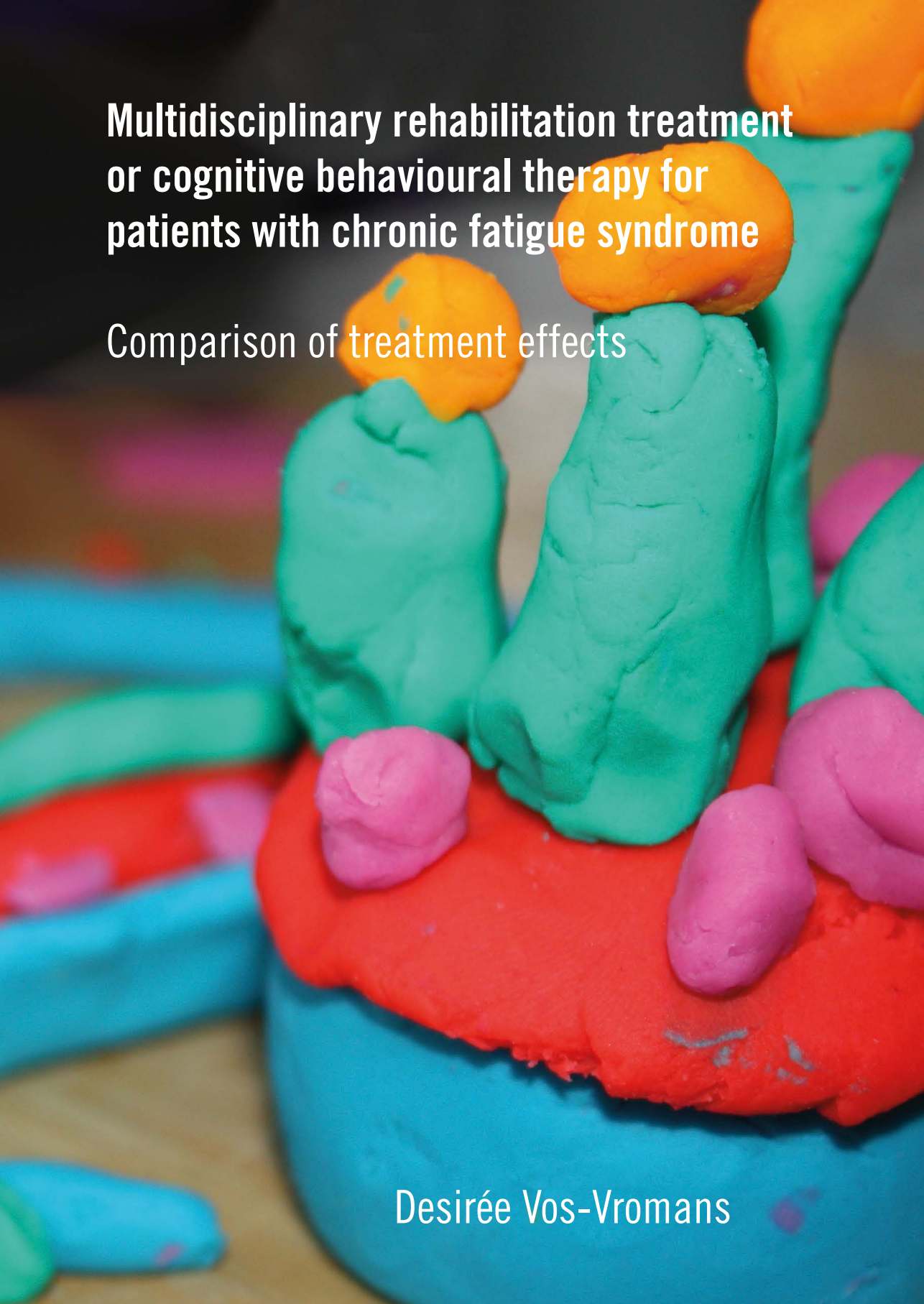
Multidisciplinary rehabilitation treatment or cognitive behavioural therapy for patients with chronic fatigue syndrome



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Comparison of treatment effects

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The research presented in this thesis was conducted at the School for Public Health and Primary Care: CAPHRI, Department of Rehabilitation Medicine of Maastricht University. CAPHRI participates in the Netherlands School of Primary Care Research CaRe. All studies presented in this thesis were performed at Revant, Rehabilitation Centre Breda (Breda, the Netherlands), Adelante, Centre of Expertise in Rehabilitation and Audiology (Hoensbroek, the Netherlands), Rehabilitation Centre Blixembosch (Eindhoven the Netherlands) and Reade Centre for Rheumatology and Rehabilitation (Amsterdam, the Netherlands).

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Contents

1

General introduction

CHRONIC FATIGUE SYNDROME

A 34-years old female patient with complaints of fatigue for approximately one year, talking about her diagnosis.

'The family doctor just said: you're depressed. But I'm not depressed. I can do everything with my head, but my body doesn't want to.

['Mijn huisarts zei, je bent gewoon zwaar depressief. Maar ik ben niet depressief. Ik kan alles met mijn hoofd, maar mijn lijf wil gewoon niet.']

Almost everyone experiences fatigue from time to time. In general, the fatigue disappears after a period of rest. However, in some people the fatigue does not disappear but persists and starts to place a substantial burden on them, their families and their careers, and hence on society. If the fatigue persists for more than 6 months, it is often called chronic fatigue. Chronic fatigue might be a result of an organic disease, like multiple sclerosis or cancer. When the underlying illness is not present or detected, a patient often is diagnosed with chronic fatigue syndrome (CFS). Although different definitions regarding CFS exist, the criteria of the US Centers for Disease Control and Prevention-94 (CDC-94) are used in the study presented in this thesis[1]. According to the CDC-94 criteria, CFS diagnosis requires: persistent or relapsing unexplained fatigue with a new or definite onset, which has endured for at least 6 months. The fatigue must not be the result of an organic disease or ongoing exertion. In addition, this fatigue is not alleviated by rest and results in substantial limitations in occupational, educational, social and personal activities. Four or more of the following symptoms have to be present for more than 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep, or malaise after exertion[1].

Although different symptoms are present, fatigue is the most prominent and disabling symptom for the majority of the patients. During treatment, the personal aim of most patients is to achieve 'a reduction of fatigue'. Therefore the study presented in the thesis was named "FatiGo" as an abbreviation of "Fatigue-Go". In clinical practice a large variety in presentation of symptoms is seen. Some patients are confined to bed while others are able to work fulltime, but in both cases the fatigue limits their ability to a certain extend in doing what they want to do[2]. The prevalence of the syndrome is estimated between 0.2% and 2.6% worldwide depending on the definition used[3]. In the Netherlands, approximately 30.000-40.000 people suffer from CFS[4]. The mean age of a patient when diagnosed with CFS is between 29 and 35 years, and 75% of the patients is female[4]. Duration of the symptoms lies between 3 and 9 years[4].

In only a few countries, the burden of CFS to society was actually measured. In the United States, the annual direct total costs per patient were estimated between $2.342 and $8.675 depending on the sample used[5,6]. The annual total loss of productivity per patient in the US was estimated at $20.000[7]. In another study, based on a sample in the

United Kingdom, annual productivity costs per patient were estimated at £22.684[8]. In the Netherlands, the annual costs for healthcare of patients with unexplained physical symptoms, including CFS, were estimated at €3.123 per patient[9]. These healthcare costs together with the annual work-related costs and paid substitution of domestic tasks were estimated at €6.815 per patient[9], which can be viewed as an indication of the total annual societal costs per patient. This also gives an indication of the high economic burden related to unexplained physical symptoms, and emphasizes the need to investigate new treatments and their benefits to the individual patient as well as to society.

MODELS EXPLAINING THE PERPETUATION OF CFS

The etiology of CFS is unclear. Many immunological, viral, psychological and neuroendocrinological mechanisms have been hypothesized[3]. There is a lack of conclusive evidence for any of these hypotheses. In order to understand and improve treatments, several researchers proposed a working mechanism model regarding the development and perpetuation of fatigue in patients with CFS. In 1998, Vercoulen presented an empirically and statistically tested model of CFS with different perpetuating factors (Figure 1)[10]. The model presents factors that may influence the fatigue and impairments in patients with CFS. The conviction that the symptoms have a somatic cause, decreases the physical activity, which in turn increases the fatigue and leads to disabilities. A stronger focus on bodily symptoms both increases the fatigue and the impairments. Prins et al introduced social support in the model in 2004[11]. Perceiving a lack of social support, or perceiving social support focusing on the symptoms, are both associated with more fatigue. This model provides the theoretical framework for cognitive behavioural therapy (CBT), an often applied approach aiming to change the perpetuating factors of CFS.

Another model, designed to understand health and illness, is the biopsychosocial model. The principle of the biopsychosocial model states that all issues relating to health are products of a complex interplay of biological, psychological and social factors. In 1977 Engel first introduced the model[12]. Following this model, various precipitating, predisposing and perpetuating factors interact, resulting in multiple pathways leading to the development and persistence of CFS. This model is used in multidisciplinary rehabilitation treatment (MRT), which addresses those components that are thought to be modifiable and have a strong relation with the precipitation, predisposition and perpetuation of CFS. These components and the personal goals of a patient are the focus of MRT and the interventions used are tailored to the individual patient.

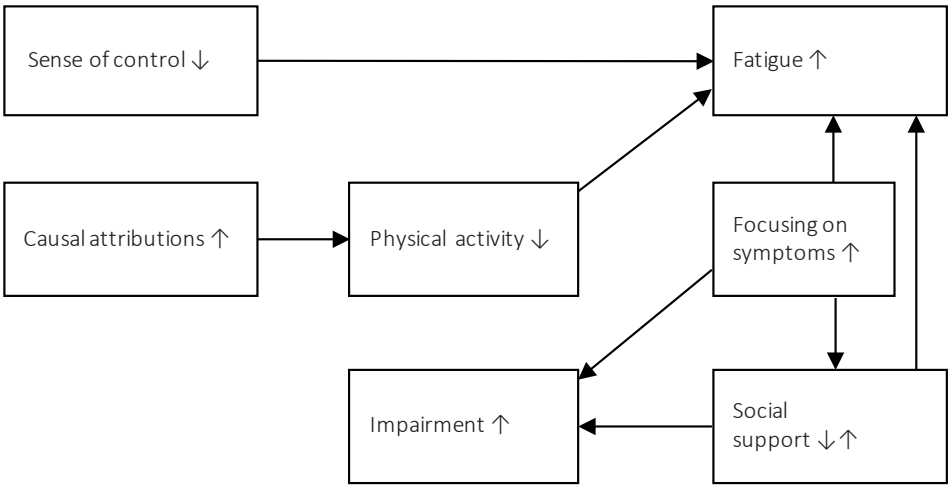

Figure 1. Model of perpetuating factors of CFS by Vercoulen and Prins with directions added

TREATMENT OF CFS

Before the start of the trial, a number of rehabilitation centres in the Netherlands, including Revant, provided multidisciplinary rehabilitation treatments to patients with chronic pain. During clinical practice, it was noticed that chronic pain was often accompanied by chronic fatigue, and sometimes chronic fatigue was the main (or only) complaint of the patient. The growing number of referred patients with chronic fatigue and CFS increased the need to develop a MRT specific for patients with CFS. Revant developed MRT, which is based on the biopsychosocial model of CFS as described earlier. In MRT, a consultant in rehabilitation medicine, a psychologist, a social worker, a physical therapist and an occupational therapist all coach the patient. MRT consists of an observational, treatment, and a follow-up phase. During the observational phase the patient is thoroughly assessed by the different therapists. In MRT, the protocol is patient centred and based on addressing those components that are thought to be modifiable and have a strong relation with the precipitation, predisposition and perpetuation of the CFS. These components and the personal goals of a patient are the focus of the treatment. After identifying the modifiable components and the personal goals, treatment aims are determined and the therapists provide an indication how the interventions will be used to achieve the personal goals. During the treatment phase various interventions are combined and tailored to the individual needs following the individual rationale. CBT and elements such as gradual reactivation, pacing, mindfulness, body awareness therapy, normalising sleep/wake rhythm and social reintegration, can be combined. After the treatment phase, a follow-up phase is planned in which the patient is supposed to apply the learned principles at home. During 2 visits with the social

worker and 2 therapists selected by the patient, the present situation is evaluated and issues of social reintegration and participation are addressed. After the development of MRT, this treatment was implemented in Revant. In 2006, when the study presented in this thesis was developed, only few studies had reported results of a multidisciplinary approach in peer-reviewed scientific journals. Two uncontrolled studies among young people[13,14] reported positive effects of multidisciplinary interventions. Viner et al (2004)[13] assessed the outcome of multidisciplinary rehabilitation group-treatment (graded activity/exercise programme, family sessions, and supportive care), compared with supportive care alone for young patients (aged 9-17 years) with CFS. Results showed positive effects of multidisciplinary rehabilitation treatment on wellness, school attendance and a decrease of fatigue. A study by Voet et al (2007)[14] in adolescents with chronic pain and fatigue also showed positive effects on fatigue severity, school/work attendance and general health after multidisciplinary rehabilitation treatment. Before the start of the trial only one RCT[15] describing the effectiveness of a rehabilitation treatment for patients with CFS was published. Taylor et al designed a group program led by a peer counsellor and himself. Although different group topics were included in the program that might have some similarity with MRT (e.g. activity pacing, cognitive coping skills training, and addressing employment issues and personal relationships), the whole package of interventions is not the same as in MRT, and patients were not coached by a multidisciplinary team. Results showed a significant decrease of fatigue and an increase in quality of life in patients after rehabilitation compared to the patients in the delayed program control group. Later, in a nonrandomized study of Torenbeek et al[16] a multidisciplinary group program with a combination of clinical and outpatient treatment in a rehabilitation centre was evaluated. A consultant in rehabilitation medicine, a psychologist, a physical therapist, a social worker, an occupational therapist, an exercise and sports coach and a group leader coached the patients. Treatment was based on the principles of CBT and graded activity. After treatment, patients experienced significantly less fatigue, less impairments and a better physical functioning.

A 49-years old female with complaints of fatigue for more than 5 years talking about her expectations before treatment.

'I have taken so many medications, and paid visits to the doctor, this is all I can do. If this isn't working I have to accept, but I can't, accept it. This is my last hope.'

['Ik heb al zoveel tabletjes geslikt, naar de dokter geweest, dit was echt mijn laatste iets eigenlijk. Als dit niet helpt, nou dan moet ik me erbij neerleggen. Maar dat kan ik ook niet, nee, ik kan me er niet bij neerleggen. Maar dit was dan wel mijn laatste strohalm.]

Although the treatments described seem to have some overlap, there was still a great variety in content among the studies investigating rehabilitation treatments for patients with CFS. They varied in interventions used, location of treatment, outcomes measured

and disciplines involved, which made it difficult to give an overall conclusion on the effectiveness of such rehabilitation treatments.

Therefore, in an uncontrolled pilot study in 2005, we evaluated MRT among 36 patients. The results were promising: fatigue severity and the impact of disease on emotional and physical functioning decreased significantly post treatment and the decrease persisted 12 months after start of treatment. Although the results of the above mentioned rehabilitation treatments for patient with CFS are promising, conclusions should be drawn carefully, because most studies, including our pilot were uncontrolled. Furthermore, none of the above mentioned studies included information about the cost-effectiveness of treatment, which might be important for the decision making process regarding treatment selection for practitioners as well as for policy makers. Therefore, these findings needed to be confirmed in a randomized controlled trial (RCT) including an economic evaluation.

During the preparation of our trial (2006-2008), different pharmacological and non-pharmacological treatments have been studied in relation to CFS. Of all studied treatments, CBT and graded exercise therapy (GET) were found to be the most effective treatments at the time[17,18] and CBT with elements of GET was the most commonly used treatment in the Netherlands. CBT is a psychotherapeutic approach in which elements of behavioural and cognitive approaches are incorporated. The model of Vercoulen[10], as described earlier, is used in CBT and the perpetuating factors are the focus of treatment. Via a dialogue with the psychologist or behavioural therapist, the patient is taught to change negative beliefs regarding symptoms of fatigue, self-expectation and self-esteem. Patients are encouraged to adopt a regular sleep/wake rhythm and gradually increase their physical activity by doing home-exercises. In studies of Tummers[19] and Heins[20], CBT is tailored for relatively active patients and passive patients. The relatively active patients, who have an activity pattern that is characterised by burst of activity followed by periods of rest, first have to attain a base level of activity without bursts before increasing the level of activity. Passive patients, who are characterized by an extremely low physical activity level, immediately start with a program of gradually increasing physical activities. In GET, treatment is aimed at increasing activity following a predefined schedule without paying attention to the fatigue[18]. Although proven effective, CBT and GET do not decrease fatigue severity or improve quality of life for all patients. Further research was needed to improve the management of CFS.

Therefore, a multi-centre RCT was developed to study the effectiveness of MRT compared to CBT. The main aim of the trial was to study which treatment, CBT or MRT, was the most effective and cost-effective in reducing fatigue and increasing quality of life, in patients with CFS.

OUTLINE OF THIS THESIS

The first and major aim of this thesis is to study which treatment, MRT or CBT, is the most effective in reducing fatigue severity and increasing quality of life, in patients with CFS. The studies in this thesis are all parts of the FatiGo trial of which the protocol[21] is described in *Chapter 2*. Patients referred to Rehabilitation Centre Blixembosch in Eindhoven, Adelante Rehabilitation Centre in Hoensbroek, Reade Centre for Rheumatology and Rehabilitation in Amsterdam, and Revant Rehabilitation Centre in Breda between November 2008 and February 2011 who met the inclusion criteria were asked to participate. Inclusion involved a multistage process to ensure suitability of the participants. After inclusion and baseline assessment, participants were randomly assigned to MRT or CBT. Both treatments took 6 months to complete and aimed to decrease fatigue severity and improve quality of life. Assessments of primary outcomes were conducted before treatment, and 26 weeks and 52 weeks after start of treatment. The results of this multi-centre RCT[22] are described in *Chapter 3*.

Both treatments, studied in the FatiGo trial, are currently recommended in the Netherlands for patients with CFS. In the trial, treatments were matched as closely to 'usual practice' as possible in order to provide a 'real-world' estimate of the comparative effectiveness and cost-effectiveness of the two treatments. A full economic evaluation was done as an integral part of the study. The aim of this economic evaluation was to investigate the one-year cost-effectiveness from a societal perspective comparing MRT and CBT in terms of reduction in fatigue, gain in health-related quality of life and gains in quality-adjusted life years. This economic evaluation is described in *Chapter 4*.

The protocol for CBT, studied in the trial, was specifically tailored for either relatively active or passive patients. The therapist responsible for CBT categorized the patient during the intake phase and then used the appropriate treatment protocol. However, evidence to support distinguishing relatively active from passive patients is limited. Therefore, the differences in actual and perceived physical functioning between active and passive patients with CFS were evaluated. In this study baseline (activity monitor) data from the FatiGo trial were used[23]. The study is described in *Chapter 5*.

To further improve the effectiveness of both MRT and CBT it is of importance to study factors that may influence the outcome of treatment. Two possible effect modifiers are expectancy and credibility. Expectancy is what the patient believes will occur after following treatment, and credibility is how believable, convincing and logical the treatment seems to the patient. Previous studies showed that these factors influence the outcome of rehabilitation treatment in patients with chronic pain. When these factors indeed would influence the outcome in patients with CFS, this might be a starting point to further improve treatment outcome. The major aim of the last study in this thesis was to

assess the influence of treatment expectancy and credibility on the outcomes of treatment. This study is described in *Chapter 6*.

Chapter 7 provides an overall description of the results of the presented studies, the methodological considerations, and the overall conclusions of all studies. Furthermore, implications for clinical practice will be given followed by recommendations for future research and future implementation of the results.

Finally, in *Chapter 8* valorisation opportunities of our findings are described.

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2

Cognitive behavioural therapy versus multidisciplinary rehabilitation treatment for patients with chronic fatigue syndrome: study protocol for a randomized controlled trial (FatiGo)

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ABSTRACT

Background. Patients with chronic fatigue syndrome experience extreme fatigue, which often leads to substantial limitations of occupational, educational, social and personal activities. Currently, there is no consensus regarding the treatment. Patients try many different therapies to overcome their fatigue. Although there is no consensus, cognitive behavioural therapy is seen as one of the most effective treatments. Little is known about multidisciplinary rehabilitation treatment, a combination of cognitive behavioural therapy with principles of mindfulness, gradual increase of activities, body awareness therapy, pacing and social reintegration. The difference in effectiveness and cost-effectiveness between multidisciplinary rehabilitation treatment and cognitive behavioural therapy is as yet unknown. The FatiGo (Fatigue-Go) trial aims to compare the effects of both treatment approaches in outpatient rehabilitation on fatigue severity and quality of life in patients with chronic fatigue syndrome.

