapy, Biomarkers, HPA-axis, Cortisol, Cytokines, Rehabilitation medicine, Randomised controlled trial

Background

Multiple sclerosis (MS) is a neurodegenerative disease characterised by demyelination, axonal loss and inflammation of the central nervous system (CNS). Although the first description of MS dates back to the mid-19th century, in spite of this long history the aetiology is still unknown and no curative treatment is available [1]. The disease is most probably caused by an interplay between immunological, environmental and genetic factors [2,3]. MS affects young and middle-aged people, with women twice as likely to be affected as men, and is known to cause a variety of clinical symptoms such as neurological impairments, fatigue, depression and pain [2].

Fatigue is one of the most often reported and disabling symptoms in MS and restricts societal participation and performance in daily life at home, at work and in leisure activities [4-6]. Although the importance of fatigue as a disabling symptom of MS is widely acknowledged, there is no consensus on the definition of fatigue. DeLuca [7] defines fatigue as the reduction in performance with either prolonged or unusual exertion. Furthermore, fatigue can be sensory, motor, cognitive or subjective. The Multiple Sclerosis Council for Clinical Practice Guidelines [8] defines fatigue in MS as a subjective lack of physical and/or mental energy that is perceived by the individual (or caregiver) to interfere with usual and desired activities. Chaudhuri and Behan [9] distinguish central fatigue from peripheral fatigue, and define central fatigue as the failure to initiate and/or sustain attentional tasks (mental or cognitive fatigue) and physical activities (physical fatigue). Peripheral fatigue is described as muscle fatigability due to disorders of muscle and neuromuscular junctions. The definitions of DeLuca [7], the MS Council for Clinical Practice Guidelines [8] and the concept of central fatigue outlined by Chaudhuri and Behan [9] concur with our view that MS-related fatigue is a multifaceted symptom. Fatigue in MS can also be subdivided into primary and secondary. Primary fatigue relates to specific pathophysiological mechanisms that are the direct consequence of the MS disease process. On the other hand, a number of factors, while not considered primary causes of MS-related

fatigue, may be secondary contributors. These factors are not unique to MS, but are the result of symptoms of MS such as sleep problems due to spasm or urinary problems, depression or physical deconditioning. Fatigue might also be a side effect of disease modifying drugs.

Although the exact pathophysiological mechanism behind MS-related fatigue is unknown, it is most likely multifactorial. A number of pathophysiological mechanisms have been proposed including dysregulation of the immune system, dysfunction of the CNS, impaired nerve conduction, neuro-endocrine/neurotransmitter dysregulation, the involvement of the autonomic nervous system and energy depletion [10,11]. Available information can be combined in a biological model in which environmental stressors such as infections, immunisation, trauma and life events influence genetically predisposed variables such as the sensitivity of the hypothalamic-pituitary-adrenal axis (HPA-axis), glucocorticoid receptors and the noradrenaline system [9,12,13]. Consequently, fatigue is triggered in susceptible individuals. In addition to disease-related, genetic and environmental factors, psychological mechanisms may play an important role in causing and sustaining MS-related fatigue [12-14].

In clinical practice, MS-related fatigue is often treated with a combination of therapies, which makes it difficult to distinguish the effect of each therapy component. Due to the limitations of available evidence, current pharmacological approaches to treating MS-related fatigue are mainly based on preliminary studies and expert consensus. Amantadine, Modafinil and Aminopyridine are pharmacological strategies mainly used by neurologists [15]. Current evidence supporting the effectiveness of non-pharmacological interventions such as Aerobic Training (AT) [16-22], Cognitive Behavioural Therapy (CBT) [23] and Energy Conservation Management (ECM) [24-26] on MS-related fatigue is encouraging, but findings are heterogeneous and only a few studies have evaluated MS-related fatigue as the primary outcome measure [27]. Moreover, the methodological quality of non-pharmacological trials is often hampered by issues such as the complexity of the (multidisciplinary) treatment, the lack of adequate control groups, treatment blinding of patients and assessors, and the expertise of the

involved therapists. These issues have resulted in an extension of the CONSORT statement for non-pharmacological trials [28]. Systematic reviews of exercise therapy and energy conservation management trials are underway or recently published [29,30].

TREFAMS is an acronym for the TReating FATigue in MS programme, and ACE refers to the rehabilitation treatment methods under study, that is, Aerobic training, Cognitive behavioural therapy, and Energy conservation management. The programme has two main objectives: (1) to assess the effectiveness of three different rehabilitation treatment strategies in reducing fatigue and in improving societal participation in individual MS patients; and (2) to study the biological mechanisms that underlie treatment effects and MS-related fatigue in general. The TREFAMS-ACE research programme includes three randomised clinical trials (RCTs), and one explanatory study on the biological mechanisms of action that underlie treatment effects and MS-related fatigue in general.

A significant body of evidence now implicates both HPA-axis abnormalities and immune markers in the pathophysiology of MS-related fatigue. MS patients with fatigue exhibited a higher activity of the HPA-axis than patients without fatigue [13,31]. Earlier studies have examined a possible relationship between cytokines and fatigue in MS [32,33]. A study of pro-inflammatory (IFN- γ , TNF- α) and anti-inflammatory (IL-10) cytokine production in MS patients showed that patients with fatigue had a significantly higher production of IFN- γ and TNF- α than patients without fatigue. IL-10 production did not significantly differ between the two groups [32]. Flachenecker and Bihler [33] found a relationship between TNF- α mRNA expression and fatigue, but not between fatigue and IFN- γ or IL-10. In view of a relationship to inflammatory markers found in two independent studies and the higher HPA-axis reactivity in MS, we hypothesise that fatigue in patients with MS is stress-related and that it is caused by an inflammatory mechanism. In addition, we assume that the extent of imbalance between pro-inflammatory and anti-inflammatory cytokines is associated with the severity of fatigue.