Methods. One hundred twenty patients, who meet the criteria of chronic fatigue syndrome, fulfil the inclusion criteria and sign the informed consent form, will be recruited. Both treatments, take 6 months to complete. The outcomes will be assessed at 6 and 12 months after start of treatment. Two weeks after start of treatment, expectancy and credibility will be measured, and patients will be asked to write down their personal goals and score their current performance on these goals on a Visual Analogue Scale. At 6 and 14 weeks after the start of treatment, the primary outcome and three potential mediators; self-efficacy, causal attributions and present-centred attention awareness, will be measured. Primary outcomes are fatigue severity and quality of life. Secondary outcomes are physical activity, psychological symptoms, self-efficacy, causal attributions, impact of disease on emotional and physical functioning, present-centred attention awareness, life satisfaction, patient personal goals, self-rated improvement and economic costs. The effects of therapy conditions on the various outcomes will be compared using an intention-to-treat approach. Data will be analysed with mixed linear regression models.

Trial registration. Current Controlled Trials ISRCTN77567702.

Discussion. The results of the trial will provide information on the effects of cognitive behavioural therapy and multidisciplinary rehabilitation treatment at 6 and 12 months follow-up, mediators of the outcome, cost-effectiveness, cost-utility, and the influence of treatment expectancy and credibility on the effectiveness of both treatments in patients with chronic fatigue syndrome.

BACKGROUND

In chronic fatigue syndrome (CFS), patients experience extreme fatigue that is medically unexplained. Many patients feel limited in their daily activities, and are not able to work at all or as much as they did before their CFS started[1]. Social and leisure activities are reduced in most patients, and quality of life is low[2].

Of the current definitions of CFS[3], we use the definition of the US Centers for Disease Control and Prevention (CDC-94): a persistent or relapsing unexplained fatigue, of new or definite onset and lasting for at least 6 months, in which fatigue is not the result of an organic disease or ongoing exertion. Rest does not alleviate the fatigue, and there is substantial limitation of occupational, educational, social and personal activities. To support the diagnosis, four or more of the following symptoms should be present for more than 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep or malaise after exertion[4]. Three studies from the UK and the USA, using this definition, show prevalence rates between 0.23 and 0.50%[5-7]. In the Netherlands approximately 30.000-40.000 patients suffer from CFS[8].

The pathophysiology of CFS is unclear. Researchers have considered somatic (e.g. viral infection, dysfunction of the central nervous system, immune dysfunction and neuroendocrine responses) and psychosocial hypotheses. A commonly used hypothesis relates CFS to stress. According to Van Houdenhove[9], patients have a reduced effort tolerance, which might be interpreted as a fundamental failure of the stress system after a period of severe or prolonged physical and/or psychosocial stress in vulnerable individuals. The failure of the stress system may lead to disturbances in nervous system, hormone and immune system. Many studies have tried to investigate different parts of these systems, but the precise mechanisms are still unclear[3,10]. Although there is no consensus on the pathophysiology of CFS, most researchers and clinicians believe that the etiology is multifactorial[3,11].

Different predisposing, precipitating and perpetuating factors play an important role in the etiology of CFS[3]. Lifestyle and personality characteristics like neuroticism and introversion are examples of predisposing factors for developing CFS[3,12]. Acute physical or psychological stress are precipitating factors that may trigger the onset of CFS[13]. Cognitions, beliefs and attributions about complaints and behavioural factors such as persistent avoidance of activities are associated with an increase of symptoms[14]. Other perpetuating factors are a strong belief in a physical cause of the illness, a strong focus on physical sensations and poor sense of control over the complaints. Social processes, for example lack of social support, also contribute to the perpetuation of CFS[15].

Although many patients suffer from CFS, many parts of this syndrome are still unclear and need further research in order to understand the pathophysiology and etiology and to improve and customize treatment to individuals in accordance with the different pathophysiology and/or etiology.

Relevance

Many studies have investigated the effects of different treatments that are targeted towards one or two aspects of the complaints. Little is known about treatments that are targeted towards more aspects of the complaints and combine different interventions in multidisciplinary settings. Although a few treatments that are targeted towards one or two aspects of the complaints have significant effect on fatigue severity and quality of life, no consensus exists on the treatment of patients with CFS. Many patients try different therapies to overcome their fatigue, varying from pharmacological treatment (for example immunoglobulin therapy and fludrocortisone therapy) to non-pharmacological treatments (for example massage therapy and osteopathy). Several reviews[3,10,16-18] compare different treatments. Immediately post-treatment, cognitive behavioural therapy (CBT) and graded exercise therapy (GET) are the only interventions found to be beneficial in reducing the severity of fatigue symptoms when compared with usual care[18,19]. At medium term (with a maximum of 14 months after baseline), CBT is also more effective than usual care, in reducing fatigue severity[18]. The review by Edmonds et al[19] showed two studies that found no significant difference between GET and treatment as usual/ relaxation in severity of fatigue at medium term. On quality of life, one study investigating the benefits of CBT compared to usual care and found no significant difference post-treatment[18]. Three studies[20-22] analysed the change in quality of life between GET and treatment as usual, and found that the physical function sub-scale improved significantly with exercise therapy immediately post-treatment. Besides studies in which CBT and GET are compared to usual care, three studies[23-25], compare CBT with other psychological therapies. They provide evidence that CBT was more effective in reducing the severity of fatigue symptoms in patients with CFS post-treatment, but the evidence of medium- and long-term follow-up was inconsistent[18]. In three other studies[26,27,28] CBT was compared to GET and showed a lack of difference between both treatments in reducing fatigue levels at post-treatment and at medium-term follow-up[18] In the randomized trial of White et al[28], CBT and GET were compared with adaptive pacing therapy (APT) and specialist medical care (SMC) alone. Participants had less fatigue and better physical function after CBT and GET than they did after APT or SMC alone.

Although several studies have shown positive effects on reducing fatigue severity after treatment, some CFS-patient groups are negative about CBT, as well as GET[29,30].

At this time, most treatments are targeted towards one or two aspects of the complaints, but various experts[8,18,31] recommend using CBT in combination with other interventions or in a multidisciplinary setting in order to increase treatment effectiveness. To date, only a few studies have reported results of a multidisciplinary approach in peer-reviewed scientific journals. Two uncontrolled studies among young people[32,33] reported positive effects of multidisciplinary interventions. Viner et al (2004)[32] assessed the outcome of multidisciplinary rehabilitation group treatment (graded activity/exercise

programme, family sessions, and supportive care) compared with supportive care alone. Results showed positive effects of multidisciplinary rehabilitation treatment on wellness, school attendance and severity of fatigue. A study by Voet et al (2007)[33] in adolescents with chronic pain and fatigue also showed strong positive effects on fatigue severity, school/work attendance and general health after multidisciplinary rehabilitation treatment. In an uncontrolled study, Torenbeek et al (2006)[34] evaluated a multidisciplinary group program with a combination of clinical and outpatient treatment in a rehabilitation centre. Patients were coached by a rehabilitation physician, psychologist, physical therapist, social worker, occupational therapist, exercise and sports coach and a group leader. Positive effects were found on fatigue severity, experienced impairments and physical functioning, post-treatment. In another uncontrolled pilot study of Vos-Vromans (2005) in Revant Rehabilitation Centre Breda, in which the MRT was evaluated among 36 patients, the results were promising: fatigue severity and the impact of disease on emotional and physical functioning decreased significantly post-treatment and persisted 12 months after start of treatment. Although the results of these studies are promising, conclusions should be drawn carefully, because all studies were uncontrolled. None of the above studies included information about the cost-effectiveness of multidisciplinary rehabilitation treatment, which might facilitate the decision making process regarding treatment selection for practitioners as well as policy makers. Therefore, these findings need to be confirmed in randomized controlled trials including an economic evaluation.

In summary, CBT is the most effective treatment at this time; therefore CBT needs to be compared with a multidisciplinary rehabilitation approach to investigate which treatment is the most effective and most cost-effective. Because effects of CBT on quality of life and other secondary outcomes in medium- and long-term are inconclusive, more research is needed to examine how to sustain the treatment effect.

Aims of the study

The FatiGo trial is designed to address the following primary objectives:

1. To assess the differences in treatment effect (change between baseline and 6-months follow-up in fatigue severity and quality of life) in patients with CFS between individual multidisciplinary rehabilitation treatment (MRT) and individual cognitive behavioural therapy (CBT).
2. To assess the differences in long-term treatment effect (change between baseline and 12-months follow-up in fatigue severity and quality of life) in patients with CFS between the two treatments.
3. To assess the difference in cost-effectiveness and cost-utility between MRT and CBT from both a healthcare and societal perspective at 12-month follow-up.
4. To assess the differences in treatment effect in psychological symptoms, self-efficacy, causal attributions, present-centred attention-awareness, impact of disease

on physical and emotional functioning, self-rated improvement and life satisfaction between MRT and CBT (at 6- and 12-months follow-up).

The secondary objectives of this trial are:

1. To assess the influence of patients treatment expectancy and credibility on the effectiveness of treatment.
2. To assess what baseline factors (other than the assigned treatment) predict a change in fatigue and increase in quality of life in all participants.
3. To evaluate whether changes in self-efficacy, changes in causal attributions and/or changes in present-centred attention-awareness (at baseline, 6 and 14 weeks after start of treatment) mediate changes in fatigue severity and changes in quality of life after treatment.

Hypotheses on the primary objectives

1. MRT is more effective than CBT in reducing fatigue severity and increasing quality of life 6 months after start of treatment.
2. MRT is more effective than CBT in reducing fatigue severity and increasing quality of life 12 months after start of treatment.
3. MRT is more cost-effective than CBT when data on medical and non-medical costs are compared over a 12-month period and shows a higher cost-utility.
4. MRT is more effective than CBT in increasing self-efficacy, non-physical attributions, present-centred attention-awareness, life satisfaction, and is more effective in decreasing the impact of disease on physical and emotional functioning and decreasing the psychological symptoms. Self-rated improvement is significantly higher in MRT than in CBT (at 6- and 12-months follow-up).

METHODS

Design

A two arm, pragmatic, multi-centre randomized controlled trial (RCT) of patients with CFS, with follow-up of 1 year (see Figure 1). The RCT includes both an effectiveness study as well as an economic evaluation.

Setting

The study takes place in the Netherlands in four rehabilitation centres: Revant Rehabilitation Centre Breda (RRCB), Rehabilitation Centre Blixembosch in Eindhoven (RCB), Reade Centre for Rheumatology and Rehabilitation in Amsterdam (RCRR) and Adelante

Rehabilitation Centre in Hoensbroek (ARC). Patients are referred to the trial by their general practitioner or a medical specialist. Patients are treated individually in an outpatient setting.

Ethical approval

Ethic approval for the FatiGo trial was provided by the Research Ethics Committee of Rotterdam (reference 2008/22).

The participants – inclusion and exclusion criteria

Subjects are patients with CFS referred to RRCB, RCRR, RCB and ARC. Patients are included if the following inclusion criteria are met:

1. The participant has given written informed consent.
2. The participant meets the CDC-94 criteria for CFS.
3. The checklist individual strength (CIS) fatigue subscore is 40 or more.
4. The participant is willing to participate in a treatment that is set up to change behaviour.
5. The participant is aged between 18 years and 60 years old.
6. The participant is able to speak, understand and write the Dutch language.

Exclusion criteria are:

1. Any medical condition, that can explain the presence of chronic fatigue.
2. A psychotic, major or bipolar depressive disorder (but not an uncomplicated depression).
3. Dementia
4. Anorexia or bulimia nervosa
5. Alcohol and/or drug abuse
6. Severe obesity (BMI ≥ 45)
7. Pregnancy
8. Previous or current CBT or MRT with regard to CFS.
9. More than 1 h travelling time to the nearest participating rehabilitation centre.

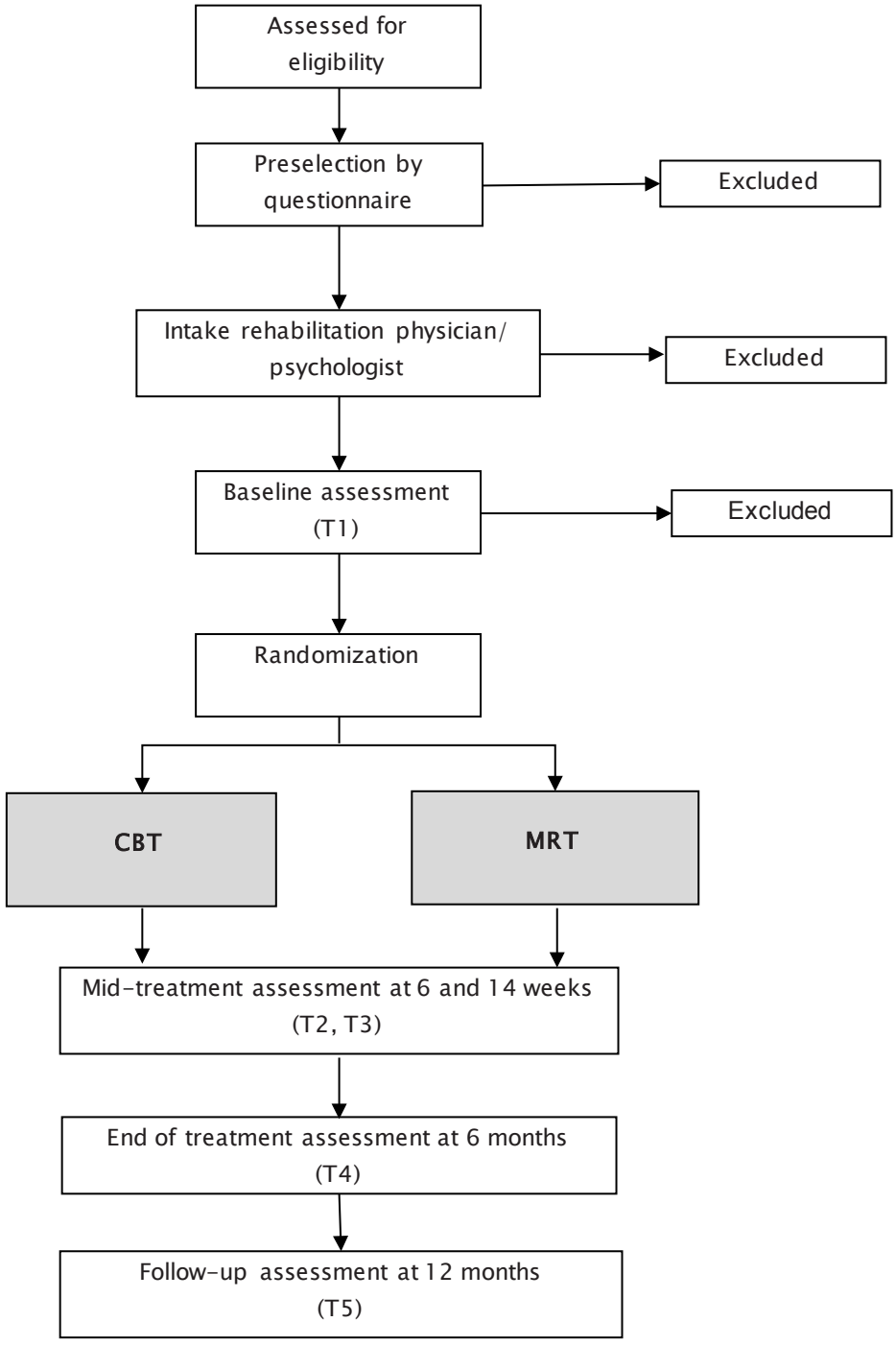

Figure 1. Flowchart of trial design

Screening for participation

When a patient is referred to one of the four rehabilitation centres, the research assistant screens the information provided by the referring general practitioner or medical specialist. The research assistant sends the patient information on the study and asks the patient to fill in the CIS to measure fatigue and the Hospital Anxiety and Depression Scale (HADS)[35]. If the patient has a CIS fatigue subscore of 40 or more, the patient is invited for an intake with the rehabilitation physician. All patients are screened by a rehabilitation physician to check the in- and exclusion criteria. The rehabilitation physician will verify whether an extensive physical examination and laboratory research according the guidelines for chronic fatigue syndrome by the Dutch Diagnostic Compass[36] has been done by a general practitioner, consultant in internal medicine, neurologist or psychiatrist to exclude any underlying illness. If the rehabilitation physician needs a second opinion to decide whether a patient meets the in- or exclusion criteria or when the HADS depression score is 11 or higher, an intake with a psychologist is planned.

The rehabilitation physician explains the procedures of the study, and if someone meets the inclusion criteria and does not meet the exclusion criteria, he asks the patient to sign a (written) agreement. The research assistant contacts the patient after 1 week to make an appointment for signing the informed consent form and for the baseline assessment.

The interventions

The two interventions to be compared, MRT and CBT, take 6 months to complete.
Three elements are incorporated in both treatment groups:

1. Modification of dysfunctional believes regarding illness symptoms and activity and development of more adequate and effective coping strategies.
2. Gradual increase of activities.
3. Normalization of sleep/wake rhythm.

These elements are incorporated in both treatments in a different way (see below).

Individual cognitive behavioural therapy (CBT)
CBT is a psychotherapeutic approach in which elements of behavioural therapy and cognitive therapy approaches are incorporated. In CBT, a model of perpetuating cognitions and behaviour of CFS[14] is used to explain the persistence of CFS. This model shows that high physical attributions will decrease physical activity and increase fatigue and functional impairment. This model also explains that a low level of sense of control over symptoms and focusing on physical sensations have a direct causal effect on fatigue severity and functional impairment. A perceived lack of social support also increases the fatigue severity and functional impairment. These perpetuating factors (high physical attributions, decreased physical activity, low level of sense of control, focusing on physi-

cal sensations and perceived lack of social support) are the focus of the intervention in CBT[37,38]. CBT is divided into three phases:

1) Intake
2) Gradual reactivation
3) Prevention of relapse

1) Intake

   During the intake phase (four sessions in 4 weeks), the cognitive behavioural therapist gets acquainted with the patient. The patient is asked about: the cause and course of the complaints, the present complaints, illness believes and illness behaviour, coping, social interactions/ participation and the expectations and personal goals of the patient. The therapist tries to determine the patient's activity level by asking about activities during the day and week, and categorizes the patient into a relatively active patient or a patient with a low activity pattern. The therapist explains the model of perpetuating cognitions and behaviour of CFS, and how to overcome CFS by changing patterns of thinking and changing behaviour.

2) Gradual reactivation
   - Graded exercise therapy (GET) is used to gradually increase physical activity. The patient follows a schedule to gradually increase activities at home (walking and bicycling). The schedule is provided by the therapist in accordance with the patient's personal goals. The patient has to increase his/her activities at home and receives feedback afterwards during the next therapy session. If needed, schedules are made to increase social and/or mental activities as well. Another important subject during gradual reactivation is the balance between different activities and the patient's personal responsibility to see to it.
   - In the dialogues with the therapist and by doing exercises at home, the patient is taught to change negative beliefs regarding symptoms of fatigue, self-expectations and self-esteem. Specific lifestyle changes are encouraged if deemed appropriate.
   - Sleep/wake rhythm: the patient is encouraged to change sleep/wake rhythm immediately at the start of treatment into a regular sleep/wake rhythm. Sleeping during the day is not allowed.
   - In accordance with the principles of GET, a plan to return to work will be made.

3) Prevention of relapse

   If activities are increased and sleep/wake rhythm is normalized, the patient is encouraged to unsettle him-/ herself and to cope with these disturbances by applying the things he/she learned during therapy. Personal goals are evaluated and relapse prevention is addressed.

   The patient assigned to this group will attend 16 individual therapy sessions, spread out over 6 months with a psychologist or behavioural therapist. The first 6 weeks, the patient has weekly contact with the therapist, followed by once every 2

weeks for the next 20 weeks. The CBT protocol is fixed and different for relatively active patients and patients with a low activity pattern[37,38]. In the treatment for the relatively active patient, the patient learns to spread out activities during the day and to vary different activities during the day. The patient learns to be active within physical and mental boundaries to overcome overburdening. With the use of cognitive therapy, cognitions and behaviour that may lead to overburdening (like not accepting boundaries in activity, and to having high expectations) are the primary focus of treatment. After reaching the baseline (without peaks in complaints of the CFS) there will be a gradual increase of activities. For patients with a low activity pattern, activities will be increased from the beginning of therapy.

Individual multidisciplinary rehabilitation treatment (MRT)

In the multidisciplinary treatment, a biopsychosocial model of CFS is used including biological, physical and psychosocial aspects[10,31]. In the biopsychosocial model of CFS various precipitating, predisposing and perpetuating factors are merged, suggesting that multiple pathways may lead to the causation and persistence of CFS[31]. The protocol of the MRT is not fixed but varies between patients, depending on the relation between treatable components (precipitating, predisposing and perpetuating factors), present complaints and personal needs of a patient. The focus of treatment can be different for each patient depending on these relations. During treatment every therapist fills in treatment checklists for every patient to register which interventions are used.
MRT is divided in three phases:

1) Observation
2) Treatment
3) Prevention of relapse

1) Observation

   During a 2-week observation, therapists (psychologist, social worker, physical therapist and occupational therapist) get acquainted with the patient. During observation, they ask the patient about: the cause and course of the complaints, the present complaints, illness believes and illness behaviour, coping, social environment the patient lives in, expectations and personal goals. The psychologist (two 1-h sessions) further elaborates on the psychological history, present psychological well-being, use of medical care including medication, stress factors, cognitions, attitudes and mood (state of mind). The social worker (two 1-h sessions) assesses the social context in which the patient lives (relationships, family and role in a family), work situation and communication. The physical therapist (five 30-min sessions) makes an estimation of the physical condition and the patient's body awareness. The occupational therapist (four 30-min sessions) aims at ergonomics, lifestyle, day/week schedule and the variety of activities during the day/week. During observation, the

treatable components are weighted in relation to the present complaints. If a strong relation exists between these components and the present complaints, these components will be addressed during treatment. In a team meeting, therapists and the rehabilitation physician discuss the components and methods that will be used during the treatment phase. The rehabilitation physician will discuss the conclusions of this meeting with the patient and asks for commitment to the proposed therapy. A treatment contract will be signed by the rehabilitation physician and the patient.

2) Treatment

Two weeks after ending the observation phase, the treatment phase starts. This phase takes 10 weeks to be completed. Depending on the patient goals/needs and the relation between treatable components and present complaints, different methods will be more or less used in the treatment phase. The following inteventions can be incorporated:

- Body awareness therapy[39,40]: Aims to establish an increased awareness and consciousness of the body and its relation to psychological well-being. The patient learns to discriminate bodily symptoms other than fatigue and pain and learns to react on these healthy bodily symptoms. The patient will be coached by a physical therapist. Bodyscan, grounding, awareness exercises of the influence of thoughts and emotions on the body are some of the exercises that will be practised during treatment. In the end, the patient will be aware of the relation between the body, its physical function, psychological well-being and social interaction, and is able to react on stress in an appropriate way.
- CBT: A psychotherapeutic approach in which elements of behavioural and cognitive therapy approaches are incorporated. CBT facilitates the identification of unhelpful, negative emotions-provoking thoughts, dysfunctional emotions, behaviours and cognitive patterns, and challenges them through a goal-oriented, systematic procedure. The patient learns to identify negative beliefs regarding the symptoms of fatigue, self-expectations or self-esteem, and is encouraged to challenge and change them into new, more realistic, more helpful alternatives.
- Gradual reactivation: At the start of treatment, activities are trained time-contingent under close supervision of the physical therapist and occupational therapist. The patient follows schedules to gradually increase activities and receives immediate feedback during treatment when needed. The schedules of fitness exercises and swimming are provided by the physical therapist in accordance with the patient's personal goals. Another schedule is provided by the occupational therapist in accordance with the patient's personal goals to increase activity and vary activities at home. In the final phase of treatment, schedules are of less importance and the patient is encouraged to increase activities on his/her own without following a schedule (see pacing).
- Pacing: During the second phase of treatment, the patient is taught to pace his/her activities during the day/week. By developing awareness of healthy bodi-

ly symptoms the patient will be able to balance his/her activities (psychological as well as physical activities) before extreme fatigue or pain prevails. The schedule of time-contingent increase is no longer followed. The patient will pace his/her activities based on his/her own experiences.

- Principles of mindfulness. Mindfulness is a nonelaborative, nonjudgmental, present-centred awareness in which each thought, feeling or sensation that arises is acknowledged and accepted as it is. The patient learns to self-regulate attention which is maintained on immediate experience, thereby allowing for increased recognition of mental events in the present moment. They also learn to observe the thoughts, emotions and sensations that arise, without making judgments about their truth, importance or value, and without trying to escape, avoid or change them. Regular practice of mindfulness skills increases self-awareness and self-acceptance, reduces reactivity to passing thoughts and emotions, and improves the ability to make adaptive choices[41]. In patients who have been chronically ill, mindfulness skills have a positive effect on depression, mood and activity level[42].
- Normalizing of sleep/wake rhythm. Sleep/wake rhythm will be discussed and with a schedule of 4 weeks will be gradually changed to the sleep/wake rhythm the patient desires. Sleeping during the day will be stopped immediately. If there are problems with the quality of sleep, principles of sleep hygiene are prescribed by the psychologist. Relaxation therapy is used to increase the efficiency of the resting moments during the day and to improve quality of sleep during the night if needed.
- Social reintegration. Under supervision of the occupational therapist and social worker the patient is coached to reintegrate into society by making a plan to return to his/ her work or school and to increase their social activities.

3) Prevention of relapse

   Six weeks after ending the treatment phase, the patient will visit the social worker. Thirteen weeks after ending the treatment phase, the patient visits two therapists of his/her choice who were involved in the previous treatment. Both after-care visits are used to stimulate and motivate the patient to practice at home what he/she has learned during treatment phase.

Although MRT and CBT have three corresponding aims: Modification of dysfunctional believes, gradual increase of activities and normalization of sleep/wake rhythm, many differences can be detected between the two treatments. The main differences are viewed in Table 1.

Table 1. Differences between CBT and MRT

CBT	MRT
Treatment focus on perpetuating factors	Treatment focus depending on the relation between the (precipitating, predisposing and perpetuating) factors, and the presented complaints.
Afterwards feedback at next therapy session	Immediately feedback during therapy
Pays no attention to physical sensations	Stimulating awareness of healthy bodily symptoms
CBT	CBT incorporated with principles of mindfulness

Training the therapists to deliver the interventions

Four rehabilitation teams deliver the MRT. Each team consists of one or two rehabilitation physicians or physician assistant (under supervision of a rehabilitation physician), one or two psychologists/ behavioural therapists, two social workers, two physical therapists and two occupational therapists. Six other psychologists/cognitive behavioural therapists deliver the cognitive behavioural therapy in the four participating rehabilitation centres. The psychologists of the CBT group are not involved in the MRT and meetings with a supervisor will be organized separately for both groups of psychologists.

CBT

All psychologists and behavioural therapists are trained in CBT. A 3-day workshop before the start of the study was held, guided by an external CBT expert, who is acquainted with the CBT protocol[38,43] to ensure that execution of CBT is similar and up to standard in each centre. During the trial seven supervision meetings are organized in which audiotaped sessions provided during the trial are used to evaluate the therapy. Therapists are free to contact their supervisor when questions arise.

MRT

Before the beginning of the study, the therapists of RRCB, who work with the protocol for at least 5 years, organized separate workshops for each involved discipline and a multidisciplinary team meeting in which the therapists got acquainted with the MRT protocol. During the trial two disciplinary supervision meetings and two multidisciplinary team supervision meetings will be held. Therapists are free to contact their supervisor when questions arise.

Recruitment of patients

The inclusion of new patients took place from November 2008 until January 2011. Potential referrers of patients to the four rehabilitation centres are informed about the developments of the trial by newsletters four times during the trial. Several articles on

internet sites and in magazines of patient support groups are published to inform patients about the trial and how they can be referred.

Outcome measures

Primary outcome measures

Primary outcome parameter:
Fatigue severity is assessed by a subscale of the CIS[44,45]. The subscale consists of eight items, each scored on a 7-point Likert scale (range 8-56). Validity and reliability of the scale are good[44,46].

Quality of life is assessed by the Short-Form 36 (SF-36)[47]. The SF-36 has eight subscales: physical functioning (10 items), role-physical (4 items), bodily pain (2 items), general health (5 items), vitality (4 items), social functioning (2 items), role-emotional (3 items), mental health (5 items). Every subscale is transformed into ratings on a scale of 0 (limited in all activities) to 100 (able to carry out vigorous activities). Validity and reliability of every subscale is high[48].

Secondary outcome measures

Secondary outcome parameters are:

1. Psychological symptoms will be measured with the Symptom Check List-90 (SCL-90). The SCL-90 is a multidimensional questionnaire designed to screen for a broad range of psychological symptoms. The questionnaire consists of 90 items. Each item is scored on a 5-point Likert scale (0 is 'not at all' and 4 is 'extremely')[45,49]. The items are combined in the following primary symptom dimensions: somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation and psychoneuroticism (total score of the SCL-90). Validity and discriminating validity are good[50].
2. Self-efficacy will be measured with the Self-Efficacy Scale-28 (SES) to compare sense of control in relation to CFS complaints[25,45]. The scale consists of seven questions. Items are scored on a 4-point Likert scale. The total score ranges from 7 to 28. A higher score means more sense of control.
3. Causal attributions will be measured with the Causal Attribution List (CAL)[25]. The CAL assesses whether the patient is likely to attribute complaints to physical or non-physical causes. The list consists of ten questions scored on a 4-point Likert scale. Total subscale scores of physical and non-physical attributions range from 5 to 20. A higher score indicates a stronger conviction.
4. Present-centred attention-awareness, which is foundational to mindfulness, will be measured with the Mindfulness Attention Awareness Scale (MAAS)[51]. The validity and reliability of the Dutch version of the MAAS is good[52]. The MAAS consists of 15

statements scored on a 6-point Likert scale. The mean total score ranges from 1 to 6. A higher score indicates a greater awareness of present experiences.

5. A patient's personal treatment goals will be measured with the Patient Specific Complaints and Goals questionnaire (PSCG)[53]. The patient selects three activities, that he/she perceives as important in his/her daily life and wants to improve. The patient rates the performance of the activity on a 100-mm Visual Analogue Scale (VAS). The left side of the VAS is marked as 'no problems at all'. On the right side the VAS is marked 'impossible'. The PSCG is a valid and reliable measure with sufficient responsiveness[53].
6. Sickness Impact Profile 8 will be used to measure the impact of disease on both physical and emotional functioning[54]. The SIP8 is derived from the SIP. The SIP8 has eight subscales: home management, mobility, alertness behaviour, sleep/rest, ambulation, social interaction, work, and recreation and pastimes. Psychometric research has indicated that the SIP is reliable and valid[55,56].
7. Physical activity will be measured by a multi-sensor armband (Sense Wear Pro Armband; BodyMedia, Inc., Pittsburgh, PA). The armband was developed to measure energy expenditure by integrating accelerometry with multiple physiologic sensors including galvanic skin resistance, heat flux, body temperature and near body ambient temperature. The armband is worn 7 consecutive days on the right upper arm over the triceps muscle and monitors various physiological and movement parameters. The armband is a reproducible and accurate measure in subjects with chronic illness with moderate functional limitations[57].
8. Six questions are used to measure self-rated improvement after therapy and the satisfaction of the patient. The questions: 'How satisfied are you with the effect of treatment?', 'Is there a difference in how you handle problems now compared to before treatment started?' and 'Is there a difference in your daily activities now compared to your situation before treatment started?' are scored on a 5-point Likert scale ('1' is very content/ much improvement and '5' is very discontented/ situation is worse). The question: 'To what extend did you achieve your personal treatment goals?' is scored on a 10-point Likert scale, range 1-10. The questions: 'Would you recommend the treatment to other CFS-patients?' can be answered with 'yes', 'no' or 'I don't know'. The question: 'Do you still consider yourself a CFS-patient?' can be answered with 'yes' or 'no'[58].
9. Life satisfaction will be measured by the Life Satisfaction Questionnaire, Dutch version (LSQ). The LSQ has one question on general life satisfaction and eight questions about domain-specific life satisfaction: self-care ability, leisure situation, vocational situation (including housekeeping), financial situation, sexual life, partner relationship, family life, contacts with friends and acquaintances. Questions are answered on a 6-point Likert scale ('1' is very dissatisfied, '6' is very satisfied). The reliability of the LSQ has been proven to be moderate to good for most domains in a patient group with chronic illness[59].

10. Quality of life and utilities (health-related quality of life) will be measured by means of the standard Dutch version of the EuroQol (EQ-5D-3L)[60]. The EQ-5D-3L contains five dimensions of health-related quality of life, namely mobility, self-care, daily activities, pain/discomfort and depression/anxiety. Each dimension can be rated at three levels: no problem, some problems and major problems. The five dimensions can be summed into a health state. Utility values are calculated for these health states, using preferences elicited from a general population, the so-called Dolan algorithm[61]. The utility values derived from the Dolan algorithm will be used to compute quality-adjusted life-years (QALYs). The Dolan algorithm has been established using a general population from the UK. Also a Dutch algorithm has become available which will be used in the sensitivity analysis[62].

Treatment expectancy and credibility

Patients' initial beliefs about the success of a given treatment have shown to have an important influence on the final treatment outcome. A study by Smeets et al (2008)[63] found evidence of predictive validity of expectancy and credibility scored by patients with chronic low back pain before following different active interventions. To measure treatment expectancy and credibility, 2 weeks after start of treatment, all participants will be asked to fill in the Dutch version of the Devilly and Borkovec questionnaire[64].

Mediation

To understand how treatment works, mediation analyses are performed. Two studies on mediation could not confirm the mediating role of physical activity in reducing fatigue in CFS. Moss-Morris (2005)[21] investigated physical activity as a mediator in the treatment effect of GET and Wiborg (2010)[65] in CBT. Since physical activity does not mediate the outcome, other parameters have to be responsible for a decrease of fatigue during therapy. In the model of Vercoulen et al[14] somatic attributions, focusing on pain and fatigue, and low self-efficacy contribute to the perpetuating of CFS complaints. Patients with CFS feel helpless and surrendered to their complaints, making it difficult to change their situation. During therapy patients learn to change cognitions in more helpful cognitions, which increases self-efficacy. They learn to accept their situation in the present, making choices based on helpful cognitions and bodily symptoms other than pain and fatigue, and learn to focus on getting better instead of focussing on complaints and somatic attributions. Our hypothesis is that by increasing self-efficacy, decreasing somatic attributions and increasing the present-centred attention-awareness during activities first, behavioural changes can be made based upon these changes and eventually severity of fatigue will decrease.

There are no studies that we are aware of that determine the mediating role of self-efficacy, somatic attributions and present-centred attention-awareness. Mediation will

be investigated by the three-step method described by Baron and Kenny[66]. Before treatment (T1), 6 and 14 weeks after start of treatment (T2, T3), CIS, SES, CAL and MAAS are filled in by the patient in order to analyse mediation at different moments during treatment phase.

Cost analysis

The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (Tic-P) will be used to measure treatment costs and additional expenses[67]. The subsection on absence from work (productivity loss by absenteeism and by loss of productivity while at work, and informal care and domestic help), is filled in every month. The subsection on healthcare costs (medical treatments, paramedic therapy, alternative therapy, self-care groups, clinical or outpatient treatment in hospital and other institutions and medication), is filled in every 3 months. Treatment hours are registered by the therapists and the rehabilitation physicians in checklists filled in after each treatment session. The valuation of healthcare costs, patient and family costs will be based on the update Dutch manual for cost analysis in healthcare research[68]. For care for which no costs-guidelines are available, estimations of the costs will be made, based on the real costs or on population based estimates from literature.

Assessment and procedures

After inclusion, the research assistant contacts the patient to make an appointment for the baseline assessment (T1). During T1 the patient is asked to wear the activity monitor for one week and to fill in the following questionnaires:

- Checklist Individual Strength (CIS)
- Short-Form 36 (SF-36)
- EuroQol-5D-3L (EQ-5D-3L)
- Symptom Check List-90 (SCL-90)
- Self-Efficacy Scale-28 (SES)
- Causal Attribution List (CAL)
- Mindfulness Attention Awareness Scale (MAAS)
- Sickness Impact Profile 8 (SIP8)
- Life Satisfaction Questionnaire, Dutch Version (LSQ).

The patient is instructed on how to fill in the Tic-P, part II on health- and non-health related costs every month during 1 year. One week after baseline assessment, the research assistant collects the activity monitor. The research assistant gives the patient a blind envelope with the treatment conditions. Treatments start within 4 weeks. Two weeks after start of treatment, a patient is asked to fill in the list of Borkovec and Devilly and the PSCG, part 1. At 3 and 9 months after T1 a patient is asked to fill in the Tic-P part I, at home. Six months after start of treatment the research assistant assesses the patient again (T4). The patient is asked to wear the activity monitor and fill in the same

questionnaires as T1 completed by the PSCG, part II, self-rated improvement questionnaire and Tic-P, part I. Twelve months after start of the treatment, the same assessment as T4 will be repeated (T5). For each patient the study takes 12 months.

Randomization

After signing the informed consent form the patients are randomly divided into two groups: CBT and MRT. For each rehabilitation centre a randomization list was generated by computer under supervision of an independent statistician. Before recruitment of patients an independent person prepared sealed envelopes for each rehabilitation centre and numbered them sequentially according to the randomization list. The envelope is given to the participating patient by an independent research assistant after baseline assessment. The patient is asked not to open the envelope in front of the research assistant. Randomization is performed for each centre to prevent differences between the treatment groups in the distribution of centres.

Adverse events

Patients are able to contact a physician, who is appointed as an independent physician for the study, at any time. Adverse events will be monitored carefully. If any adverse event occurs or a patient withdraws from treatment, the researcher of research assistant will ask the patient and the therapist(s) why the patient is withdrawing. If deterioration is reported, the patient is offered appropriate help if needed. Referrals to other institutions are registered. Each patient withdrawing from treatment is asked to participate in the follow-up measurements. Patients who are not willing to participate in the follow-up measurements are asked to fill in questionnaires at home without wearing the activity monitor. Reasons for not wanting to participate in the follow-up measurement are registered.

Analyses

Sample size

Based on available literature[25,34,69] and our pilot study, mean CIS fatigue scores at the start of CBT or MRT are about 50-52 with a standard deviation (SD) of 3.9-5.9. Following previous trials[28,34], we assume that a difference of 0.5 SD of the mean group score at baseline is clinically relevant. This equals a difference of about 3.0 points on the CIS fatigue subscale. With a sample size of 48 patients in each treatment-arm, accepting an alpha error of 0.05 and a power of 0.80, it is possible to measure a minimal difference of 3.0 points on the CIS fatigue subscale. To compensate for an estimated 25% dropout, a total of 120 people will be included.

Analyses of efficacy

The effects of therapy conditions on the various outcomes will be compared using an intention-to-treat approach. Data will be analysed with mixed linear regression models. The follow-up measurement will be the dependent variable and the baseline value of the particular outcome will be added as covariate as well as random intercepts for individuals to allow for dependence within patients and centres[70]. Effect modification will be evaluated by introducing interactions between therapy condition and the potential modifiers in the equation. There will be a post-hoc analysis of the non-response group and the missing values. Drop-out patients will be asked about the reason for stopping treatment or not attending a measurement. Patient characteristics of the drop-outs will be compared to those of the group that completed each treatment. For the analyses we will use SPSS statistical software.

Economic analyses

Healthcare costs will be measured using the Tic-P. Total costs are calculated by using an update of the Dutch manual for costing in economic evaluations[68]. Clinical outcomes 12 months after start of treatment will be used in the economic evaluation. Student *t*-test for statistical significance will be used to measure differences between MRT and CBT. Fatigue severity during 1 year of follow-up will be used as the primary outcome measure for cost-effectiveness.

A cost-utility analysis will be performed by relating the mean total costs to the mean health-utility (EQ-5D-3L) scores of both groups. The costs per QALY of both treatments will be compared. Our primary (base-case analyses) will be performed according to the intention-to-treat principle, including data from all participants regardless of whether they received the intervention or not. For the analyses we will use SPSS statistical software and Excel (for the bootstraps).

Respondents for whom at least 75% of the data per measurement instrument are available will be included in the analysis. Missing data on item level will be handled using SPSS missing value analysis. Completely missing measurements will be handled using multiple imputation (MI). A baseline analysis will be performed to examine the comparability of groups at baseline for both costs and outcomes. If necessary, methods will be applied to control for differences in baseline[71]. To investigate whether data are normally distributed a Kolmagorov-Smirnov test will be performed. Despite the usual skewness in the distribution of costs, the arithmetic means will be generally considered the most appropriate measures to describe cost data[72,73]. Non-parametric bootstrapping is a method based on random sampling with replacement based on individual data of the participants[74]. The bootstrap replications will be used to calculate 95% confidence intervals around the costs (95% CI), based on the 2.5th and 97,5th percentiles. If cost data are distributed normally, *t*-tests will be used.

The incremental cost-effectiveness ratio (ICER) will be determined on the basis of incremental costs and the effects of the MRT in comparison with CBT. The cost-effectiveness ratio will be expressed in terms of costs per unit of outcome; the cost-utility ratio will focus on the incremental cost per QALY gained. The robustness of the ICER will be checked by non-parametric bootstrapping. Bootstrap simulations will also be conducted in order to quantify the uncertainty around the ICER, yielding information about the joint distribution of cost and effect differences. The bootstrapped cost-effectiveness ratios will be subsequently plotted in a cost-effectiveness plane, in which the vertical line reflects the difference in costs and the horizontal line reflects the difference in effectiveness. The choice of treatment depends on the maximum amount of money the society is prepared to pay for a gain in effectiveness, which is called the ceiling ration. Therefore the bootstrapped ICERs will also be depicted in a cost-effectiveness acceptability curve showing the probability that MRT is cost-effective using a range of ceiling ratios. Additionally, to demonstrate the robustness of our base-case findings a multi-way sensitivity analysis will be performed.