AT is aimed at improving physical fitness and at reducing an inactive, deconditioning lifestyle. Improved physical fitness may lead to normalisation of HPA-axis functioning [34], a reduction in pro-inflammatory cytokines and/or an increase in anti-inflammatory cytokines [35], leading to a reduction in MS-related fatigue. We hypothesise that an improved physical fitness due to AT will be accompanied by reduced fatigue and, as a consequence, improved societal participation.

CBT focuses on fatigue-maintaining cognitions and behaviour, examples of which are insufficient coping with MS or MS-related fatigue, fear of disease progression, dysregulation of activity or sleep, low social support and focusing on fatigue. The general aim of CBT is to

improve daily functioning and to decrease fatigue by changing fatigue-maintaining cognitions and behaviour, within the limits of the MS [36]. We hypothesise that CBT may reduce perceived stressors (for example, environmental, psychological and biological), and consequently may lead to normalisation of HPA-axis functioning and cytokine profiles.

ECM includes energy conservation strategies, ergonomic advice and coaching aimed at more efficient use of available energy. Energy conservation strategies have been defined as the identification and development of activity modifications to reduce fatigue through a systematic analysis of daily work, home and leisure activities in all relevant environments [8]. Packer *et al.* [37] were the first to develop an ECM treatment protocol for a 6-week group course. In a clinical trial, this group course proved to be effective in patients with MS, both immediately following the course and after 1 year [24,25]. The treatment goal of ECM is to promote a positive attitude aimed at stimulating active decision-making and the optimal use of available energy in relation to the unique needs of each individual. We hypothesise that ECM may lead to a reduction in environmental and psychological stressors and consequently to the normalisation of biological stressors (HPA-axis functioning, cytokines), which may in turn lead to reduced fatigue and improved participation.

Accordingly, the following research questions have been formulated in the TREFAMS-ACE programme:

1. What is the effectiveness of Aerobic Training on fatigue and participation? Can this effect be attributed to an increase in fitness parameters?
2. What is the effectiveness of CBT on participation and fatigue? Can this effect be explained by altered cognitions regarding fatigue?
3. What is the effectiveness of Energy Conservation Management advice on fatigue and participation? Can this effect be attributed to the implementation of ergonomic advice or adherence to altered time-schedules?
4. Which treatment strategy reduces fatigue and improves participation most effectively?
5. Does effective therapy lead to normalisation of HPA-axis function, a reduction in pro-inflammatory cytokines or an increase in anti-inflammatory cytokines?

Methods/Design

Design

TREFAMS-ACE is a multicentre programme that includes three single-blinded RCTs with repeated measurements in time, in which the effectiveness of Aerobic Training, CBT and Energy Conservation Management on MS-related fatigue and participation in patients with

MS will be investigated. All RCTs will use the same two-parallel-arms design (Figure 1), the only difference being the specific intervention applied [28]. Patients will be randomised to receive either a high-intensity trial-specific treatment, which consists of a series of 12 therapist-led sessions in 4 months, or a low-intensity treatment by an experienced MS-nurse, which consists of three consultations in 4 months. Participants will be followed for 1 year.

In addition to the three clinical trials, a fourth study has been defined that will focus on biological outcome measurement and understanding the biological mechanisms of action underlying MS-related fatigue [38,39]. This study should also help to improve our understanding of the biological mechanisms of the four interventions under study (see Figure 1).

The medical ethics committee of the VU University Medical Center approved the TREFAMS-ACE programme. Additionally, local feasibility statements were obtained from each participating medical centre.

Participants

The 270 adult patients (90 patients per RCT, and 45 per intervention group) required will have to fulfill the following inclusion criteria: (a) definitive diagnosis of MS; (b) severely fatigued; (c) ambulatory patients; (d) no evident signs of an exacerbation, or a corticosteroid treatment in the past 3 months; (e) no current infections; (f) no anaemia; (g) a normal thyroid function. The exclusion criteria are: (a) depression; (b) primary sleep disorders; (c) severe co-morbidity; (d) current pregnancy or having given birth in the past 3 months; (e) pharmacological

treatment for fatigue that was started in the past 3 months (for example, Amantadine, Modafinil, Ritalin, Pemoline); (f) non-pharmacological therapies for fatigue that took place in the past 3 months. See Table 1 for the operationalisation of the inclusion and exclusion criteria.

Recruitment strategy

To avoid contamination of interventions, each RCT will be carried out at a different (university) medical centre: the AT study will be conducted in the St Antonius Hospital, Nieuwegein, in collaboration with the University Medical Center Utrecht, the CBT study will be conducted at the VU University Medical Center in Amsterdam and at the University Medical Centre Nijmegen (UMCN), and the ECM study will be conducted at the Erasmus MC-University Medical Center, Rotterdam, and Rehabilitation Center Leijpark in Tilburg. Patients will initially be recruited through the participating main study centres. The Dutch patient organisation Multiple Sclerosis Vereniging Nederland (MSVN) has been involved since the design phase of the research programme, and has offered to help with recruitment. If the main study centres are not able to recruit sufficient participants, recruitment will also take place in hospitals and rehabilitation centres in the neighbourhood of the main study centres. MS-nurses, neurologists and residents in neurology and rehabilitation medicine will inform potentially eligible patients about the TREFAMS-ACE study. A neurologist or a rehabilitation physician will check the inclusion and exclusion criteria listed in Table 1 in the case of a potentially eligible patient. Subsequently,