Mediation analyses

In the mediation analysis, we investigate whether self-efficacy, somatic attributions and/or present-centred attention-awareness intervenes in the relationship between treatment and outcome. Multiple regressions are used to explore which factors mediate the outcome. Mediation is suggested when the change in the putative mediating factors is significantly related to treatment as the independent variable, outcome is significantly related to treatment as the independent variable, and finally, the relationship between outcome and treatment decreases (or goes to zero) when the change in the mediation factor is entered into the equation[66].

Participant non-adherence with treatment

Participant non-adherence with treatment will be measured both by recording attendance and by therapist ratings of adherence to therapy.

Trial management and oversight

The day to day management of the trial is carried out by the principal investigator, Desirée Vos-Vromans, in consultation with other members of the trial team and the research assistants. Every rehabilitation centre has one or two research assistants.

DISCUSSION

Treatment facilities for patients with CFS in multidisciplinary rehabilitation settings are rare, because most health insurance companies and rehabilitation centres are not con-

vinced of the benefit of MRT for this group. MRT in this form is unique and never been investigated in a multi-centre RCT. The results of the FatiGo trial will provide information on the effects of CBT and MRT, mediators of the outcome, cost-effectiveness, cost-utility and the influence of treatment expectancy and credibility on the effectiveness of both treatments in patients with CFS.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

All authors contributed to the overall design of this study, and are involved in the ongoing management of the trial. DV is the principal investigator with overall responsibility for the FatiGo trial. RG en LR participated in developing MRT, training and supervising the therapists and rehabilitation physicians. SE developed the health economic analysis plan. All authors read and approved the final article.

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3

Multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome: a randomized controlled trial

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ABSTRACT

Objectives. The aim of this trial was to evaluate the difference in treatment effect, at 26 and 52 weeks after the start of treatment, between cognitive behavioural therapy (CBT) and multidisciplinary rehabilitation treatment (MRT) for patients with chronic fatigue syndrome (CFS).

Design. Multi-centre, randomized controlled trial of patients with CFS. Participants were randomly assigned to MRT or CBT.

Setting. Four rehabilitation centres in the Netherlands.

Subjects. A total of 122 patients participated in the trial.

Main outcome measures. Primary outcomes were fatigue measured by the fatigue subscale of the Checklist Individual Strength and health-related quality of life measured by the Short-Form 36. Outcomes were assessed prior to treatment and at 26 and 52 weeks after treatment initiation.

Results. A total of 114 participants completed the assessment at 26 weeks, and 112 completed the assessment at 52 weeks. MRT was significantly more effective than CBT in reducing fatigue at 52 weeks. The estimated difference in fatigue between the two treatments was -3.02 [95% confidence interval (CI) -8.07 to 2.03; P = 0.24] at 26 weeks and -5.69 (95% CI -10.62 to -0.76; P = 0.02) at 52 weeks. Patients showed an improvement in quality of life over time but between-group differences were not significant.

Conclusion. This study provides evidence that MRT is more effective in reducing long-term fatigue severity than CBT in patients with CFS. Although implementation in comparable populations can be recommended based on clinical effectiveness, it is advisable to analyse the cost-effectiveness and replicate these findings in another multi-centre trial.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as medically unexplained disabling fatigue that persists for more than 6 months. Fatigue is accompanied by other complaints such as joint pain, poor concentration and post-exertion malaise, resulting in restrictions in daily activities and participation[1]. According to the biopsychosocial model, these restrictions influence and can be influenced by personal and external factors and vary between patients resulting in differences in clinical presentation of the syndrome[2]. Although increasing evidence suggests that central sensitization might be the explanation for many symptoms of CFS[3,4], the exact etiology of the condition is unknown. Uncertainty regarding the etiology combined with the heterogeneity of the clinical presentation has resulted in a lack of consensus concerning the definition of CFS. This lack of consensus is likely to be responsible for variation in estimates of the prevalence of the syndrome, which range from 0.2% to 2.6% worldwide[5].

The heterogeneity of symptoms[6,7] and the varying opinion regarding the etiology of CFS have also resulted in the administration of a variety of pharmacological and non-pharmacological treatments[8,9]. Two commonly used treatments that are supported by evidence of their effectiveness are cognitive behavioural therapy (CBT)[10] and graded exercise therapy[11]. The aim of CBT is to modify dysfunctional beliefs and behaviours, and usually includes a graded increase in activity[10]. Although effective[10,12], CBT and graded exercise therapy do not improve fatigue severity and quality of life for all patients. The importance of tailoring treatment to the patient was first recognized by Prins et al[13] who concluded that the CBT protocol in use was not suitable for a subgroup of patients with CFS showing a passive activity pattern. Cella et al[14] concluded that patients with CFS who reported a higher frequency of weight fluctuations, physical shaking and pain and who were more symptom focused and anxious had a poor CBT outcome compared to other patients, which supports the idea of a tailored approach. To further improve the management of CFS, investigation of multidisciplinary treatments has been advocated[10]. An example of such therapy is multidisciplinary rehabilitation treatment (MRT)[15] in which different interventions, including CBT, are combined. A collaborating team from multiple disciplines examines and analyses patients' functions, activities and level of participation, social environment and personal factors in order to develop an individual rationale for the development and persistence of fatigue. Following this individual rationale, CBT and elements such as gradual reactivation, pacing, mindfulness, body awareness therapy, normalization of sleep/wake rhythm and social reintegration are combined in a treatment programme. All intervention elements are administered at a rehabilitation centre under the close supervision of trained therapists who monitor and provide feedback as appropriate. It is hypothesized that a different combination of factors is responsible for the persistence of fatigue in each patient. Therefore every patient requires a tailored treatment programme with different elements to deal with these factors. In addition, the patient is able to practise activities under the close super-

vision of a therapist and receives direct feedback. This, together with close attention to the relationships and reciprocity between cognition, emotion, body awareness and behaviour in a social environment might increase the effectiveness of treatment. Although different multidisciplinary treatments for patients with CFS exist, the effectiveness of this type of intervention is unclear. A literature search resulted in only three randomized controlled trials (RCTs) in this field[16-19]. Positive effects of different rehabilitation treatments for patients with CFS were reported from two RCTs[18,19]. In addition, a number of nonrandomized, observational studies[20-26] either without[20,21,24] or with a control group[22,23,25,26] have been performed. These studies investigated a range of rehabilitation treatments with different interventions, durations and locations of treatment and therapists. Based on the results of these observational studies, rehabilitation treatments seem to be effective in decreasing fatigue or increasing quality of life.

However, to our knowledge, MRT as described above has not previously been investigated in comparison with CBT. A pragmatic multi-centre RCT was designed to compare the effectiveness of MRT and CBT alone[15]. Both treatments were provided according to a standard protocol, where possible, and representative of current clinical practice[27]. The primary objective of the study was to evaluate the difference in treatment effect (changes in fatigue severity and quality of life between baseline and both 26 and 52 weeks after the start of treatment) in patients with CFS.

METHODS

Study participants

Patients referred to the Revant Rehabilitation Centre in Breda, Rehabilitation Centre Blixembosch in Eindhoven, Reade Centre for Rheumatology and Rehabilitation in Amsterdam and Adelante Rehabilitation Centre in Hoensbroek between December 2008 and January 2011 were invited to participate if they met the US Centers for Disease Control and Prevention (CDC-94) criteria for CFS[1]. According to the CDC-94 criteria, CFS diagnosis requires: persistent or relapsing unexplained fatigue with a new or definite onset, which has endured for at least 6 months. The fatigue must not be the result of an organic disease or ongoing exertion. Fatigue is not alleviated by rest and results in substantial limitations in occupational, educational, social and personal activities. Four or more of the following symptoms also had to be present for more than 6 months: impaired memory or concentration, sore throat, tender cervical or axillary lymph nodes, muscle pain, pain in several joints, new headaches, unrefreshing sleep or malaise after exertion. Other inclusion criteria for study entry were: a Checklist Individual Strength (CIS)[28] fatigue subscale score of 40 or more, willingness to participate in a treatment aimed at changing behaviour, age between 18 and 60 years and comprehension of written and verbal Dutch.

Patients were excluded if they suffered from a medical condition explaining the presence of chronic fatigue, had a psychotic, major or bipolar depressive disorder, dementia, anorexia, bulimia nervosa or a body mass index ≥45 kg/m^2; alcohol and/or drug abuse, and pregnancy were also exclusion criteria. Patients who had already received CBT or MRT for CFS in the past, or had to travel for more than 1 h to the nearest participating rehabilitation centre, were also excluded.

Study design

The present study was a two-arm pragmatic, multi-centre, RCT, with follow-up assessments at 26 and 52 weeks after treatment initiation for patients with CFS[15].

Study inclusion was a multistage process to ensure the suitability of participants. Potentially eligible patients were initially identified via clinical referral notes by a research assistant at the relevant rehabilitation centre. They were then asked to complete a questionnaire regarding their complaints and life situation, and the Hospital Anxiety and Depression Scale (HADS)[29] and the CIS[28]. In the absence of any exclusion criteria and if the CIS fatigue subscale score was 40 or more[13], the patient was invited for assessment by a consultant in rehabilitation medicine. The consultant confirmed the inclusion and exclusion criteria and verified whether an extensive physical examination and laboratory research tests had been performed to exclude any underlying illness. In the case of an indication of underlying illness, the patient was referred to a specialist in internal medicine, neurology or psychiatry for further investigation. An interview with a psychologist was scheduled if the HADS depression subscale score was 11 or more (to exclude a major or bipolar depressive disorder) or if the consultant suspected another psychiatric illness or motivational problem. In some regions in the Netherlands, the incidence of Q fever increased during the trial. As Q fever can cause similar symptoms to those of CFS, patients from high-risk regions were additionally tested for Q fever and excluded from the study in case of a positive diagnosis. Assessments of primary outcomes were conducted before treatment, and 26 weeks and 52 weeks after the start of treatment. To identify mediators of the outcome, patients completed questionnaires at home at 4 and 14 weeks after treatment initiation. After the baseline assessment and a 1-week period of wearing an activity monitor, patients were randomly assigned to either MRT or CBT. Treatments were standardized by providing manuals to all therapists. Treatments were provided individually and delivered by clinical staff, trained in the study protocol, at the participating rehabilitation centres. Both treatments took 6 months to complete and aimed to decrease fatigue severity and improve quality of life. For every participant, the number of treatment sessions was registered to monitor treatment adherence. Receiving less than 70% of all treatment sessions was regarded as a protocol deviation.

All patients provided written informed consent. The study was approved by the Research Ethics Committee of Rotterdam (reference 2008/22).

Interventions

Multidisciplinary rehabilitation treatment

This treatment is based on the biopsychosocial model of CFS, in which various precipitating, predisposing and perpetuating factors interact, resulting in multiple pathways leading to the development and persistence of CFS[30]. The MRT protocol was patient-centred, based on addressing those components that are thought to be modifiable and have a strong relation with the precipitation, predisposition and perpetuation of the CFS. These components and the personal goals of a patient were the focus of the treatment. After identifying the modifiable components and the personal goals, treatment aims were determined and the therapist provided an indication of how the interventions would be used to achieve the personal goals. MRT consisted of an observational phase in which the patient underwent thorough assessment (interview, physical examination, baseline assessment and goal setting) by an interdisciplinary team consisting a physical therapist (PT), occupational therapist (OT), psychologist and social worker over a period of 2 weeks (with a total contact time of 8.5 h). This phase was followed by 2 weeks without treatment in which the therapists and the consultant in rehabilitation medicine discussed their findings and defined the treatable components and proposed treatment. Following this, the consultant discussed the results with the patient. After the consultation, there was a 10-week treatment phase (individual sessions; with a total contact time of 33 h). Weekly visits to the PT and OT and biweekly visits to the psychologist and social worker were scheduled. MRT included CBT and, depending on the individual analysis, elements of body awareness therapy, gradual reactivation, pacing, mindfulness, gradual normalization of sleep/wake rhythm and social reintegration. Every therapist had a different focus. The PT and OT focused on the gradual reactivation of the patient by increasing activities under close supervision in the rehabilitation centre (increasing fitness activities and swimming) and at home (increasing physical and mental activities tailored to the needs of the patient). Another focus of the PT was body awareness therapy which aims to establish an increased awareness and consciousness of the body and its relation to psychological well-being. Both the PT and OT taught the patient to pace activities, to avoid bursts of extreme activity followed by extreme fatigue. Under the supervision of the OT and social worker, the patient was coached to reintegrate into society by making a plan to return to work or school and to increase social activities. The psychologist and OT both addressed the gradual normalization of a patient's sleep/wake rhythm. According to the CBT principles, the psychologist focused on modification of dysfunctional beliefs regarding illness symptoms, activity, self-expectations and self-esteem and the development of more effective coping strategies. During treatment sessions every therapist followed the principles of CBT and incorporated them with mindfulness principles including increasing self-awareness and self-acceptance, reducing reactivity to passing thoughts and emotions and improving the

ability to make adaptive choices in the present moment. Interdisciplinary team meetings were scheduled to discuss the progress and focus of treatment and how interventions should be tailored. After the treatment phase of 10 weeks, a follow-up phase of 12 weeks was planned. During these 12 weeks, patients returned for 2 days to meet with the social worker and two therapists of their choice. Issues of social reintegration and participation were discussed and patients were encouraged to continue using the principles learned during the treatment phase. Most therapists had previous experience in treating patients with complaints of chronic pain and/or chronic fatigue and were familiar with CBT. They had received training for each discipline (3–5 day) and attended two team meetings and two supervision meetings for each discipline during the trial. Therapists were able to contact their supervisor as needed during the trial. Treatment protocols were available and every therapist registered the number of sessions and the interventions used during treatment.

Cognitive behavioural therapy

This treatment is a psychotherapeutic approach incorporating elements of behavioural and cognitive therapy. The model of perpetuating cognitions and behaviour such as high physical attributions, decreased physical activity, low sense of control, focus on physical sensation and perceived lack of social support inform the intervention[31]. Through dialogue with the psychologist or behavioural therapist and implementation during home exercises, the patient was taught to change negative beliefs regarding symptoms of fatigue, self-expectation and self-esteem. Patients were also encouraged to adopt a regular sleep/wake rhythm from the beginning of treatment. Time-contingent schedules were made to gradually increase physical activity at home. Patients received 16 sessions of 45–60 min each, spread over 6 months. During the first 6 weeks, the patient had weekly contact with the psychologist or behavioural therapist, followed by biweekly contact for the next 20 weeks. The protocol was specifically tailored for either relatively active or passive patients. The relatively active patients started by practising at a certain activity level in which an increase of symptoms is avoided. For the passive patients, physical activities were gradually increased from the beginning of therapy. CBT is a monodisciplinary treatment given by a psychologist or cognitive behavioural therapist, experienced in treating patients with complaints of chronic pain and/or chronic fatigue and familiar with CBT. The psychologists and behavioural therapists attended a 3-day course to familiarize themselves with the CBT protocol for CFS. During the trial, five supervision meetings were held and the psychologists or cognitive behavioural therapists were able to contact the supervisor at any time as needed. The psychologists and cognitive behavioural therapists from the CBT group were not involved with treatment in the MRT group.

The main differences between MRT and CBT are shown in Table 1.

Randomization and masking

Prior to study commencement, an independent statistician produced computer-generated randomization lists. These lists were stratified by rehabilitation centre with block randomization of six patients at each centre. Sealed, opaque numbered envelopes were prepared by an independent research assistant according to the randomization lists, and distributed to the rehabilitation centres before the start of recruitment. The patients received the randomization envelope 1 week after the baseline assessment on returning the accelerometer to the centre. To ensure that the research assistants were blinded to treatment allocation, patients were asked not to open the envelope in front of the research assistants or inform them about the allocated treatment. Another sealed envelope with the same allocation was given to the department of planning and control to schedule the treatment. As with most trials of complex interventions, it was not possible to arrange for participants, therapists and consultants in rehabilitation medicine to be blinded to treatment allocation.

Table 1. Main differences between MRT and CBT

MRT	CBT
Combination of mindfulness-based CBT, gradual reactivation, body awareness therapy, pacing, social reintegration	CBT
Focus on healthy bodily symptoms and increasing body awareness	Ignore bodily symptoms of fatigue and pain
Gradual normalizing sleep/wake rhythm	Instantly normalize sleep/wake rhythm
First time-contingent increase in activity, later increase in activity with feedback of healthy bodily symptoms (during treatment sessions and home exercises)	Time-contingent increase in activity (home exercises)
Protocol tailored to the individual patient	Protocol tailored to relatively active and passive patient
Focus of treatment: components that are thought to be modifiable and have a strong correlation with the precipitation, predisposition and perpetuation of CFS	Focus of treatment: components that are thought to have a strong correlation with the perpetuation of CFS
Direct feedback during activity (in treatment session) and after home exercises (in following treatment session)	Feedback after home exercises in following therapy session
Therapists: consultant in rehabilitation medicine, physical therapist, occupational therapist, psychologist or cognitive behavioural therapist, social worker	Therapist: psychologist or cognitive behavioural therapist
Contact 44.5 h	Contact 16 h

MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy CFS, chronic fatigue syndrome.

Outcomes

Primary outcomes

Fatigue severity was measured by the CIS fatigue subscale, which contains eight items scored on a seven-point Likert scale (total score ranging from 8–56; lower scores indicate less fatigue)[28].

Health-related quality of life was measured by the Short-Form 36 (SF-36)[32], which consists of eight subscales (range 0–100; higher scores indicate a better quality of life). The SF-36 subscales can be summed to provide a physical component summary score and a mental component summary score[33]. Psychometric properties of the CIS and SF-36 are satisfactory[34,35]. The CIS and SF-36 are both self-rated questionnaires. The CIS was measured during all assessments, whereas the SF-36 was only evaluated at baseline, 26 and 52 weeks after start of treatment.

Secondary outcomes

Psychological symptoms were measured with the Symptom Check List-90[36], a self-administered, 90-item multidimensional questionnaire designed to screen for somatization, obsessive–compulsive behaviour, interpersonal sensitivity, depression, anxiety, anger–hostility, phobic anxiety and paranoid ideation (scale range 90–450; higher scores indicate higher degree of psychoneuroticism). Self-efficacy was measured with the Self-Efficacy Scale (SES)[28], a seven-item questionnaire (scale range 7–28; higher scores indicate more sense of control). Causal attributions were measured with the Causal Attribution List (CAL)[28], a 10-item questionnaire (scale range 5–20; higher scores indicate stronger conviction). Present-centred attention-awareness was assessed using the Mindfulness Attention Awareness Scale (MAAS)[37], a 15-item questionnaire (scale range 1–6; higher scores indicate greater awareness of present experiences). Patient treatment goals were evaluated using the Patient Specific Complaints and Goals questionnaire[38]. This is a self-administered questionnaire in which patients select three activities that they perceive as important in daily life and want to improve. Patients rate the performance of the activity on a 100-mm Visual Analogue Scale. The mean score of the three activities are calculated (scale range 0–100; higher scores indicate more problems with performing the activities). The impact of disease on physical and emotional functioning was assessed with the Sickness Impact Profile 8[39], a questionnaire that assesses the impact of disease on home management, mobility, alertness behaviour, sleep/rest, ambulation, social interaction, work and recreation/pastimes (scale range 0–6160; higher scores indicate higher functional impairment). An activity monitor (Sense Wear Pro Armband; Bodymedia, Inc., Pittsburgh, PA, USA) was used to measure physical activity. The armband has an integrated two-axial accelerometer that registers the peak acceleration (in counts) every minute in two directions (longitudinal and transverse axis). A count is a measure of frequency and intensity of acceleration and deceleration

(with higher counts indicating a higher degree of physical activity). Life satisfaction was measured with the nine-item Life Satisfaction Questionnaire, Dutch Version (scale range 1–6; higher scores indicate higher general life satisfaction)[40]. Self-rated improvement and satisfaction with the results was measured using the Improvement and Satisfaction questionnaire (EET), which includes five questions with different response categories. The EET was completed at 26 and 52 weeks after start of treatment; the CAL, MAAS and SES were completed at all assessments and the other secondary outcomes measures at baseline, 26 and 52 weeks. To decide whether a patient showed a clinically significant improvement and moved from the range representative of CFS-patients to the range seen in healthy individuals, a cut-off score of 35 on the CIS fatigue subscale was used[21]. The number of patients with a score below (improved) and above or equal to this cut-off of 35 (not improved) was determined.

Data processing

Before analysing data from the EET, responses to each of the five questions were dichotomized to categorize patients as satisfied or not satisfied and, improved or not improved. The categories 'very much satisfied' and 'satisfied' were merged into one category 'satisfied'. The categories 'neutral', 'dissatisfied' and 'very much dissatisfied' were merged into 'not satisfied'. In addition, the categories 'very much improved' and 'improved' were grouped as 'improved' and the categories 'neutral', 'declined' and 'very much declined' as 'not improved'.

To analyse physical activity, data were processed from the two accelerometers of the activity monitor using MATLAB software (The Math Works Inc., Natick, MA, USA). The procedure has been described previously by Vos-Vromans and colleagues[41].

Statistical analysis

Estimates necessary for the *a priori* power analysis of this superiority trial were based on previously published data[13,21,42]. These included mean baseline CIS fatigue subscore of 50–52 with a standard deviation of 3.9–5.9 and clinically relevant difference in change from baseline scores between groups of 3.0 points at 52 weeks with a within-group standard deviation of change score of 5.0. Allowing for a 25% dropout rate, 60 patients per group were required to detect this difference with 80% power at a significance level of 0.05. The longitudinal effect of MRT versus CBT on all outcomes was assessed using linear mixed models based on restricted maximum likelihood, as these models account for the correlation between repeated measures within the same patient and missing data. Along with treatment allocation, time (in weeks from baseline) and interaction of time by treatment allocation, rehabilitation centre was included as a fixed factor, because randomization was stratified by centre. Choice of the best-fitting covariance structure (i.e. structure of variances over different time-points and correlations between time-points) was based on

Akaike's information criterion. An intention-to-treat analysis was used, which means that data from all patients initially assigned to a treatment were analysed, regardless of whether or not they completed or received the treatment. Missing data were not imputed. The questions from the EET were analysed separately using binary logistic regression with centre and treatment as covariates. To measure a statistically significant difference between MRT and CBT regarding a clinically significant improvement, a *post hoc* binary logistic regression analysis was performed with treatment allocation and centre as covariates.

To assess whether treatment responses (changes in fatigue severity) to CBT and MRT were moderated by the levels of somatization, self-efficacy, depressive symptoms and education at baseline, the interactions between these variables and treatment allocation were tested. Linear mixed models were used, as described above, with each variable entered into the model separately. The three-way (and all lower-order) interactions between time and treatment allocation and the entered variable were included to test for effect modification.

To measure treatment adherence, the number of sessions were registered by computer.

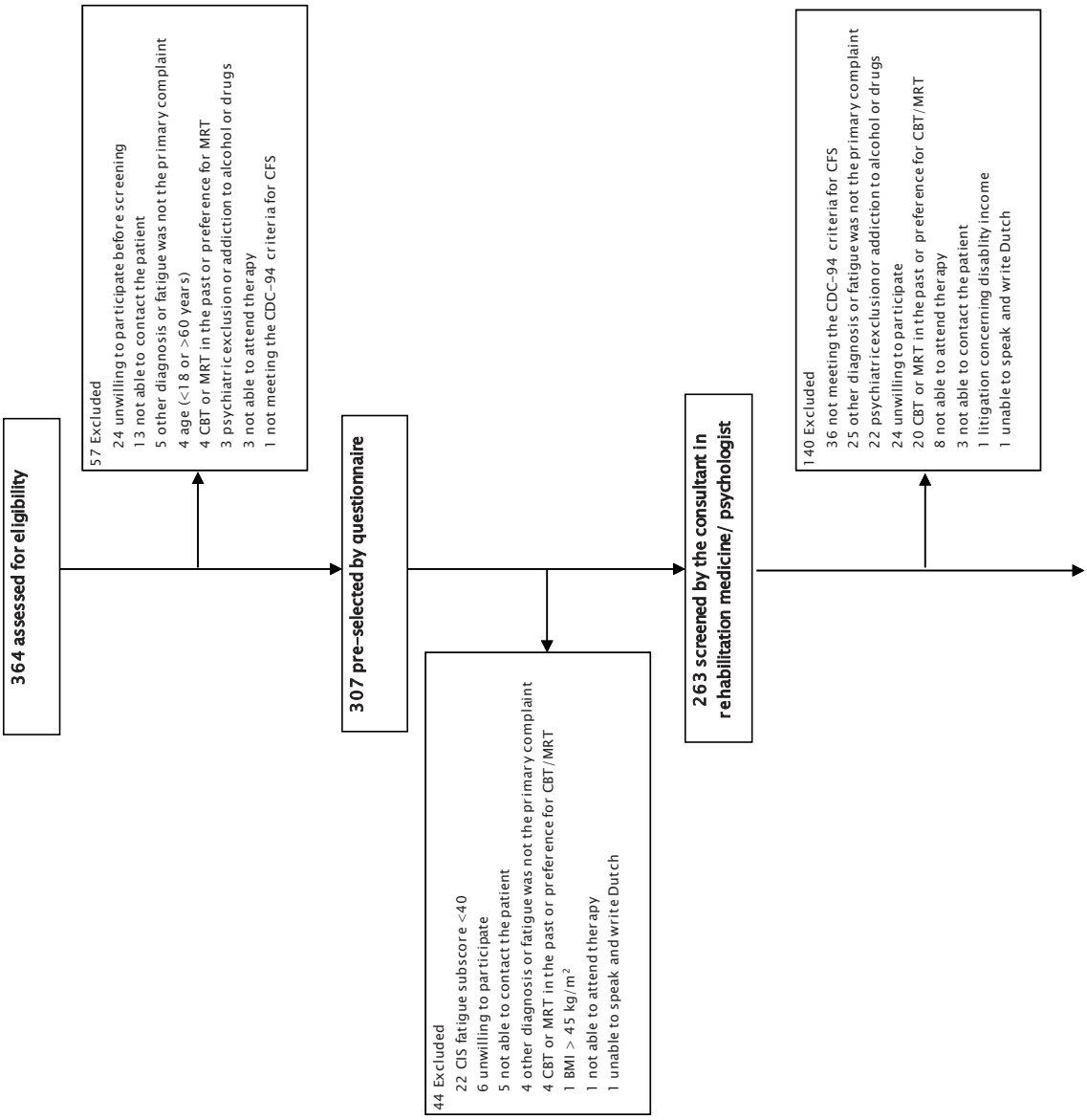
All analyses were performed using SPSS Statistics for Windows (version 20.0; IBM Corp., Armonk, NY, USA). Two sided P-values ≤ 0.05 were considered statistically significant.

This study is registered at http://isrctn.org (number ISRCTN77567702) and the published protocol is freely available (open access)[15].

RESULTS

Between December 2008 and January 2011, 364 patients were referred to the participating rehabilitation centres with a main complaint of fatigue. A total of 242 patients were excluded for various reasons, and 122 eligible participants completed the baseline assessment and were randomly assigned to either CBT (N = 60) or MRT (N = 62) (Figure 1). The mean (SD) duration between completing the questionnaires at referral and baseline was 90 (50.58) days. The mean (SD) duration between baseline and start of treatment was 25 (17.19) days for MRT and 22 (13.52) days for CBT. This difference was not significant. At 26 and 52 weeks, outcome data assessments were available for 114 (55 CBT, 59 MRT) and 112 (55 CBT, 57 MRT) participants, respectively. At baseline, 26 and 52 weeks, activity monitor data were available for 122, 97 and 80 participants, respectively. Skin rash and unwillingness to either wear the monitor or travel to the rehabilitation centre to collect the monitor were the main reasons for not providing activity monitor data.

In total, 18 participants (12 CBT, six MRT) withdrew from treatment, of whom two (one CBT, one MRT) reported an increase in complaints and three did not experience improvement. Reasons for stopping treatments are shown in Figure 1. Of the 104 participants receiving treatment, five in the CBT group did not reach the 70% level of adherence to treatment; all participants in the MRT group reached the 70% adherence level.


364 assessed for eligibility
57 Excluded
24 unwilling to participate before screening
13 not able to contact the patient
5 other diagnosis or fatigue was not the primary complaint
4 age (<18 or >60 years)
4 CBT or MRT in the past or preference for MRT
3 psychiatric exclusion or addiction to alcohol or drugs
3 not able to attend therapy
1 not meeting the CDC-94 criteria for CFS
307 pre-selected by questionnaire
44 Excluded
22 CIS fatigue subscore <40
6 unwilling to participate
5 not able to contact the patient
4 other diagnosis or fatigue was not the primary complaint
4 CBT or MRT in the past or preference for CBT/MRT
1 BMI > 45 kg/m2
1 not able to attend therapy
1 unable to speak and write Dutch
263 screened by the consultant in rehabilitation medicine/ psychologist
140 Excluded
36 not meeting the CDC-94 criteria for CFS
25 other diagnosis or fatigue was not the primary complaint
22 psychiatric exclusion or addiction to alcohol or drugs
24 unwilling to participate
20 CBT or MRT in the past or preference for CBT/MRT
8 not able to attend therapy
3 not able to contact the patient
1 litigation concerning disability income
1 unable to speak and write Dutch

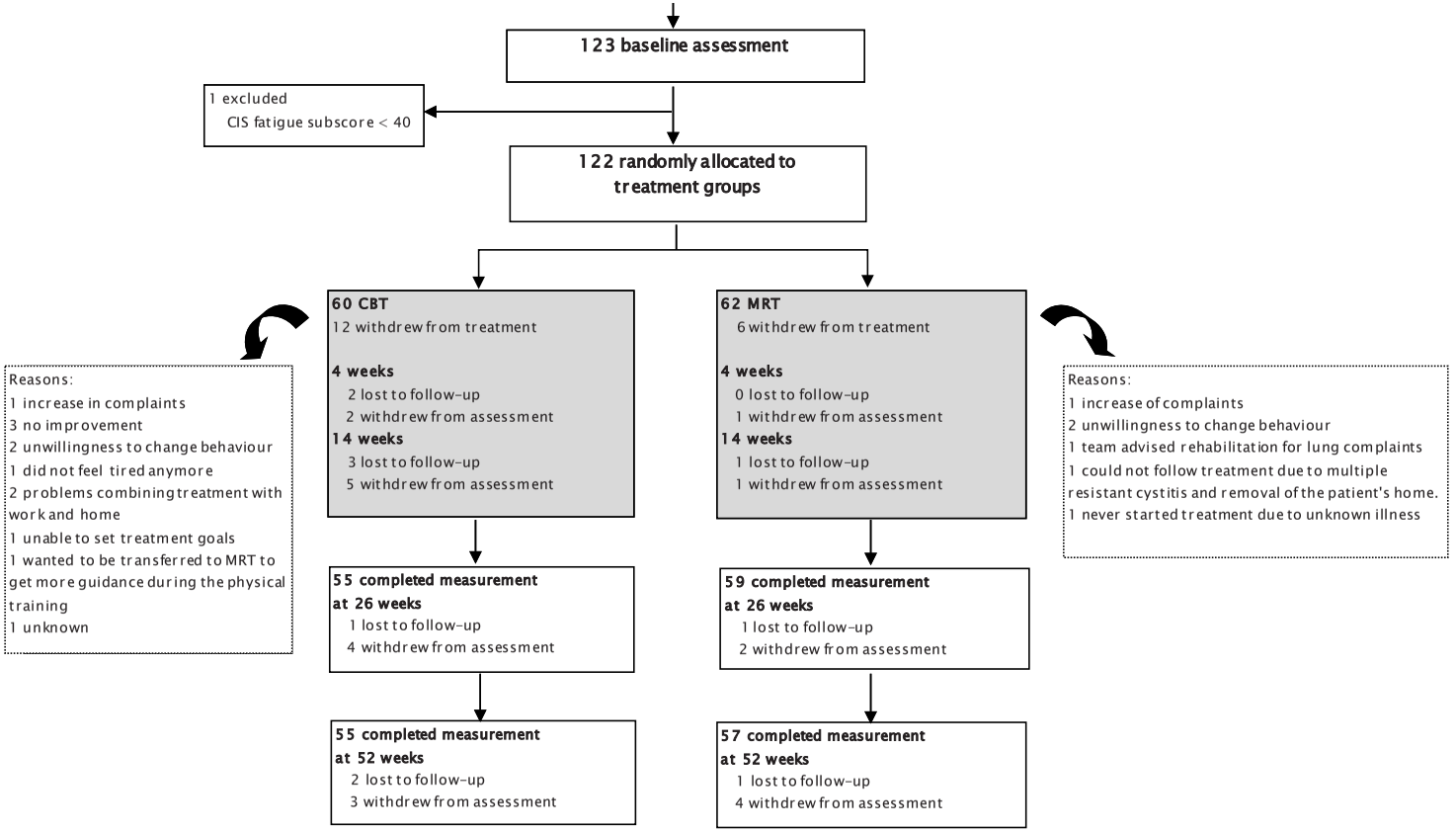


Figure 1. CONSORT trial profile

MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CFS, chronic fatigue syndrome; BMI, body mass index; CDC-94 criteria, US Centers for Disease Control and Prevention (CDC-94) criteria; CIS, Checklist Individual Strength.

Table 2 shows the demographic and clinical characteristics at referral, with no significant differences between groups (P > 0.05). Two participants (one CBT, one MRT) did not complete the questionnaires at referral. The mean age of participants was 40 years (range 18–59 years) and 80% were female.

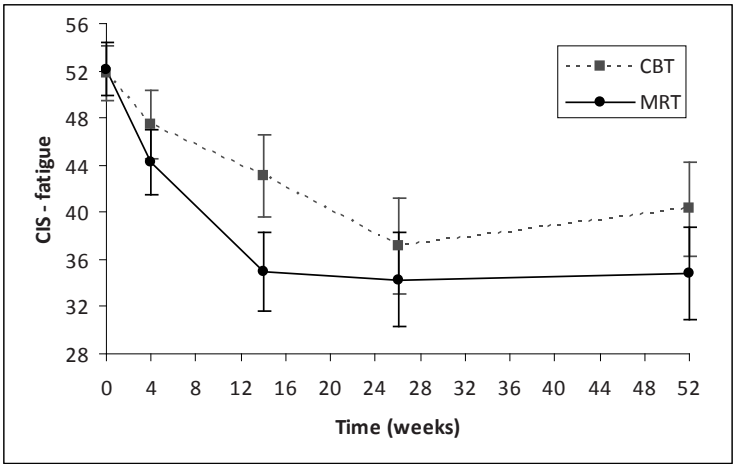
Table 2. Characteristics of the study participants at baseline

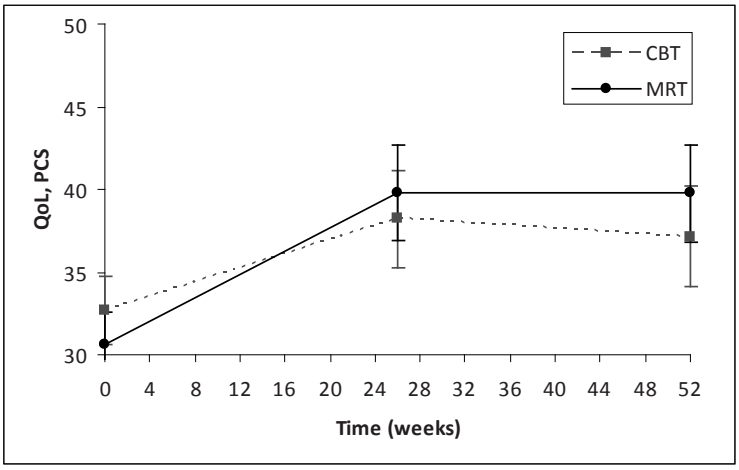
	MRT (N = 62)	CBT (N= 60)
Demographic data		
Age, mean (SD), years	40.0 (10.2)	40.6 (12.0)
Female sex, N (%)	50 (80.7)	47 (78.3)
Country of birth, N (%) [a]		
The Netherlands	55 (88.7)	55 (91.7)
Other European country	5 (8.1)	1 (1.7)
Country outside Europe	1 (1.6)	3 (5.0)
Education (at referral) ('low'/'medium-high'/missing), N	38/23/1	38/21/1
Situation (at referral), N (%)[a]		
Single	14 (23.0)	10 (17.0)
Married or living with partner	40 (65.6)	37 (62.7)
Relationship but not living with partner	2 (3.3)	4 (6.8)
Living with parents	5 (8.2)	5 (8.5)
Other	0 (0.0)	3 (5.1)
Clinical data, mean (SD)		
CIS, fatigue subscale	51.47 (5.08)	51.05 (5.09)
SF-36, quality of life, MCS	46.57 (9.23)	44.38 (9.02)
SF-36, quality of life, PCS	30.59 (7.93)	32.60 (7.78)
Duration of complaints (at referral), N (%)		
0.5–1 year	3 (4.8)	8 (13.3)
1–2 years	16 (25.8)	14 (23.3)
2–5 years	19 (30.7)	13 (21.7)
> 5 years	24 (38.7)	25 (41.7)

[a] Missing data for two patients at referral (one CBT, one MRT). No missing data at baseline.
MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CIS, Checklist Individual Strength; SF-36, Short-Form 36; MCS, mental component summary score; PCS, physical component summary score.

Table 3 shows the mean differences in fatigue and quality of life between CBT and MRT over the course of the study. The differences [(95% confidence interval (CI)] in fatigue severity between groups at 4, 14, 26 and 52 weeks were -3.24 (-6.26 to -0.22; P = 0.04), -8.17 (-12.20 to -4.14; P < 0.001), -3.02 (-8.07 to 2.03; P = 0.24) and -5.69 (-10.62 to -0.76; P = 0.02) respectively. No significant differences in quality of life were found be-

tween the groups. Effect sizes (Cohen's d) of fatigue severity ranged from 0.20 to 0.46, indicating a small to medium effect. Mean fatigue levels decreased and health-related quality of life levels increased in both groups during the treatment phase (0–26 weeks). Between completion of treatment and the 52-week follow-up, fatigue severity increased in the CBT group, whereas it remained the same in those receiving MRT (Figure 2).





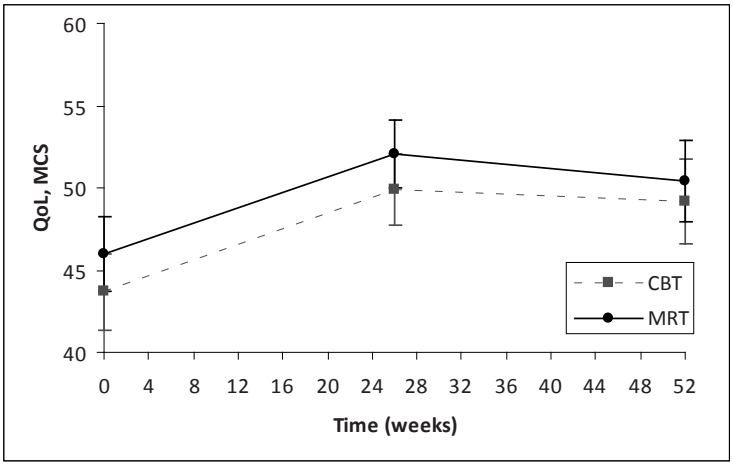


Figure 2. Fatigue severity and quality of life by treatment group[a]

[a] Values are estimated means and 95% confidence intervals.

CIS, Checklist Individual Strength; CBT, cognitive behavioural therapy; MRT, multidisciplinary rehabilitation treatment; QoL, Quality of life; PCS, physical component summary score; MCS, mental component summary score.

At 52 weeks 49% of the patients in the MRT group had a CIS fatigue subscale score of less than 35 compared to 26% of the patients receiving CBT. This difference between treatment allocation was statistically significant (P = 0.014).

Tables 4 and 5 present the results of the secondary outcomes. Self-efficacy and achievement of personal goals increased more during the follow-up period in the MRT group than in the CBT group. The mean (95% CI) differences for self-efficacy and achievement of personal goals at 52 weeks were 1.89 (0.40 to 3.38; P = 0.01) and -17.28 (-26.95 to -7.62; P = 0.001), respectively. At 52 weeks of follow-up, 37 participants in the MRT group (66.1%) were satisfied with the results of treatment compared to 22 participants in the CBT group (40.0%; P = 0.006) and significantly more participants would recommend treatment to others in the MRT (N = 47; 83.9%) than CBT (N = 28; 51.9%; P = 0.001). No significant between-group differences were found regarding changes in attention and awareness, functional impairment, physical and non-physical attributions, psychological symptoms, physical activity and satisfaction with life.