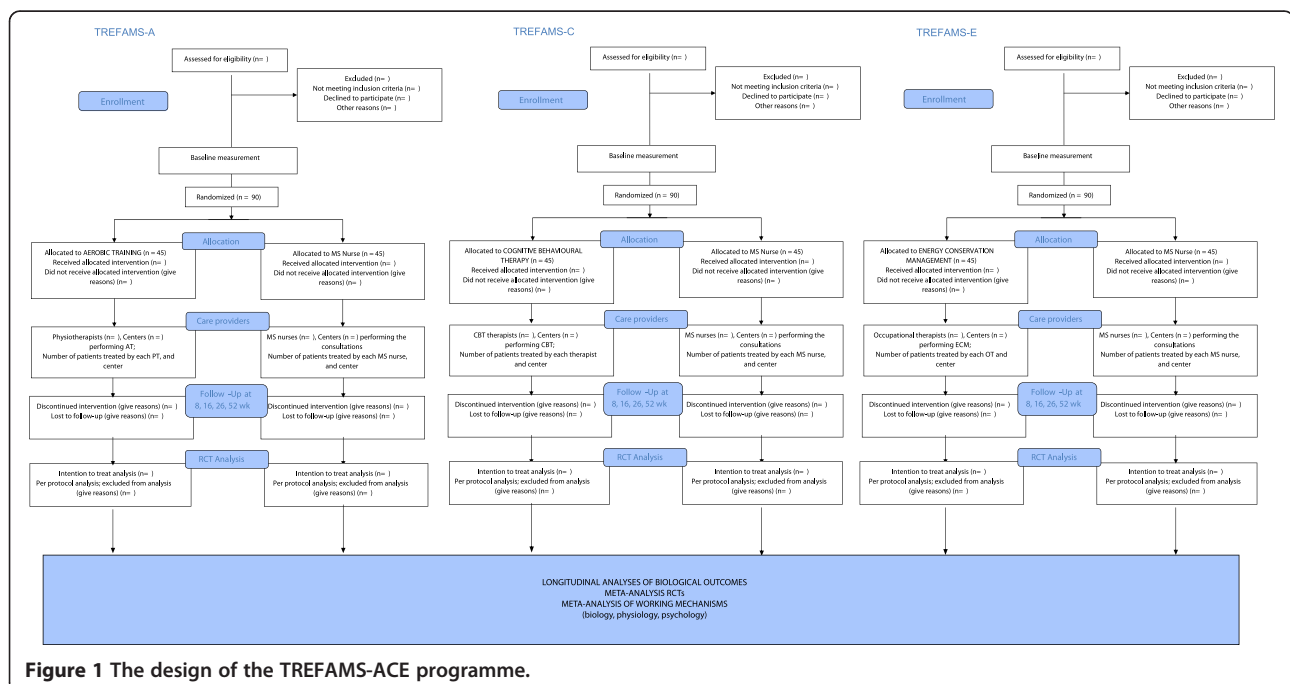


Figure 1 The design of the TREFAMS-ACE programme.

Table 1 Inclusion and exclusion criteria TREFAMS-ACE trials

Inclusion criteria	Exclusion criteria
Definitive diagnosis of MS	Depression (HADS depression >11)
Severely fatigued (CIS20r-fatigue ≥ 35)	Primary sleep disorders
Aged between 18 and 70 years	Severe co-morbidity (CIRS item scores ≥ 3)
Ambulatory patients (an EDSS score ≤ 6)	Current pregnancy or having given birth in the past 3 months
No evident signs of an exacerbation or a corticosteroid treatment in the past 3 months	Pharmacological treatment for fatigue in the past 3 months
No infections (normal leukocytes and C-reactive protein in blood)	Non-pharmacological therapies for fatigue in the past 3 months
No anaemia (normal haemoglobin and haematocrit in blood)	
No thyroid dysfunction (normal thyroid stimulating hormone (TSH) in blood)	

patients eligible for participation will be asked to complete an informed consent form before participating in the study.

Interventions

Aerobic training (AT)

AT aims to improve the participant's fitness and consists of 12 physiotherapist-led exercise sessions on a bicycle ergometer (Table 2). Moreover, participants will be provided with an identical bicycle ergometer at home on which they will be asked to perform additional training sessions, leading to the recommended three sessions per week. Each 30-min interval-type training session consists of six cycles of 5 min. Each cycle consists of 3 min of low intensity exercise, 1 min of moderate intensity exercise and 1 min of high intensity exercise. At the start of the treatment and after 8 weeks of training, current fitness levels will be assessed with a graded maximal exercise test to volitional exhaustion. Following the 8-week maximal exercise test, exercise intensities will be adjusted to meet the newly obtained fitness level. After completion of the supervised training programme, patients will be encouraged to continue exercising and to remain physically active. Generally, physiological adaptations to aerobic training occur when: (1) the training intensity is at least 60% VO₂max, and (2) the training is

carried out at least three times a week [40]. The current treatment protocol addresses both factors.

Cognitive behavioural therapy (CBT)

CBT is directed at behaviours or cognitions that perpetuate fatigue. Examples are dysfunctional cognitions with respect to MS, fatigue or pain, persistent focusing on symptoms, deregulation of physical and social activities and a lack of social support [41,42]. It is thought that fatigue will decrease if these perpetuating factors are identified by the patient him/herself and changed. CBT consists of 12 sessions over a 4-month period. Ten different modules have been developed to target specific fatigue maintaining factors [43] (Table 3). CBT will be customised to each individual patient using indicator criteria for each module that are based on cutoff scores on questionnaires and on a diagnostic interview (Table 3). In the final therapy sessions, special attention will be paid to integrating the skills obtained into daily life and how to handle behavioural relapses. The effectiveness of this theory-based CBT strategy has already been investigated in several other patient populations and healthcare settings [44-48].