Table 3. Observed means and estimated effects of MRT compared with CBT on fatigue severity and quality of life

	MRT N = 62	CBT N = 60	Cohen's d[a]	Between-group (CBT and MRT) difference (95% CI)[b]	P-value
CIS, fatigue subscale					
Baseline	51.47 (5.08)	51.05 (5.09)			
4 weeks[c]	43.27 (8.38)	46.77 (7.94)	0.38	-3.24 (-6.26 to -0.22)	0.04
14 weeks[c]	34.14 (12.37)	42.65 (8.81)	0.25	-8.17 (-12.20 to -4.14)	<0.001
26 weeks	33.42 (13.96)	36.16 (13.71)	0.20	-3.02 (-8.07 to 2.03)	0.24
52 weeks	33.84 (14.33)	40.05 (12.79)	0.46	-5.69 (-10.62 to -0.76)	0.02
Quality of life, MCS (SF-36)					
Baseline	46.57 (9.23)	44.38 (9.02)			
26 weeks	52.61 (7.10)	50.76 (8.82)	0.23	2.25 (-0.68 to 5.17)	0.13
52 weeks	51.10 (10.22)	49.88 (9.16)	0.13	1.59 (-1.96 to 5.13)	0.38
Quality of life, PCS (SF-36)					
Baseline	30.59 (7.93)	32.60 (7.78)			
26 weeks	40.05 (10.66)	38.36 (11.31)	0.15	1.63 (-2.42 to 5.68)	0.43
52 weeks	40.19 (11.29)	36.67 (10.40)	0.32	2.67 (-1.45 to 6.79)	0.20

Data are observed means (SD), unless otherwise stated.

[a] Cohen's d is the mean observed difference between CBT and MRT divided by the pooled SD.

[b] Estimated differences between groups are calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance).

[c] Mid-treatment assessments at 4 and 14 weeks.

MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CI, confidence interval; CIS, Checklist Individual Strength; MCS, mental component summary score; SF-36, Short-Form 36; PCS, physical component summary score.

Table 4. Observed means and estimated effects of MRT compared with CBT on the secondary outcomes

	MRT	CBT	Between-group (CBT and MRT) difference (95% CI)[a]	P-value
Self-efficacy (SES)				
Baseline	17.42 (2.90)	17.63 (3.04)		
26 weeks	21.14 (4.28)	19.67 (4.28)	1.65 (0.07 to 3.23)	0.04
52 weeks	20.64 (3.71)	18.49 (4.25)	1.89 (0.40 to 3.38)	0.01
Attention and awareness (MAAS)				
Baseline	3.81 (0.84)	3.76 (0.84)		
26 weeks	4.35 (0.85)	4.16 (0.82)	0.25 (-0.04 to 0.53)	0.10
52 weeks	4.46 (0.85)	4.17 (1.00)	0.32 (-0.008 to 0.64)	0.06
Functional impairment (SIP8)				
Baseline	1418.27 (614.24)	1222.17 (633.53)		
26 weeks	760.66 (631.23)	743.16 (610.15)	9.80 (-205.28 to 224.88)	0.93
52 weeks	774.68 (689.00)	791.62 (643.97)	50.78 (-186.68 to 288.24)	0.67
Physical attributions (CAL)				
Baseline	13.15 (2.75)	13.17 (2.33)		
26 weeks	11.97 (3.44)	12.94 (3.74)	-1.10 (-2.38 to 0.19)	0.09
52 weeks	12.41 (3.59)	13.26 (3.02)	-0.68 (-1.90 to 0.54)	0.27
Non-physical attributions (CAL)				
Baseline	9.94 (2.70)	10.23 (2.50)		
26 weeks	10.93 (3.13)	10.25 (2.64)	0.76 (-0.32 to 1.84)	0.17
52 weeks	10.39 (2.77)	9.58 (2.46)	0.76 (-0.21 to 1.74)	0.12
Psychological symptoms (SCL-90)				
Baseline	158.73 (39.86)	163.87 (34.40)		
26 weeks	129.63 (36.06)	136.17 (31.17)	-7.29 (-19.31 to 4.74)	0.23
52 weeks	130.15 (34.08)	139.15 (32.68)	-7.83 (-19.84 to 4.19)	0.20
Satisfaction with life (LSQ)				
Baseline	3.87 (0.72)	4.00 (0.72)		
26 weeks	4.41 (0.76)	4.37 (0.69)	0.07 (-0.18 to 0.32)	0.59
52 weeks	4.35 (0.90)	4.31 (0.75)	-0.01 (-0.28 to 0.30)	0.94
Personal goals (PSCG)				
Baseline	72.61 (12.51)	78.19 (15.72)		
26 weeks	34.87 (18.68)	46.65 (25.23)	-12.24 (-20.95 to -3.53)	0.006
52 weeks	30.71 (20.98)	49.92 (27.53)	-17.28 (-26.95 to -7.62)	0.001
Physical activity				
Baseline	206233.65 (40264.16)	202033.66 (43379.41)		
26 weeks	227283.24 (45698.55)	210019.75 (48068.09)	15572.61 (-3242.93 to 34388.14)	0.10
52 weeks	218214.41 (48564.30)	215262.14 (57074.22)	2009.58 (-19140.04 to 23159.19)	0.85

Data are means (SD), unless otherwise stated.

[a] Estimated differences between groups are calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance).

MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CI, confidence interval; SES, Self-Efficacy Scale; MAAS, Mindfulness Attention and Awareness Scale; SIP8, Sickness Impact Profile 8; CAL, Causal Attribution List; SCL-90, Symptom Checklist-90; LSQ, Life Satisfaction Questionnaire; PSCG, Patient Specific Complaints and Goals questionnaire.

Table 5. Self-rated improvement and satisfaction with the results (EET) at 26 and 52 weeks of follow-up

	MRT	CBT	P-value[a]
26 weeks			
Self-rated improvement and satisfaction with the results			
'satisfaction with the results'	41 (71.9)	29 (53.7)	0.05
'achieving personal goals?[b]	6.70 (2.44)	5.72 (2.72)	0.06
'difference in dealing with problems'	50 (87.7)	47 (87.0)	0.86
'difference in daily activities'	46 (80.7)	41 (75.9)	0.57
'would recommend therapy to others'	48 (85.7)	34 (63.0)	0.007
'not feeling CFS-patient anymore'	17 (30.4)	23 (41.8)	0.14
52 weeks			
Self-rated improvement and satisfaction with the results			
'satisfaction with the results'	37 (66.1)	22 (40.0)	0.006
'achieving personal goals?[b]	6.46 (2.49)	5.30 (2.60)	0.05
'difference in dealing with problems'	49 (87.5)	38 (70.4)	0.03
'difference in daily activities'	45 (80.4)	32 (59.3)	0.02
'would recommend therapy to others'	47 (83.9)	28 (51.9)	0.002
'not feeling CFS-patient anymore'	18 (32.1)	19 (35.2)	0.73

Values are numbers of patients with improvement (%) in the MRT and CBT groups, unless otherwise stated.
[a] P-values are calculated using binary logistic regression with centre and treatment allocation as covariates
[b] Scores on the 'achieving personal goals' item range from 1 to 10, with higher scores indicating more achievement of personal goals.
MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; EET, Improvement and Satisfaction questionnaire.

Finally, there was a significant interaction between education level at baseline and treatment allocation on improvement of fatigue severity at 52 weeks (P = 0.04; Table 6). This indicates that individuals with low education levels seem to benefit more from MRT, as compared to CBT, than those with higher education levels. There was no significant interaction between baseline scores of somatization, self-efficacy or depressive symptoms and treatment allocation, indicating no effect modification.

Table 6. Estimated differences in fatigue severity between MRT and CBT depending on education level

	Between-group (CBT and MRT) difference (95% CI)[a]	P-value
Low level of education		
26 weeks	-5.68 (-12.05 to 0.69)	0.08
52 weeks	-9.27 (-15.48 to -3.05)	0.004
Medium/high level of education		
26 weeks	2.44 (-5.80 to 10.68)	0.56
52 weeks	0.72 (-7.44 to 8.88)	0.86

[a] Data are presented as estimated differences between MRT and CBT. The estimated differences between groups are calculated using linear mixed models with centre, treatment allocation, time and interaction between education, time and treatment allocation (and their lower-order interactions) as covariates (unstructured covariance).
MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CI, confidence interval.

DISCUSSION

In this trial, we evaluated whether MRT, a multidisciplinary treatment with a combination of different interventions including CBT, is more effective than CBT alone in patients with CFS. The severity of fatigue at 4, 14 and 52 weeks after the start of treatment was significantly more reduced in patients in the MRT group compared to those receiving CBT. At 26 weeks there was no significant difference in fatigue severity between the CBT and MRT groups. After the end of treatment at 26 weeks, the reduced level of fatigue was sustained until 52 weeks of follow-up in patients who received MRT; during this period the mean fatigue level of the patients in the CBT group increased. The fact that MRT resulted in a larger effect at 52 weeks is especially relevant in patients with CFS, which typically follows a chronic course. In recognition of the importance of long-term outcome in patients with CFS, follow-up of the participants in this trial at 5 years after the end of treatment is planned. Although quality of life increased in both groups during treatments, a significant difference was not found between CBT and MRT.

Our findings are in line with the results from two nonrandomized studies by Schreurs et al[20] and by Goudsmit et al[22]; both groups found a decrease in fatigue severity after rehabilitation treatment. To our knowledge, the present study is the first RCT to compare the effects of MRT with CBT. Our results provide evidence that MRT is more effective in sustaining the decrease in fatigue severity and that patients are more satisfied with the results at 52 weeks compared to CBT, suggesting that implementation of MRT in rehabilitation centres seems recommendable. A tailored treatment including elements of different interventions with direct feedback from the therapist whilst increasing activities and paying more attention to the body awareness, thereby increasing

patients' insight into the relation and reciprocity between the mind and body, might cause a change in behaviour and influence sensitization processes in the central nervous system[3]. Future research is recommended to confirm this idea and to identify the exact mechanisms involved.

The superiority of MRT, as demonstrated by the fatigue severity scores, is further supported by the effects on self-efficacy, achievement of personal goals, self-rated improvement and satisfaction with the results.

This trial has a number of strengths; in particular, internal validity is high due to robust randomization and concealed allocation procedures, trial registration and protocol publication, intention-to-treat analysis and prespecification of primary outcomes and analytical methods. The drop-out rate was low (<10%) and only 10 participants did not provide data at the follow-up assessment. Furthermore, (i) standardized instruments were used, (ii) there was a long period of follow-up and (iii) both treatments were carried out at the same location to ensure between-group equivalence of treatment expectations.

Several limitations should also be considered. Patients who were unable to attend three half-day therapy sessions during the week were excluded from participation; however only 12 of 364 patients referred were excluded on this basis. In addition, 35 patients who were excluded before randomization did not meet the CDC-94 criteria of CFS and 54 patients were unwilling to participate; this should be taken into account when generalizing the results to the total population of patients referred to secondary healthcare with fatigue as the main complaint. Another limitation of the study is the difference in amount of treatment. According to the protocol, patients in the MRT group received 44.5 h of treatment compared to 16 h in the CBT group (both over a period of 26 weeks). Because both treatments are currently recommended in the Netherlands for patients with CFS, we matched treatments as closely to 'usual practice' as possible in order to provide a 'real-world' estimate of the comparative effectiveness of the two treatments. Thus while the difference in duration of attention given to patients might have influenced the results, this represents current clinical practice. However a recent meta-analysis[43] showed that the number of sessions moderated the effectiveness of CBT, with 16 sessions being the most effective immediately post-treatment. No data are available on the relationship between number of CBT sessions and long-term outcome. Further, it is unknown how many sessions of MRT lead to the most effective treatment. Future studies should analyse dose–response relations for MRT with regard to post-treatment and long-term effectiveness. Finally the MRT protocol incorporated different interventions as described earlier and the therapists were able to vary these interventions depending on the modifiable components and the personal goals of treatment in each patient. It remains unclear which of the specific interventions had the greatest impact on outcome. However, providing different treatment elements on the basis of individual assessment of contributing factors is also the most important feature

of MRT. Nevertheless, future research should seek to identify which specific parts of the MRT are the most important in influencing outcome.

Final outcome might also be influenced by factors other than those specifically targeted by the treatment. In the effect modification analysis, the interaction between education level and treatment allocation was associated with the final result of treatment. Patients with a lower level of education might be less willing to accept that CFS may respond to a solely psychological treatment such as CBT and be more willing to believe that physical therapy and occupational therapy are necessary. Previous research also showed that treatments in which a physiological explanation of fatigue perpetuation was provided had larger effect sizes compared to trials in which a solely psychologically based explanation of the chronicity was given[43]. A physiological explanation may be viewed as more credible by patients. Future research should further analyse which patient characteristics have the greatest impact on the positive outcome.

In conclusion, this study provides evidence that MRT is more effective in reducing long-term fatigue severity than CBT in patients with CFS. Although implementation in comparable populations can be recommended based on clinical effectiveness, these findings should be replicated in another multi-centre trial and the cost-effectiveness analysed.

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Conflict of interest statement

No conflicts of interest to declare.

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4

Economic evaluation of multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome

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Vos-Vromans DCWM, Evers SMAA, Huijnen IPJ, Köke AJA, Hitters WMGC, Rijnders LJM, Pont M, Knottnerus JA, Smeets RJEM. Economic evaluation of multidisciplinary rehabilitation treatment versus cognitive behavioural therapy for patients with chronic fatigue syndrome.

ABSTRACT

Background. Multidisciplinary rehabilitation treatment (MRT) is more effective in reducing fatigue at long-term compared to cognitive behavioural therapy (CBT) for patients with chronic fatigue syndrome (CFS) but evidence on its cost-effectiveness is lacking.

Aims. To compare the cost-effectiveness of MRT versus CBT for patients with CFS from a societal perspective.

Methods. A multi-centre randomized controlled trial comparing MRT with CBT was conducted among patients with CFS (N = 122). The societal costs (healthcare costs, patient and family costs, and costs for loss of productivity), fatigue severity, quality of life, quality-adjusted life-year (QALY), and cost-effectiveness ratios (ICERs) were measured over one year follow-up. The main outcome of the cost-effectiveness analysis was fatigue measured by the Checklist Individual Strength (CIS). The main outcome of the cost-utility analysis was the QALY based on the EuroQol-5D-3L utilities. Sensitivity analyses were performed, and uncertainty was calculated using the cost-effectiveness acceptability curves and cost-effectiveness planes.

Results. Data of 109 patients (57 MRT and 52 CBT) were analyzed. MRT was significantly more effective in reducing fatigue at 52 weeks. Mean difference in QALY between the treatments was not significant (0.09, 95% CI: -0.02, 0.19). The total societal costs were significantly higher for patients allocated to MRT (difference €5389, 95% CI: 2488, 8091). MRT has a high probability of being the most cost effective, taking fatigue as primary outcome. The ICER is €856 per unit of the CIS fatigue subscale. The results of the cost-utility analysis, using the QALY, indicate that the CBT had a higher likelihood of being the most cost-effective.

Conclusions. The probability of being the most cost-effective treatment is higher for MRT when taking the disease-specific outcome as primary outcome variable. Taking QALY as primary outcome, CBT has the highest probability of being the most cost-effective.

INTRODUCTION

Chronic fatigue syndrome (CFS) is defined as medically unexplained disabling fatigue that persists for more than 6 months, which often leads to a decrease in quality of life, restrictions in personal and social activities and a limited ability to work[1]. The prevalence of CFS is estimated between 0.2-2.6% worldwide[2]. However, only in few countries the burden of CFS to society has been measured. In the United States, the annual direct total costs per patient were estimated between $2342 and $8675 depending on the sample used[3,4]. Annual total loss of productivity per patient in the US were estimated at $20000[5]. In another study, based on a sample in the United Kingdom, annual productivity costs per patient were estimated at £22684[6]. In the Netherlands the annual costs for healthcare of patients with unexplained physical symptoms, including CFS, were estimated at €3123 per patient[7]. These healthcare costs together with annual work-related costs and paid substitution of domestic tasks were estimated at €6815 per patient[7]. Although this study involved patients with a variety of unexplained physical symptoms it provides an indication of the high economic burden and the need to investigate new treatments and their benefits for the patient and society. One commonly used treatment with evidence supporting its effectiveness and cost-effectiveness is cognitive behavioural therapy (CBT)[8]. Taking quality-adjusted life-years (QALY) as primary outcome, previous studies showed that CBT is a cost-effective treatment when compared to guided support groups[9,10], graded exercise therapy, specialist medical care or adaptive pacing therapy[9,11]. When fatigue is the primary outcome, CBT is equally cost-effective as counseling[12] and cost-effective compared to guided support groups or a natural course group[10]. Although cost-effective, CBT does not improve fatigue severity and quality of life for all patients[8]. To further improve the effectiveness, investigation of multidisciplinary treatments that include CBT in combination with other interventions has been advocated[8]. In response to this hypothesis a multidisciplinary rehabilitation treatment (MRT) was developed and studied in a randomized controlled trial (RCT) comparing MRT with CBT[13]. Results of that trial revealed that one year after start of treatment, MRT is more effective in reducing severity of fatigue compared to CBT[14]. No statistically significant differences in quality of life were found between MRT and CBT. Studies investigating cost-effectiveness of multidisciplinary rehabilitation treatments for patients with CFS are scarce. The only study investigating the cost-effectiveness of a rehabilitation treatment is the FINE trial[15]. This trial compared a rehabilitation treatment to supportive listening and treatment as usual. The rehabilitation treatment in the FINE trial was a mono-disciplinary treatment with other treatment modalities as provided in MRT. Results of the FINE trial indicated that pragmatic rehabilitation was not cost-effective when looking at the costs per QALY measured by the EuroQol-5D-3L (EQ-5D-3L). Recently, studies among patients with chronic illnesses in which fatigue is a common complaint, the use of disease-specific outcome measures besides generic measures are advised since the generic measures might not be sensitive enough to

measure change after treatment[16-18]. To provide a more disease-specific outcome the fatigue severity measured by the Checklist Individual Strength (CIS), subscale fatigue and quality of life measured with the Short-Form 36 (SF-36) were included. Studies regarding the cost-effectiveness of MRT or MRT compared to CBT have never been done. Therefore, as an integral part of the RCT, the cost-effectiveness was analyzed. The aim of the present study is to report the one-year cost-effectiveness and cost-utility from a societal perspective comparing MRT and CBT in terms of reduction in fatigue and gain in health-related quality of life and gains in QALYs.

METHODS

Study design and participants

This multi-centre, two-arm RCT was registered in the ISRCTN database (Trial Registration Number: ISRCTN77567702). A detailed description of the design of the trial has been published elsewhere[13]. Participants were recruited from four outpatient rehabilitation centres in the Netherlands. Patients were asked to participate if they met the US Centers for Disease Control and Prevention (CDC-94) criteria for CFS[1]. Other inclusion criteria were: a CIS fatigue subscale score of 40 or more[19], willingness to participate in a treatment aimed at changing behaviour, age between 18 and 60 years, and comprehension of written and verbal Dutch. Patients were excluded if they suffered from a medical condition explaining the presence of chronic fatigue, had a psychiatric or depressive disorder, dementia, anorexia, bulimia nervosa, alcohol and/or drug abuse, a body mass index equal or more than 45, or were pregnant. Patients who already had received CBT or MRT for CFS in the past, or had to travel more than 1 h to the nearest participating rehabilitation centre, were also excluded. At baseline, 26 weeks (directly after end of treatment) and 52 weeks after start of treatment outcomes were accessed. Embedded in the RCT was an economic evaluation study, which consisted of a cost-effectiveness analysis (primary outcome: fatigue) and a cost-utility analysis (primary outcome: QALY). The Research Ethics Committee of Rotterdam (reference 2008/22) approved the study.

Interventions

In MRT, a consultant in rehabilitation medicine, social worker, psychologist, physical therapist and occupational therapist worked as an interdisciplinary team together with the patient for 6 months. The protocol prescribed a total of 44.5 face-to-face contact hours. Gradual reactivation, pacing, mindfulness, body awareness therapy, normalizing sleep/wake rhythm and social reintegration were combined with CBT and tailored to the individual needs and goals of the patient. Treatment is based on the biopsychosocial

model, suggesting that multiple factors (physical, mental and social factors) may lead to the development and persistence of CFS[20].

CBT is a psychotherapeutic approach in which elements of behavioural and cognitive therapy approaches are incorporated to change behavioural and cognitive factors, which are assumed to perpetuate the symptoms of CFS[21]. CBT was delivered by a psychologist or cognitive behavioural therapist. The protocol of CBT prescribed a total of 16 face-to-face contact hours during 6 months. Both treatments aimed at decreasing severity of fatigue and increasing quality of life. Treatments are described earlier[13].

Outcome measures

Primary outcomes

For the cost-effectiveness analysis, the primary outcome is fatigue severity, which was measured by the Checklist Individual Strength subscale fatigue (CIS fatigue). The CIS fatigue subscale has eight items scored on a 7-point Likert scale, with a total score ranging from 8-56. Lower scores indicate less fatigue[22]. In the currently presented cost-effectiveness analyses the CIS fatigue scores were recoded, which means that a higher score indicates a more positive effect (less fatigue).

For the utility analysis, QALYs were generated from the standard Dutch version of the EuroQol-5D-3L (EQ-5D-3L)[23]. The EQ-5D-3L contains five dimensions of health-related quality of life, namely mobility, self-care, daily activities, pain/discomfort and depression/anxiety. Each dimension can be rated at three levels: no problem, some problems and major problems. The five dimensions were summed into a health state. Utility values were calculated for these health states, using preferences elicited from a general population from the UK, the so-called Dolan algorithm[24]. Utilities were calculated for every assessment. The accrual of QALYs from baseline to 52 weeks follow-up was calculated using the area under the curve, assuming a linear change between each available time point.