Energy conservation management (ECM)

The ECM treatment protocol is based on a group course for energy conservation developed by Packer et al. [37].

Table 2 AT programme

45-min session of bicycle ergometer training	Details
Warming-up	• 5 min at 25% to 40% Wmax
Aerobic training	• Six cycles of 5 min: 3 min 40% Wmax, 1 min 60% Wmax and 1 min 80% Wmax • Cadence: 60-80 revolutions per min (rpm) • Heart rate should not exceed 80% of the predicted maximal heart rate • Training intensity will be updated once during the training, according to the 8-week maximal exercise test • The work rate can be adjusted, based on the clinical expertise of the supervising physiotherapist
Cooling down	10 min • All training sessions and adjustments to the work rate are recorded in the training log
Home exercises	Participants will be provided with an identical bicycle ergometer at home so that they can perform additional training sessions, leading to the recommended three sessions per week

Table 3 CBT modules

Module	Questionnaires and instruments
<p>1. Formulating goals</p> <p>This module applies to all participants. Concrete and obtainable treatment goals are formulated during therapy. Goals comprise activities that the participant wishes to do when the fatigue has decreased or disappeared.</p>	For all participants
<p>2. Sleep/wake rhythm</p> <p>The importance of a regular sleep/wake rhythm and good sleep hygiene is explained to the patient. Furthermore, the sleep/wake rhythm of will be discussed and suggestions for improvement given.</p>	SIP sleep and rest ≥ 60 [49]
<p>3. Beliefs regarding MS</p> <p>Participants will receive realistic information about MS. Dysfunctional cognitions about MS or the future are identified and challenged, and the participant is supported in forming more functional cognitions. Problems regarding acceptance of the disease are also addressed.</p>	<p>Impact of Event Scale (IES) ≥ 20 [50]</p> <p>Pictorial Representation of Illness Measure (PRISM): Burden of MS heavier than burden of fatigue [51]</p> <p>Illness Cognition Questionnaire (ICQ), concentration ≤ 12 [52]</p> <p>Cognitive Behavioural Responses to Symptoms Questionnaire (CBRSQ) [53,54]:</p> <p>Resting behaviour > 14.3;</p> <p>All-or-nothing behaviour > 12.9;</p> <p>Symptom focusing > 15.5;</p> <p>Catastrophising > 12.6;</p> <p>Embarrassment > 16.4;</p> <p>Damage > 20.5;</p> <p>Fear avoidance > 15.3</p> <p>HADS [55]</p> <p>Depression > 9</p> <p>Anxiety > 9</p> <p>Fear of disease Progression Questionnaire (FoP-Q), ≥ 4 on at least 75% of the 34</p> <p>Anxiety items [56,57]</p>
<p>4. Beliefs regarding fatigue</p> <p>Participants are supported in changing dysfunctional views about fatigue such as a lack of self-efficacy, catastrophising fatigue and somatic attributions.</p>	<p>SES-28 fatigue ≤ 19</p> <p>Jacobsen Fatigue Catastrophising Scale ≥ 16 [58,59]</p>
<p>5. Focusing on fatigue</p> <p>The concept of persistent focusing on fatigue and its consequences are discussed. Participants practise redirecting their attention from fatigue to activities and other sensations. Talking about fatigue is discouraged.</p>	<p>Illness Management Questionnaire (IMQ), focusing on symptoms ≥ 4 [60]</p>
<p>6. Regulation of physical activity</p> <p>Depending on their level of activity, participants learn how to divide their activities, followed by a systematic increase in regular physical activity to obtain predefined goals.</p>	Activity Interview and Activity Monitor
<p>7. Regulation of social activity</p> <p>Patients are empowered to expand social activities and deal with problems that can arise during social interaction.</p>	<p>SIP social interaction ≥ 100 [49]</p> <p>SF36 social functioning ≤ 65 [61]</p>
<p>8. Regulation of mental activity</p> <p>Participants are supported with regards to practising and expanding mental activities such as working on the computer or reading. Participants learn how to deal with possible cognitive deficits such as concentration or memory problems.</p>	CIS20r concentration ≥ 18 [62]
<p>9. Role of the environment</p> <p>Unrealistic expectations of the environment are addressed and more realistic expectations are promoted. Participants learn how to express their limits and boundaries to 'significant others'.</p>	<p>Social Support List (SSL) [63]</p> <p>Discrepancies ≥ 50;</p> <p>Negative interactions ≥ 14</p>
<p>10. Handling pain</p> <p>Dysfunctional cognitions about pain are challenged and replaced by more functional cognitions.</p>	<p>SF36 bodily pain ≤ 60 [61]</p> <p>Pain Catastrophising Scale (PCS) ≥ 16 [64]</p>

The TREFAMS intervention, called Individual ECM treatment (IECM), is individualised and consists of 12 45-min sessions over 4 months, given by a trained occupational therapist. For the IECM, the original content of the Packer et al. group programme will be divided up to fit the 4-month treatment period. Attention will also be paid to individual learning and approaching styles to assimilate the programme contents. Motivational interviewing will be used as a communication technique to assist patients in exploring and resolving ambivalence to change. Table 4 shows the content of the IECM. A variety of teaching methods will be used, including providing information, discussions, long-term and short-term goal setting, practice activities and homework activities, to assist the patient's integration of energy conservation principles into the performance of everyday tasks. The aim of ECM is not so much to correct the underlying mechanisms of fatigue, nor to accept that the solution is to decrease activity levels or reduce the breadth and extent of activities. Instead, the aim is to promote a positive attitude aimed at active decision-making and the optimum use of the available energy to fit the unique needs of each individual. ECM is also intended to reduce the impact and severity of fatigue, to increase patients' use of energy-conserving strategies and to improve their confidence in their ability to manage fatigue [37].