Secondary outcomes

As a secondary outcome for the cost-effectiveness and cost-utility analyses, health-related quality of life was measured by the Short-Form 36 (SF-36)[25]. The SF-36 has 8 subscales which were combined in two summary scores; the mental (MCS) and physical component summary score (PCS). The outcomes at 52 weeks follow-up were used in the cost-effectiveness analysis.

Costs

Costs from a societal perspective were registered from baseline until 52 weeks after baseline. These costs included healthcare costs, patient and family costs, and costs following productivity losses. Healthcare costs included costs for all healthcare services

including costs for the interventions and costs for all medication (including over the counter medication). Patient and family costs included travelling costs to all healthcare institutions, parking costs for the visits to the hospital and domestic help which would be normally done by the patient her/himself and unpaid informal care provided by family or other unpaid people. Productivity losses were measured by costs of absenteeism of work. Table 1 shows the identified categories. The Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P) was used to measure the costs of healthcare, patient and family and productivity losses[26]. TiC-P, part I, a questionnaire on absence from work, informal care and domestic help, was filled in every month. TiC-P, part II, a questionnaire on healthcare costs was filled in every three months.

The valuation of healthcare costs and the patient and family costs was based on the update Dutch manual for cost analysis in healthcare research[27]. Costs were indexed to the year 2012 by means of the consumer price indexes of the Dutch Central Bureau of Statistics. For care for which no costs-guidelines were available, estimations of the costs were made, based on the real costs or on population based estimates from literature. Table 1 shows the costs per identified category. Medication costs were based on the tariffs from the Dutch College of Health insurances (www.medicijnkosten.nl). Treatment hours for MRT and CBT were computer-registered by the therapist and the consultant in rehabilitation medicine after each treatment session. The duration of the treatment sessions were summed and costs calculated using the Dutch diagnosis dependent treatment combination for cost-pricing the interventions (www.dbconderhoud.nl). According to this procedure the following costs per treatment category were used: 0-2 h of outpatient rehabilitation treatment €200, 2-6 h of treatment €539, 6-18 h €1364, 18-49 h €3557, 49-129 h €8620, 129-299 h €19392, 299 h and more €37268.

To value the travelling costs, the number of visits to the healthcare services was multiplied by the mean distance and again multiplied by the costs per kilometre[27]. An assumption of 26.4 kilometres was made for the mean distance to a rehabilitation centre. This assumption is based on the ratio between number of hospitals divided by the number of rehabilitation centres in the Netherlands multiplied by the mean distance between a hospital and a patient's home.

Every month the patient reported the days lost from work due to fatigue as well as his/her wages (TiC-P, part II). Following the human capital approach, total hours of absenteeism was multiplied by the hourly wages and afterwards multiplied by factor 0.8. The 0.8 factor is a correction because productivity in the Netherlands decreases with a 0.8 factor as working hours decrease due to absenteeism[27]. The national mean aged and gender specific wages were taken when the patient preferred not to fill in his/her wages.

Table 1. Costs and valuation per category

Category	Unit	Valuation (in €)
Healthcare costs		
General practitioner	Per consult	29.74
Regional Institution for ambulatory mental healthcare (RIAGG)	Per consult	115.91
Psychiatrist, psychologist, psychotherapist in private practice	Per consult	95.60
Psychiatrist, psychologist in outpatient academic hospital	Per consult	36.12
Psychiatrist, psychologist in outpatient in general hospital	Per consult	30.80
Psychiatrist, psychologist in outpatient psychotherapeutic setting or in psychiatric hospital	Per consult	183.76
Psychiatrist, psychologist in outpatient in other hospital	Per consult	108.61
Company physician	Per consult	173.90
Medical specialist (outpatient hospital)	Per consult	33.46
Paramedics	Per consult	32.50
Social worker	Per consult	69.04
Centre for alcohol and drug abuse (CAD)	Per consult	98.28
Alternative healer	Per consult	59.31
Self-help group	Per consult	67.76
Daytreatment in academic hospital	Per day	252.81
Daytreatment in general hospital	Per day	168.89
Daytreatment in psychotherapeutic setting or psychiatric hospital	Per day	163.58
Daytreatment in other setting	Per day	187.22
Admission in academic hospital	Per day	610.77
Admission in general hospital	Per day	462.06
Admission in psychotherapeutic setting or psychiatric hospital	Per day	246.43
Admission in other setting	Per day	391.42
Medication prescribed by the general practitioner or medical specialist including delivery costs (€6.28)	Per piece	[a]
Costs for writing a prescription by the general practitioner or medical specialist	Per prescription	14.87
Costs for home care by a trained professional	Per hour	37.62
Patient and family costs		
Travelling costs for the interventions, external interventions and for retrieving medication at the pharmacy[b]	Per km	0.21
Parking costs for visiting the hospital	Per visit	3.19
Domestic help or unpaid informal care from family/friends	Per hour	13.23
Productivity losses		
Hours of absenteeism	Per hour	Hourly wage x 0.8

[a] Costs for medication were calculated by taking the average of the highest and lowest price per piece of medicine in 2012 on www.medicijnkosten.nl.

[b] Travelling costs are counted for every visit and once every three months for retrieving medication at the pharmacy. In the Dutch manual for cost analysis in healthcare research the distance is given to the nearest institution in 2008, namely general practitioner 1.1 km, RIAGG 7.0 km, psychiatrist, psychologist, psychotherapist in private practice, social worker and alternative healer 3.6 km, hospital, company physician, self-help group and CAD 7.0 km, paramedics 2.2 km, rehabilitation centre 26.4 km.

Statistical methods

An intention-to-treat analysis was used, which means data of all patients initially assigned to a treatment were analysed, regardless of whether or not they completed or received the treatment. Patients were included in the cost-effectiveness analysis if they filled in 75% of all 16 TiC-P questionnaires, otherwise they were excluded from the analyses. Remaining missing values were imputed by using the last observation carried forward method. If variables from the previous time period were missing the last observation carried backward method was used. If variables were missing in every monthly or 3-monthly questionnaire, the averages of the analysed participants were used.

Effectiveness analysis

Baseline differences between CBT and MRT of the primary and secondary outcomes were calculated using *t*-tests. The longitudinal effect of MRT versus CBT on the outcomes was assessed using linear mixed models based on restricted maximum likelihood[14]. Along with treatment allocation, time (in weeks from baseline), and interaction of time by treatment allocation, rehabilitation centre was included as a fixed factor, because randomization was stratified by centre. Choice of the best fitting covariance structure, i.e. structure of variances over different time-points and correlations between time-points, was based on Akaike's Information Criterion. Two sided P-values smaller than or equal to 0.05 were considered statistically significant. Analyses were performed using SPSS Statistics for Windows (version 20.0; IBM Corp., Armonk, NY, USA.).

Cost-effectiveness analysis

The costs from societal perspective during the follow-up period of 52 weeks were cumulated and the total costs from the two intervention groups were compared by the non-parametric bootstrapping method with 95% confidence intervals in percentiles. Base-case cost-effectiveness and cost-utility analyses and sensitivity analyses were done. In the base-case analysis, the cost-effectiveness was performed by relating the mean total costs to the severity of fatigue and quality of life at 52 weeks. A cost-utility analysis was performed by relating the mean total costs to the mean health utility (QALY) scores of both groups. The costs per QALY of both treatments were compared. The incremental cost-effectiveness ratio (ICER) was determined on the basis of incremental costs and the effects of the MRT in comparison with CBT. The cost-effectiveness ratio presented the costs per unit of outcome and the cost-utility ratio focused on the incremental cost per QALY gained. The robustness of the ICER was checked by non-parametric bootstrapping to quantify the uncertainty around the ICER. The bootstrapped cost-effectiveness ratios were subsequently plotted in a cost-effectiveness plane. The choice of treatment depends on the maximum amount of money society is prepared to pay for a gain in effectiveness, which is called the ceiling ratio. In the Neth-

erlands, no explicit ceiling ratio or ICER threshold value is defined, but the Council of Public Health and Health Care advised to use a ceiling ratio for the QALY related to the burden of disease[28]. The burden of disease ranges from '0' indication no burden of disease to a score of '1', indicating a maximum burden of disease. Although the exact burden of disease for patients with CFS is unknown, NICE guidelines for treatment of CFS declare the burden of disease to be comparable with other chronic conditions like multiple sclerosis and rheumatoid arthritis[29]. A more recent study[7] showed the burden of disease among patients with unexplained physical symptoms, including CFS, is high and comparable with major depression and cancer. In a report of the National Institute for Public Health and the Environment (RIVM) in 1998[30] burden of disease of different illnesses are described. Taking multiple sclerosis, the burden of disease is between 0.33 and 0.67, which is comparable with moderate to severe depression (burden of disease 0.35-0.76). Since the exact burden of disease of CFS is unknown, the burden is estimated between 0.33 and 0.76. Following the report "Zinnige en duurzame zorg" ("Sensible and sustainable care") of the Council of Public Health and Health Care, the estimated willingness to pay for treatment for patients with CFS lies between €27.000 to €60.000 for one QALY. The bootstrapped ICERs were depicted in cost-effectiveness and cost-utility acceptability curves showing the probability that MRT is cost-effective while using a range of ceiling ratios. Costs, cost-effectiveness, cost-utility and sensitivity analyses were carried out by Microsoft Office Excel 2003.

Sensitivity analysis

Finally different sensitivity analyses were performed to demonstrate the robustness of our base-case findings. Sensitivity analyses were performed by varying different parameters on which assumptions were made. The following sensitivity analyses were performed: (1) Costs were calculated using the friction cost method instead of the human capital approach and (2) Costs were calculated from a healthcare perspective instead of a societal perspective. During the base-case analysis it was noticed that as patients had to fill in their hours of absence while reintegrating or working part-time due to their illness, inconsistencies were found within the answers. Assumptions had to be made in order to calculate the correct hours of absence. The estimated minimum hours of absence was used in the base-case analysis. The estimated maximum hours of absence was used in sensitivity analysis (3). To analyse whether results of the base-case analyses regarding the disease-specific outcome were the same using another outcome, sensitivity analyses 4 and 5 were performed. In sensitivity analysis (4), an overall improvement score was used. Improvement was measured by the Improvement and satisfaction questionnaire (EET), question 4 "Is there a difference in your daily activities now compared to your situation before treatment started?" ('1'=improved and '0'= not improved)[14]. (5) Since many different definitions of improvement exist, another sensitivity analysis was performed using the CIS fatigue subscale as dichotomous variable of im-

provement. Previous studies[31,32] used the CIS cut-off score of 35 to measure clinically significant improvement[33]. Finally a sensitivity analysis (6) was performed using the Dutch algorithm instead of the UK algorithm to calculate the QALY.

RESULTS

Overall, 364 patients were referred to the participating rehabilitation centres with a major complaint of fatigue. The most common reason for exclusion was unwillingness to participate in a trial (54 patients), not meeting the CDC-94 criteria for CFS (34 patients), and other diagnosis or fatigue not being the primary complaint (34 patients). Finally, 122 participants were included in the trial and completed the baseline assessment, of which 62 participants were randomized to MRT and 60 to CBT. The treatment-effects of the 122 included patients are described previously in the study of Vos-Vromans et al[14]. From 13 patients (5 MRT and 8 CBT) less than 75% of the questionnaires of the TiC-P were available and were therefore excluded for further analysis (see Figure 1). 109 patients (57 MRT and 52 CBT) remained in the analysis. Out of 1744 questionnaires, 17 questionnaires were incomplete or missing and were imputed (4 TiC-P part I, 13 TiC-P part II) using the above mentioned method of imputation. Patient characteristics at baseline in the MRT group did not significantly differ from those in the CBT group. Table 2 shows the baseline characteristics of all participants stratified according to intervention group.

Table 2. Baseline characteristics (N = 109)

Variable	MRT (N = 57)	CBT (N = 52)
Age	40.38 (10.33)	41.62 (12.13)
Female sex, N (%)	45 (79)	43 (83)
CIS fatigue	51.42 (5.19)	50.88 (5.36)
Health-related quality of life		
SF-36, PCS	31.02 (8.07)	32.04 (7.49)
SF-36, MCS	46.40 (9.30)	44.83 (8.46)
Utility		
EQ-5D-3L UK Dolan tariff	0.48 (0.25)	0.56 (0.24)
SF-36, UK Brazier tariff	0.59 (0.07)	0.58 (0.09)

Data are mean (SD) unless otherwise stated.
MRT, Multidisciplinary rehabilitation treatment; CBT, Cognitive behavioural therapy; CIS, Checklist Individual Strength; EQ-5D-3L, EuroQol-5Dimensions; SF-36, Short-Form 36; PCS, Physical component summary score; MCS, Mental component summary score.

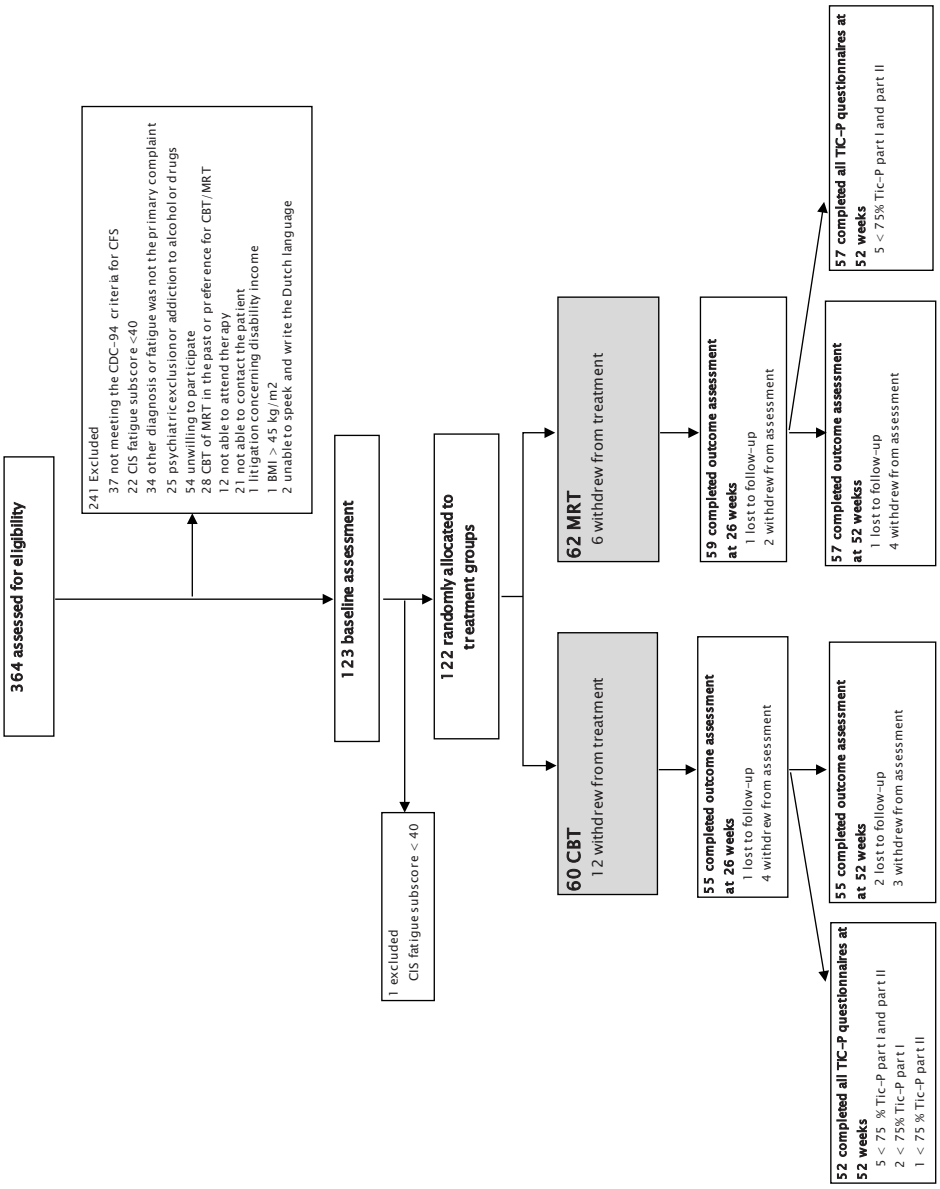

Figure 1. CONSORT trial profile

Effects

Table 3 shows the results of the effectiveness analyses. The mean difference between MRT compared to CBT is -6.48 (95% CI: -11.54, -1.42). At 52 weeks the fatigue is significantly lower in patients from the MRT group compared to CBT. The mean difference of

MRT compared to CBT on quality of life is, 3.53 (95% CI: -0.67, 7.74) and 1.36 (95% CI: -2.28, 5.00) for the PCS and MCS, respectively. The mean difference for the QALY is 0.09 (95% CI: -0.02, 0.19). Differences in quality of life and QALY between the groups are not statistically significant.

Table 3. Results regarding effectiveness analyses

Outcome	MRT Mean (SD) (N=57)	CBT Mean (SD) (N=52)	Mean difference MRT vs CBT [95% CI] at 52 weeks[a]	Incremental effect of MRT vs CBT[b]
CIS fatigue				
Baseline	51.42 (5.19)	50.88 (5.36)		
26 weeks	33.12 (14.07)	36.84 (13.18)		
52 weeks	33.84 (14.33)	40.27 (12.29)	-6.48 [-11.54, -1.42]*	6.43
SF-36, PCS				
Baseline	31.02 (8.07)	32.04 (7.49)		
26 weeks	40.39 (10.43)	37.67 (10.90)		
52 weeks	40.19 (11.29)	36.61 (10.37	3.53 [-0.67, 7.74]	3.66
SF-36, MCS				
Baseline	46.40 (9.30)	44.83 (8.46)		
26 weeks	52.75 (7.08)	50.41 (8.93)		
52 weeks	51.10 (10.22)	50.25 (9.00)	1.36 [-2.28, 5.00]	0.86
QALY				
Baseline	0.48 (0.25)	0.56 (0.24)		
26 weeks	0.71 (0.17)	0.62 (0.31)		
52 weeks	0.69 (0.28)	0.61 (0.27)	0.09 [-0.02, 0.19]	0.05

MRT, Multidisciplinary rehabilitation treatment; CBT, Cognitive behavioural therapy; QALY, Quality-adjusted life-year.

[a] Results of the effectiveness analyses: Values are calculated with linear mixed models with centre, time, treatment allocation and time by treatment allocation as covariates (unstructured).* indicates a statistical significant effect of $P < 0.05$.

[b] Results of the cost-effectiveness analyses: Values are calculated with 5000 bootstrap analyses in the base-case

Costs

The mean costs per treatment group are presented in table 4. Healthcare costs are significantly higher for the MRT group compared to the CBT group (difference €5681, 95% CI: €4632, €6793). Patient and family costs are lower for the MRT (difference -€1457, 95% CI: -€3470, €146), but did not reach significance. As part of the productivity costs due to absenteeism, patients were able to fill in questions regarding loss of productivity while at work. During analyses it was noticed that it was not always clear to the patient whether or not to fill in this part of the questionnaire, making this part less

reliable. Therefore loss of productivity while at work was excluded for analysis. Productivity costs due to absenteeism are higher for the MRT group but did not reach a level of significance (difference €1263, 95% CI: €-667, €3146). The total societal costs are significantly higher for patients allocated to MRT compared to CBT (difference €5389, 95% CI: €2488, €8091).

Table 4. Mean costs (in €)

Cost type	Mean per group		Mean difference [95% CI][a]	
	MRT (N = 57)	CBT (N = 52)		
Healthcare costs				
General practitioner care	152.79	162.56	-10	[-62, 48]
Mental healthcare specialist	211.25	163.55	48	[-97, 190]
Paramedical care	255.37	182.31	73	[-103, 288]
Medical specialist care	125.88	108.15	18	[-52, 93]
Hospital care	286.05	185.74	100	[-270, 614]
Medication and OTC medication	90.13	136.56	-46	[-115, 18]
Alternative healers	89.10	93.33	4	[-78, 93]
Company physician	560.38	299.62	261	[37, 479]
Interventions (MRT and CBT)	7210.89	1922.59	5284	[4568, 5979]
Total	8989.06	3308.43	5681	[4632, 6793]
Patient and family costs				
Travelling and parking	237.95	129.48	108	[82, 133]
Informal care	1393.25	2933.07	-1606	[-3637, -30]
Total	1635.10	3021.11	-1457	[-3.470, 146]
Productivity costs	3716.71	2434.98	1263	[-667, 3146]
Societal costs	14307.95	8845.71	5389	[2488, 8091]

MRT, Multidisciplinary rehabilitation treatment; CBT, Cognitive behaviour therapy; OTC, Over the counter medication.