MS-nurse consultations

The low-intensity treatment by experienced MS-nurses consists of three consultations of 45 min over a 4-month period. The content of the consultations led by the MS-nurse will cover two important aspects to control for: (1) reliable information on MS-related fatigue; and (2) attention from an experienced MS professional in order to reassure the patient that his/her concerns or questions will be taken seriously [65]. In the first consultation, the patient receives a booklet containing general information about MS-related fatigue and factors that may influence fatigue. This booklet was designed by the TREFAMS-ACE research team to provide patients with standardised information about fatigue, without adding details regarding specific interventions so as to avoid overlap with the trial-specific interventions. In the remaining two consultations, participants will have the opportunity to discuss their personal experiences in coping with fatigue, ask questions about the booklet and discuss other fatigue-related issues. The consultations with the MS-nurses should not be considered as 'usual care' because, due to the TREFAMS-ACE study design, the MS-nurses are restricted in referring patients to a psychologist, physiotherapist or other healthcare professional within the hospital. In the Netherlands, timely referral is an important aspect of normal MS-nursing practice.

Table 4 Individual energy conservation management

Sessions	Content of the sessions
Introduction session	<ul style="list-style-type: none"> • Getting to know the patient, identification of problems in daily life with help of the COPM, impact of fatigue on daily life • Hand out workbook IECM, activity list per day/week to give insight in load and loadability of the patient, and learning style assessment
Analysis of the problems	<ul style="list-style-type: none"> • Discuss activity/participation problems, outcomes of load and loadability from the activity lists • Analysis of problems, determine questions of help, and the learning and approaching style • Formulate the problems and treatment goals
Treatment sessions	<ul style="list-style-type: none"> a. Information about fatigue <ul style="list-style-type: none"> • types, causes and factors influencing fatigue • banking (saving) and budgeting (deciding how to spend) energy b. Importance of rest <ul style="list-style-type: none"> • how fatigue can influence your daily life • rest as a way of relieving fatigue c. Balancing your schedule <ul style="list-style-type: none"> • components of a balanced lifestyle • how to balance (light and heavy) activities • planning a weekly schedule d. Communication <ul style="list-style-type: none"> • expressing needs to others • breaking down negative attitudes about fatigue and rest e. Priorities and standards <ul style="list-style-type: none"> • breaking down activities in order to simplify them as much as possible • budgeting energy, making decisions about priorities and standards f. How to do activities g. Ergonomics, body positions and assistive devices <ul style="list-style-type: none"> • organisation of needed environments (work, home) to promote good body mechanics • Organisation of needed environments to save energy • Technology and equipment that can save energy • Structure of body/biomechanics • How to use body properly/ergonomics
Evaluation session	

Therapist training

All involved therapists were selected based on their experience with the intervention and with treating MS patients. Furthermore, all received training that was focused

on one of the four treatment protocols used in the TREFAMS-ACE study.

Physiotherapists experienced in cardio-respiratory training were introduced to the exercise protocol, the use of the bicycle ergometer, study materials and measurements in TREFAMS-AT.

The psychologists involved in the TREFAMS-CBT study all received an additional 4-day CBT training course at the Expert Centre Chronic Fatigue of UMCN. The training course consisted of an introduction to the protocol, training in the content of each treatment module and how to determine which modules are indicated for a specific participant. The skills needed to change patient cognition and behaviours were practised during role-playing, with the help of simulated patients. To ensure the quality of the CBT, weekly peer conversations between therapists, in which experiences with the TREFAMS-CBT participants will be shared, are part of the therapist training.

Occupational therapists already familiar with energy conservation strategies and the Packer group course 'Managing Fatigue' received a 1-day training course in the implementation of the individual Energy Management Course (IECM). This course was given by the researcher, together with an expert therapist in energy conservation management. Training consisted of a thorough explanation of the content of the 12 sessions and how sessions can be individually tailored. In addition, occupational therapists not yet qualified in applying Motivational Interviewing had to attend a 3-day Motivational Interviewing course.

All MS-nurses involved in one of the RCTs participated in a 1-day training course. In this course the MS-nurses shared their approach to taking a fatigue-related nursing history, they were instructed as to how to provide relevant information on MS-related fatigue without giving concrete therapeutic advice, and they were informed of the restrictions concerning the referral of patients to other healthcare professionals within the hospital (MS team members). These newly-learned skills were practised using role-playing.

Outcome measures

Outcome measures consist of validated self-reported questionnaires, blood and saliva, activity monitoring and physical fitness tests. All primary and secondary outcomes will be assessed 1 week prior to, and at 0, 8, 16, 26 and 52 weeks after randomisation. The self-reported questionnaires will be offered to patients via the internet or on paper, and will be completed at home. Within each self-reported questionnaire, the sequence of questions will be randomised between measurement occasions. The drawing of blood samples (according to the study protocol), physical fitness tests and assessor-based interviews will take place at the outpatient clinic of the participating

centres. Saliva sampling will take place at home and includes several time-points per day.

Primary outcome measures

1. Fatigue will be measured with the Checklist Individual Strength (CIS20r), domain fatigue [62,66]. This multidimensional questionnaire consists of 20 items, divided into four dimensions of fatigue and related behavioural aspects, including: (a) the subjective experience of fatigue (8 items); (b) reduction in motivation (4 items); (c) reduction of physical activity (3 items); and (d) reduction in concentration (5 items). The CIS20r focuses on fatigue in the past 2 weeks. Each item is answered using a 7-point scale. The CIS20r fatigue score is a sum score that can vary between 8 and 56 points. Recently, the reproducibility, distribution-based responsiveness and concurrent validity of the CIS20r were investigated in patients with MS [67]. Despite good test-retest reliability, a smallest detectable change of 11.8 points was found, leading to the recommendation to monitor trial participants repeatedly over time using a set of complementary fatigue scales [67]. A systematic review of the measurement properties of 31 fatigue questionnaires confirms this recommendation [68].

2. Societal participation will be assessed with the Impact on Participation and Autonomy questionnaire (IPA) [69]. The IPA questionnaire was developed to assess the severity of restrictions in participation and individual needs related to participation and autonomy. The IPA is a generic questionnaire that addresses: (a) perceived participation, reflected in 31 items in five domains, that is, autonomy indoors, autonomy outdoors, family role, social relations, work and education; and (b) the experience of problems related to every aspect of participation, reflected in eight problem experience scores [69]. An anchor-based responsiveness study in a heterogeneous outpatient rehabilitation population showed that the IPA was moderately able to detect within-patient improvement over time [69]. No studies on the responsiveness and minimal important change of the IPA in patients with MS are yet available [70].

Secondary outcome measures

MS-related fatigue is a multifaceted symptom with various types of expression. Therefore, several other fatigue measures are also included. The impact of fatigue will be measured with the Modified Fatigue Impact Scale (MFIS) and the Fatigue Severity Scale (FSS) [71,72]. The MFIS assesses the effects of fatigue in terms of physical, cognitive and psychosocial functioning. The FSS evaluates the severity and impact of fatigue in patients with MS. A patient-reported diurnal course of fatigue during 1 day will be assessed using short message services (SMS) technology. Moreover, the Rehabilitation Activities

Profile (RAP) and the Medical Outcome Study Short Form 36 (SF36) will be used to measure daily functioning and participation [61,73].

Determinants

These include descriptive variables, mediators (that is, intervening causal variables), confounding or effect-modifying factors that have been shown to be related to the interventions, and fatigue and participation in MS patients [53,74]. In multifactorial, complex situations such variables can act in different ways in different situations or different analyses and will therefore be further specified in forthcoming articles.

Demographic and disease characteristics

Demographic information includes age, gender, ethnicity, living situation, level of education, work and income. The disease-related variables that will be assessed include the type of MS, neurological symptoms, the Expanded Disability Status Scale (EDSS), the number of exacerbations in the year prior to inclusion, the use of disease modifying drugs and other medication, comorbidities and healthcare use. The EDSS and the Cumulative Illness Rating Scale (CIRS) will be assessed by a physician at baseline and after 52 weeks [75-77]. Cognitive deficits will be assessed at baseline by the Mini Mental State Examination [78].

Physical activity and physical fitness

The amount of physical activity and frequency of movement will be registered by means of a tri-axial activity monitor (ActiGraph GT3X+) that will be worn for 7 days. The Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) is a self-reported questionnaire that assesses physical activity over the preceding 7 days. The PASIPD assesses physical activity in three domains: recreation, household and occupation activities [79,80].

In a subgroup of participants, cardio-respiratory fitness will be assessed by means of a maximum capacity test (VO₂max test). Participants will perform this test on an electromagnetic bicycle ergometer. Work rate will be progressively increased by 25 + 10 W/min (women) or 25 + 15 W/min (men) until volitional exhaustion, rpm <45 or for safety reasons. In addition, patients will walk as far as possible during a 2-min walk test (2MWT).

Cognitive and behavioural factors

Coping style is measured with the Coping Inventory for Stressful Situations (CISS-21) [81,82]. Three main coping styles can be distinguished: task-oriented coping, emotion-oriented coping and avoidance coping. The General Self Efficacy Scale will be used to assess optimistic self-beliefs for coping with a variety of difficult life demands [83]. Possible mood disorders will be assessed

with the Hospital Anxiety and Depression Scale (HADS) [55]. The HADS consists of two subscales: depression and anxiety. The tendency to fall asleep during daytime is measured with the Epworth Sleepiness Scale [84]. Perceptions of fatigue will be measured with the Brief Illness Perception Questionnaire (B-FPQ), which assesses cognitive and emotional representations of fatigue [53]. The B-FPQ is an adaptation of the Brief Illness Perception Questionnaire (B-IPQ), which measures illness perceptions [85]. Fear of progression of MS is measured with the Fear of disease Progression Questionnaire (FoP-Q) [56,57]. Five factors are distinguished: affective reactions, partnership/family, work, loss of autonomy and coping. The Illness Cognitions Questionnaire (ICQ) measures three different generic illness cognitions: helplessness, acceptance and disease benefits [52]. The Social Support List is used to measure the level of social interactions, discrepancies and negative interactions [63].

Biological markers

An important part of the TREFAMS research programme concerns the integration and longitudinal study of clinical parameters and biological parameters [38]. HPA-axis functioning will be assessed through the collection and analysis of salivary cortisol. To determine the Cortisol Awakening Response (CAR), saliva will be collected immediately after awakening and after respectively 30 min, 45 min and 60 min post-awakening. Following the fifth sample at 22:00 the participant takes 0.5 mg dexamethasone (low dose dexamethasone suppression test) and saliva is again collected the next morning, immediately after awakening.

Blood will be drawn to determine levels and activity of pro- and anti-inflammatory cytokines [39,86]. Blood and saliva will be collected at the same fixed time-points as for the other outcome measures.

Energy saving strategies

To assess which strategies the participants in all three RCTs use to influence their fatigue, we developed the Fatigue Strategies Questionnaire (FSQ). This questionnaire is based on the Energy Conservation Strategies Survey (ECSS) [87] to which we have added a number of strategies on physical activity, cognition and behaviour. Participants will be asked about the strategies they use and how effective these strategies are. To facilitate the meta-analysis of ECM interventions, the participants of the TREFAMS-ECM trial will fill in the original ECSS at 16 weeks [87].

Sample size

Sample size was calculated based on the CIS20r subscale fatigue. In order to detect a clinically relevant difference of 8 points on the CIS20r subscale fatigue between the study groups in an MS population, with a SD of 12.7, a power of

80%, an alpha of 0.05 and an attrition rate of 20%, 45 patients per group will be needed [47,88]. This amounts to 90 patients for each trial and 270 patients for the entire TREFAMS-ACE programme. Sample size calculation was not adjusted for longitudinal data analyses with repeated measures [89], or for an eventual clustering by care providers or participating centres. Balancing these two factors, we expect that the power of our study will be >80%.

Randomisation

Patients eligible for participation in the study will be randomised to either the trial-specific intervention or the consultations with the MS-nurse after the baseline measurements have been completed. The randomisation scheme is computer-generated with random variable block sizes. An independent investigator within each main study centre will need to login to the web-based randomisation facility to carry out the randomisation, and will inform the patient and the therapist as to the therapy allocation.

Blinding

The assessors responsible for physical fitness tests and interviewer-based measures will be told in which week patients need to be measured but will not know which treatment patients receive. Patients will be instructed not to disclose which treatment they are receiving. Furthermore, the analyses of blood and salivary in the clinical chemistry laboratory, and the statistical analyses of the between-group differences, will be performed by research staff blinded to the treatment allocation of the participants.

Serious adverse events

Based on previous research, AT, CBT, ECM and consulting the MS-nurse are expected to be safe treatment methods in patients with MS [16-21,23-26,90,91]. However, all therapists and assessors involved in the studies will be instructed to report all serious adverse events (SAE) to the principal investigators, after which they will be reported to the Medical Ethical Committee. An SAE is any untoward medical occurrence in a participant that is not necessarily associated with the treatment, but that is lethal, and/or threatens the life of the participant, and/or requires hospitalisation or prolongation of existing hospitalisation, and/or causes persistent or significant disability or incapacity.

Treatment fidelity and compliance

Data regarding therapy compliance will be subtracted from the administrative hospital databases and therapist notes. Participants will receive an overview of all appointments prior to the first session. If participants cancel or do not attend a session, this session will be rescheduled within the 16-week time frame. Because therapy consists of 12 therapist-led sessions in 16 weeks, some rescheduling is

possible. Sessions will not be rescheduled if that means that the 16-week time window will be extended by >1 week.

Statistical analyses of the RCTs and meta-analyses

The primary analyses of each separate RCT will be based on the intention-to-treat principle using longitudinal data-analysis techniques, such as Generalised Estimating Equations or Hierarchical Linear Mixed Models. To detect the direct effects of the interventions, longitudinal models will be constructed to analyse the differences between the intervention groups regarding the course of within-group changes during the 1-year follow-up period. Furthermore, a meta-analysis of all TREFAMS-ACE data will be conducted to investigate the relative effects of each treatment strategy. In addition, statistical mediation analyses will be used to examine the working mechanisms of the interventions related to, among others, changes in HPA-axis functioning and changes in pro- and anti-inflammatory cytokine levels.

Discussion

The TREFAMS-ACE study will investigate the effectiveness of three different non-invasive, non-pharmacological rehabilitation treatment strategies aimed at reducing fatigue and improving societal participation in patients with MS. Furthermore, the mechanisms that underlie treatment effects will be studied. This research programme is expected to produce four related PhD-theses. By publication of the design, we wish to be fully transparent as to the quality of the TREFAMS-ACE programme and thus aim to avoid most of the methodological weaknesses reported in current Cochrane reviews in the field of rehabilitation [92-95].

The TREFAMS-ACE study has a number of important strengths, the first of which is a design including three almost identical RCTs on the effectiveness of AT, CBT and ECM, respectively. Our study may provide greater insight into the exact pathophysiological mechanism(s) behind MS-related fatigue and the pathways through which AT, CBT and ECM exert their effect. Because the same design and the same outcome measures are used, at the end of the TREFAMS study an overall analysis can be performed that allows factors to be controlled for that might otherwise cause heterogeneity in a regular meta-analysis of independent RCTs. This will enable a close comparison of the treatment strategies within each trial as well as a strong overall meta-analysis. Second, the large cohort of fatigued MS patients that will be formed will enable us to study the biological mechanisms that explain fatigue and the mechanisms underlying the possible effectiveness of the treatment strategies. Recently, Fischer *et al.* [38] formulated four criteria for biomarker selection in clinical trials: the biomarker has to be linked to the clinical outcome, that is, MS-related fatigue in our study, and the biomarker should be modifiable in

the desired direction. Furthermore, the biomarker should be validly and reliably measured, and finally, the duration of the clinical trial should be sufficiently long, with an appropriate number of assessments, to allow the biological and clinical outcome parameters to change. All four criteria will be fulfilled by the TREFAMS-ACE programme [86,96]. Third, due to the follow-up period of 1 year, we will be able to investigate whether patients implement the newly-learned skills in daily life and whether the effect of therapy will be maintained over a longer period of time. Fourth, the baseline data of the three RCTs can be pooled, allowing several interesting cross-sectional analyses. Fifth, there is valuable support from the Dutch patient organisation, MSVN. The participation of patient organisations in health research is important when setting research agendas, during the design phase and during the study period, but it will also enhance practical relevance during later dissemination and implementation of study results [97]. Finally, a strong network of academic rehabilitation departments and MS centres will be formed, as the four study teams work together closely. This will generate high quality knowledge on the treatment of MS-related fatigue and will also promote dissemination and sharing of expertise.

Some specific issues that apply to non-pharmacological trials included in the TREFAMS-ACE programme need to be discussed [28]. Regarding the blinding procedure, everyone involved in an RCT should ideally be blinded but this is not always feasible, as is often the case in RCTs evaluating rehabilitation interventions [28,98,99]. Although patients are not blinded and the two primary outcome measures are both patient-reported, the assessment of the physical fitness parameters, the analyses of blood and salivary in the clinical chemistry laboratory and the statistical analyses of the between-group differences will all be performed by research staff blinded to the treatment allocation of the participants.

With respect to the complexity of the interventions, we decided to offer patients individual and mono-disciplinary interventions, and no multidisciplinary group intervention [100-102]. Two of the four active treatment intervention programmes, that is, CBT and ECM, have long been available and further improved in recent years [30]. The AT programme is largely based on the general principles of exercise physiology [40]. The scientific underpinnings of the valuable work of specialised MS-nurses is probably the weakest aspect.

Contamination of treatment interventions is another specific issue that might complicate the interpretation of the study results. To avoid contamination via caregivers in the same study centres, we designed three independent RCTs. Moreover, to avoid overlap between the CBT and the ECM interventions, in the developmental phase of the individual ECM protocol cognitive behavioural

aspects were further specified and should now totally focus on managing energy. To prevent contamination caused by participants, all participants are requested not to start with co-interventions for fatigue during the treatment period of the study. Because of the intensity of the treatment, we expect that simultaneous interventions aimed at reducing fatigue will probably only occur in a small number of patients. Other co-interventions, for example, disease modifying drugs, are monitored throughout the study at every measurement.

Finally, the inclusion of participants may be slower than anticipated. In theory, a large number of MS patients are fatigued but it may be difficult to awaken the interest of every fatigued MS patient. To enhance participation, we arranged a number of patient-friendly measures, such as the setting-up of several study centres, travel allowance and the scheduling of appointments. In order to recruit a large group of MS patients, we enlarged our network by involving regional patient associations. In this respect, the support of and close cooperation with the Dutch patient organisation Multiple Sclerosis Vereniging Nederland (MSVN) since the design phase of the research programme has been very important.

The TREFAMS-ACE study will provide insight into the effectiveness of four mono-disciplinary rehabilitation treatment methods for MS-related fatigue in individual patients. The primary aim of these treatment methods is to reduce fatigue and to improve societal participation. Furthermore, to enhance our understanding of how these rehabilitation interventions work, a study on biological outcome measures has been added. To improve current practice, tailored and more focused rehabilitation programmes based on the most effective treatment may represent - with a clearer picture of mechanisms of action - a first step in understanding which types of patients may better respond to certain therapies. Therefore, the TREFAMS-ACE results will also be added to systematic reviews [29,30] and used to develop and update clinical practice guidelines for the treatment of MS-related fatigue [8,103].

Trials' status

Patient recruitment commenced in October 2011. At the time of manuscript submission 104 patients have been randomised.

Abbreviations

AT: Aerobic training; B-IPQ: Brief Illness perception questionnaire; CBRSQ: Cognitive and behavioural responses to symptoms questionnaire; CBT: Cognitive behavioural therapy; CIRS: Cumulative illness rating scale; CIS20r: Checklist individual strength; CISS: Coping inventory for stressful situations; CNS: Central nervous system; COPM: Canadian occupational performance measure; ECM: Energy conservation management; EDSS: Expanded disability status scale; FSQ: Fatigue strategies questionnaire; FSS: Fatigue severity scale; HADS: Hospital anxiety and depression scale; HPA-axis: Hypothalamic-pituitary-adrenal axis; IECM: Individual energy conservation management; IES: Impact of event scale; ICQ: Illness cognition

questionnaire; IMQ: Illness management questionnaire; IPA: Impact on participation and autonomy; MFIS: Modified fatigue impact scale; MS: Multiple sclerosis; OT: Occupational therapist; PCS: Pain catastrophising scale; PRISM: Pictorial representation of illness measure; PT: Physiotherapist; RCT: Randomised clinical trial; SAE: Serious adverse events; SES-28: Self-efficacy scale 28; SF36: Medical outcome study short form 36 items; SIP: Sickness impact profile; SSL: Social support list; TREFAMS-ACE: Treating fatigue in multiple sclerosis - aerobic training, cognitive behavioural therapy, energy conservation management; TSH: Thyroid stimulating hormone; UMCN: University medical centre Nijmegen; VO2max: Maximum oxygen consumption; Wmax: Maximum work rate.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

HB and VG are the principal investigators and originated the idea for the study, developed the overall design and obtained funding for the TREFAMS-ACE research programme. MH will conduct the AT trial, LB will conduct the ECM trial and AM will conduct the biomarker study. All authors helped in finalising the manuscript. All authors read and approved the final manuscript. The TREFAMS-ACE study group advises the principal investigators and supervises the PhD students.

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