[a] The upper and lower confidence limits art he 2.5th and 97,56th percentile based on 1000 bootstrap replications.

Cost-effectiveness and cost-utility from a societal perspective

Figure 2 and 3 present the cost-effectiveness acceptability curves of the base-case cost-effectiveness and cost-utility analysis. In the cost-effectiveness analysis the slope of the MRT acceptability curves for fatigue and quality of life are steep and increase instantly to 94-99% likelihood of being the most cost-effective option from a societal perspective. The ICER is €856 per unit of the CIS fatigue subscale meaning that the costs for improvement on the CIS fatigue subscale are low. For the SF-36 PCS and MCS the ICER is €1505 and €6416, respectively. In the cost-utility analysis, considering a threshold of €27000 per QALY, MRT had a 5% likelihood of being the most cost-effective option from

a societal perspective. When changing the threshold to €60000, MRT has a 29% likelihood of being the most cost-effective. The ICER is €118074 per QALY, meaning that the costs for a QALY gained are high. Table 5 shows the cost-effectiveness and cost-utility results with the different ICER values. Cost-effectiveness and -utility planes are shown in figure 4 and 5.

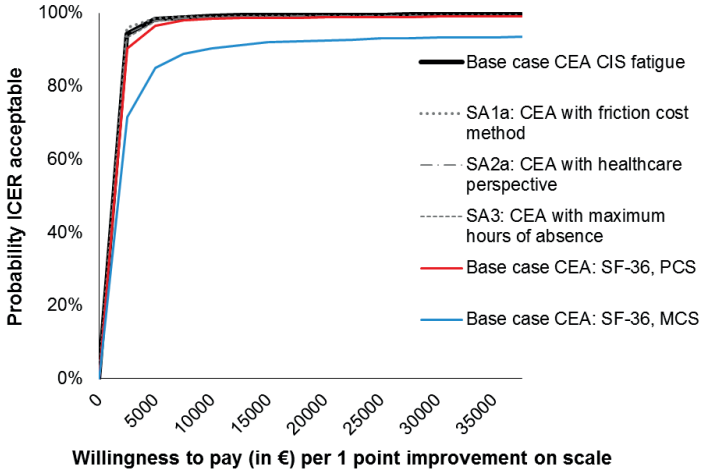

Figure 2. Acceptability curves (base case and sensitivity analysis) of the cost-effectiveness (outcome CIS fatigue, SF-36 PCS and MCS) at 52 weeks follow-up

SA, Sensibility analysis; CEA, Cost-effectiveness analysis; CIS, Checklist Individual Strength; SF-36, Short-Form 36; PCS, Physical component summary score; MCS, Mental component summary score.

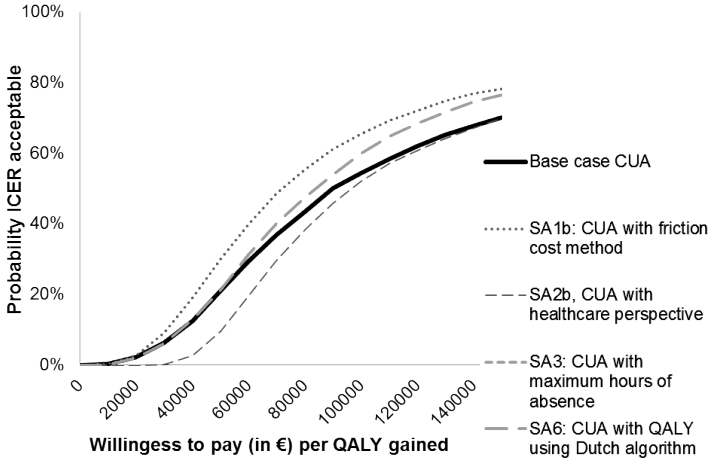

Figure 3. Acceptability curves (base-case and sensitivity) of cost-utility (QALY) at 52 weeks follow-up

SA, Sensibility analysis; CUA, Cost-utility analysis

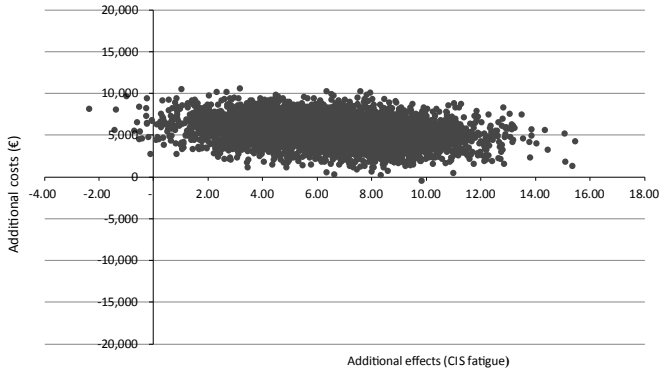

Figure 4. Cost-effectiveness plane (primary outcome: CIS fatigue)

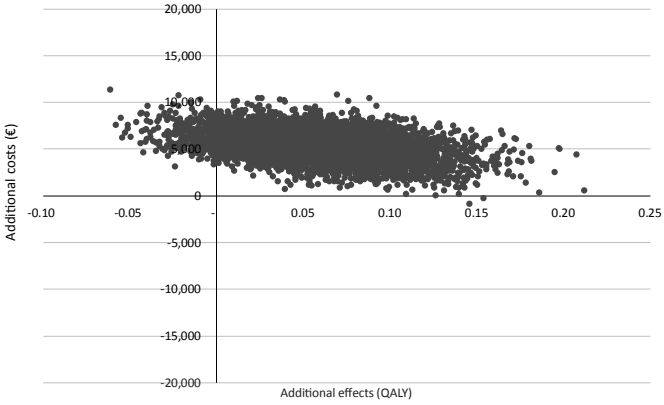

Figure 5. Cost-utility plane (primary outcome: QALY)

Table 5. Mean total costs and group differences at 52 weeks after baseline (N = 109)

Parameters varied							Outcomes[b]		Costs (€)			
Outcome	Type	Prod costs	Abs	Cost Perspect	Log	Outcome	MRT	CBT	MRT	CBT	Mean cost-differences (95% CI)[a]	ICER (€/unit of outcome)[b]
Fatigue	Base	HCA	Min	Societal	-	CIS	30.16	23.73	14308	8846	5389 [2488, 8091]	856
PCS	Base	HCA	Min	Societal	-	SF-36	40.23	36.57	14308	8846	5389 [2488, 8091]	1505
MCS	Base	HCA	Min	Societal		SF-36	51.27	50.27	14308	8846	5389 [2488, 8091]	6416
QALY	Base	HCA	Min	Societal	UK	EQ-5D-3L	0.65	0.60	14308	8846	5389 [2488, 8091]	118074
Fatigue	Sens 1a	*FCM*	Min	Societal	-	CIS	30.16	23.73	11117	6588	4450 [2100, 6518]	682
QALY	Sens 1b	*FCM*	Min	Societal	UK	EQ-5D-3L	0.65	0.60	11117	6588	4450 [2100, 6518]	94.018
Fatigue	Sens 2a	HCA	Min	*Healthcare*	-	CIS	30.16	23.73	8989	3308	5681 [4632, 6793]	903
QALY	Sens 2b	HCA	Min	*Healthcare*	UK	EQ-5D-3L	0.65	0.60	8989	3308	5681 [4632, 6793]	124.519
Fatigue	Sens 3a	HCA	*Max*	Societal	-	CIS	30.16	23.73	15133	9558	5541 [2062, 8940]	861
QALY	Sens 3b	HCA	*Max*	Societal	UK	EQ-5D-3L	0.65	0.60	15133	9558	5541 [2062, 8940]	118749
Improve	Sens 4	HCA	Min	Societal	-	*EET4*	0.80	0.62	14308	8846	5389 [2488, 8091]	29970
Improve	Sens 5	HCA	Min	Societal	-	*CIS improved*	0.25	0.49	14308	8846	5389 [2488, 8091]	22807
QALY	Sens 6	HCA	Min	Societal	*Du*	EQ-5D-3L	0.71	0.67	14308	8846	5389 [2488, 8091]	109310

MRT, Multidisciplinary rehabilitation treatment; CBT, Cognitive behavioural therapy; Prod costs, Productivity costs; Abs, Hours of absenteeism with min indicating a minimum of hours and max indicating the maximum hours of absenteeism; Cost perspect, Costing perspective; Log, logarithm used for calculating QALY; Base, Base-case analysis; Sens, Sensitivity analysis; HCA, Human capital approach; FCM, Friction cost method; DBC, Costs for the interventions using the DBC standard; CIS, Checklist Individual Strength subscale fatigue recoded (higher score indicating less fatigue) at 52 weeks after start of treatment; SF-36, Short-Form 36; EQ-5D-3L, EuroQol-5 Dimensions; UK, Dolan algorithm used for calculating QALY; Du, Dutch algorithm used for calculating QALY; Improve, outcome parameter used for improvement; EET4, Improvement and satisfaction questionnaire, question 4 "Is there a difference in your daily activities now compared to your situation before treatment started? ('1'=improved and '0'= not improved); CIS improved, patients are improved if the CIS fatigue subscale was <35.

[a] The upper and lower confidence limits are the 2.5th and 97,5th percentile based on 1000 bootstrap replications.

[b] Values are calculated with 5000 bootstrap replications in the base-case and sensitivity analysis.

Sensitivity analyses

Table 5 shows the mean costs per treatment group for the different costs and effect scenarios used in the base-case and sensitivity analyses. In all scenarios, MRT has the highest mean costs. Only small differences exist between the different methods of costing, except for the friction method. Using the friction method for costing productivity losses, the costs in both treatment groups decreased: 26% in MRT and 22% in CBT, respectively. Varying the cost or QALY outcome parameters revealed similar results for the base-case and sensitivity analysis. In the utility analysis CBT is still the most favourable treatment and in the cost-effectiveness analysis the MRT is the most favourable treatment. As shown in figures 2 and 3, the sensitivity analyses did not have a large impact on the results of the cost-utility acceptability curves. When looking at the different scales for improvement (sensibility analysis 4 and 5), the probability of MRT being the most cost-effective is higher compared to CBT (see Figure 6). Since we do not know exactly how many society is willing to pay for an improved patient the probability of MRT being cost-effective is unknown.

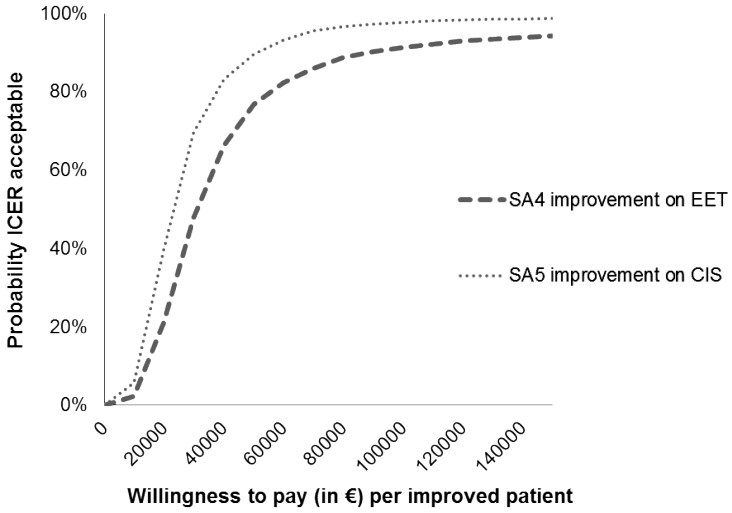

Figure 6. Acceptability curves (sensitivity analysis) of cost-effectiveness (outcome improvement on CIS and EET) at 52 weeks follow-up

SA, Sensibility analysis; EET, Improvement and satisfaction questionnaire, question 4 "Is there a difference in your daily activities now compared to your situation before treatment started?" ('1'=improved and '0'= not improved); CIS, Checklist Individual Strength, patients are improved if the CIS fatigue subscale was <35.

DISCUSSION

The main aim of the trial was to assess the difference in effectiveness, cost-effectiveness and cots-utility between CBT and MRT. To our knowledge, an economic study comparing CBT and MRT has never been done. Due to limited resources and high demands on healthcare, economic evaluations have an important role in decision-making and health policy. Policy makers need to make decisions on how to optimize the allocation of resources available, therefore this study is important to policy makers as well as to patients and therapists.

MRT was found to be more cost-effective on the disease-specific outcomes fatigue severity and the physical and mental component of the health-related quality of life and less cost-effective when the QALYs are the outcome of interest.

The cost-effectiveness was analyzed from a societal perspective over a period of 52 weeks after baseline. Societal costs, which were mainly dominated by the costs of the intervention, were significantly higher in the MRT group compared to the CBT group. While MRT was associated with statistically significant improvements in disease-specific health status, this was not reflected in generic health status. The incremental effect of MRT was higher for fatigue and quality of life measured by the SF-36 and lower for the QALY. This led to contradictory results of the cost-effective and cost-utility analyses. In all cost-effectiveness base-case and sensitivity analyses, MRT turned out to be the most efficient strategy for treatment of patients with CFS. In all cost-utility analyses, CBT turned out to be the most cost-efficient strategy for treatment. The latter results were also found in studies comparing CBT with other treatments or a natural course group[9,10,34]. Due to higher costs for the MRT intervention together with similar effects on the QALY, the incremental costs for a QALY are much higher for MRT compared to CBT. The question arises whether our findings reflect an absence of a clinically significant treatment effect or, alternatively, a lack of sensitivity in the ability of the generic quality of life measures to detect a clinically meaningful improvement in patients with CFS. Differences between generic health-related quality of life measures and disease-specific measures have been discussed in previous research[35-37]. In patients who are chronically ill, treatments like MRT often focus on improving autonomy and participation of the patient in society. Both domains are not included in the EQ-5D-3L. Future studies should assess the extent to which differences in the EQ-5D-3L following treatment reconcile with improvements on disease-specific measurements for patients with CFS after treatment. In addition, as Van Leeuwen et al stated in their study in 2015[38], the Adult Social Care Outcomes Toolkit and the ICEpop CAPability might also be valuable outcome measures in economic evaluations of care interventions because they are at least as reliable as the EQ-5D-3L and are associated with aspects of quality of life broader than health, for example occupation, dignity, control over daily life and the ability to 'do' and 'be' the things that are important in life[38].

Looking at the cost-effectiveness of treatment and taking improvement as main outcome measure, the cost-effectiveness increases compared to using the QALY in these analyses. But these criteria for improvement are mainly based on statistical methods and not on the patient's own opinion. For further research, it is recommended to evaluate improvement based on important domains for the individual patient and also to get insight what society is willing to pay for an improved patient with CFS to facilitate cost-effectiveness analysis of treatments. During the process of resource allocation decision-making, it is important to take into account both disease-specific and generic health status measurements, as an underestimation of the treatment effect might occur using only generic measurements.

Based on the differences between the results of the cost-utility and cost-effectiveness, discussion will occur whether or not MRT should be implemented in other rehabilitation centres. Both patient and clinician seek the most effective care for the problem for which the patient is visiting the clinician, regardless the impact of their decision on costs by the society as a whole. From a clinician's or patient's point of view, MRT is the most effective treatment to decrease fatigue, increase quality of life and gain QALY's. From a health insurers and policy makers perspective, besides treatment effects, costs are important and the question arises how much society is willing to pay for an increase in well-being of patients with CFS. Policy makers are now facing a dilemma. In order to make a decision on healthcare it might be worthwhile to take other components into account when deciding to implement MRT as a treatment for patients with CFS in rehabilitation centres in the Netherlands. Scarcity of effective treatments for patients with CFS and patient preferences are relevant issues when making healthcare decisions. At this moment there is a scarcity of effective treatments for patients with CFS[39], which might stimulate the implementation of MRT. Preferences of the patient should also be taken into account when making a healthcare decision. In the trial significantly more patients from the MRT group would recommend treatment to others compared to patients with CBT[14], which might give an impression of the preferences of treatment for patients with CFS. Further research is needed on this topic. Another point, which should be taken into account, is the fact that costs for the MRT were probably overestimated since treatment was new. Costs for MRT might decrease as this treatment becomes more routinely executed and therapists are better skilled in treating patients more effectively. Additionally, costs of both interventions might become lower when therapists are able to decrease the number of sessions when achieving a patient's personal goal earlier or when specific interventions are not needed to achieve a patient's goal. In the clinical practice this is already the case, but due to the treatment protocols in this trial, in which a minimal hours of treatment is prescribed, this was not an option.

In the MRT and CBT intervention the societal costs are mainly dominated by the costs for the intervention. Future research is needed to study how the interventions can be more cost-effective. It might be possible to offer parts of these interventions in

groups of patients instead of individuals, which will decrease costs of treatment. Whether treatment effect remains similar should be evaluated in future studies. Since the productivity costs are highest in the MRT group, it is also worthwhile paying more attention to returning to work. In CBT returning to work is part of the protocol. In MRT returning to work is only included in the treatment if it is part of the patient's personal goal. If not, returning to work is no part of the MRT procedure. In order to decrease the costs from a societal perspective, making 'returning to work' a fixed part of the MRT protocol is useful despite the fact that it might not be a personal goal of the patient. Whether this changes the cost-effectiveness of treatment needs to be evaluated in future research.

Strengths and limitations

This trial has a number of strengths; in particular internal validity is high due to robust randomization and concealed allocation procedures, a priori trial registration, intention-to-treat analysis and pre-specification of primary outcomes and analytic methods. Data used in our analyses were derived from a single RCT, representing a potential limitation in the generalizability of our findings. The fact that 37 patients did not meet the CDC-94 criteria of CFS and were excluded before randomization and 54 patients were unwilling to participate in the trial, should be taken into account when generalizing the results to the total population of patients with fatigue as a main complaint referred to secondary healthcare. In clinical practice CDC-94 criteria are not always used to decide to treat patients in a rehabilitation centre. Other limitations were: First, we relied on self-reported information regarding healthcare, productivity losses and patient-family costs. There may be issues of accuracy with this approach but it was largely unavoidable given impossibility to register otherwise. Moreover, as these measurements were similar in both groups these issues did not affect comparability. Other studies have shown that the used method is acceptable[40,41]. Second, the loss of productivity while being at work was not taken into account. Future studies should include loss of productivity while at work by using the Tic-P with an extra instruction to the patient on how and when to fill in this part of the questionnaire.

CONCLUSION

Using fatigue severity as primary outcome for cost-effectiveness, MRT is more likely to be cost-effective compared to CBT. Taken the QALY, CBT is more cost-effective than MRT. To further improve interpreting cost-effectiveness analysis of treatments in patients with CFS it is important to clearly define criteria for improvement and how much money society is willing to pay for an improved patient.

Funding

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Conflict of interest statement

None of the authors has any conflicts of interest.

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5

Differences in physical functioning between relatively active and passive patients with chronic fatigue syndrome

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ABSTRACT

Background. According to the cognitive behavioural therapy (CBT) protocol for patients with chronic fatigue syndrome (CFS), therapists are advised to categorize patients in relatively active and passive patients. However, evidence to support the differences in physical functioning between these subgroups is limited. Using the baseline data from a multi-centre randomized controlled trial (FatiGo), the differences in actual and perceived physical functioning between active and passive patients with CFS were evaluated.

Methods. Sixty patients, who received CBT during the FatiGo trial were included. Based on the expert opinion and using the definitions of subgroups defined in the CBT protocols, the therapist categorized the patient. Data from an activity monitor was used to calculate actual physical functioning, physical activity, daily uptime, activity fluctuations and duration of rest during daily life. Perceived physical functioning was assessed by measuring physical activity, physical functioning and functional impairment with the Checklist Individual Strength, Short-Form 36 and Sickness Impact Profile 8.

Results. Relatively active patients have a significantly higher daily uptime and show significantly less fluctuations in activities between days. Passive patients experience a significantly lower level of physical functioning and feel more functionally impaired in their mobility. However, no significant differences were found in the other actual or perceived physical functioning indices.

Conclusions. A clear difference in actual and perceived physical functioning between relatively active and passive patients with CFS as judged by their therapists could not be found. Future research is needed to form a consensus on how to categorize subgroups of patients with CFS.

INTRODUCTION

Chronic fatigue syndrome (CFS) is a condition characterized by persistent fatigue, which is not the result of an identifiable organic disease or ongoing exertion and lasts for at least 6 months. Rest does not alleviate the fatigue. CFS often leads to a substantial limitation in occupational, educational, social and personal activities[1].

Although results are conflicting, several studies found the actual as well as the perceived physical functioning to be lower in patients with CFS compared to healthy, age matched controls[2-5]. A possible explanation for the conflicting results in physical functioning might be the large variations in actual and perceived physical functioning within the population of patients with CFS. The study of van der Werf[2] investigated the differences in perceived physical functioning between subgroups of patients. The average daily physical activity level, measured by the actometer of the total group of patients, was used as reference value to form subgroups. The number of days below or above this reference value determined in which subgroup a patient was categorized. Results showed that two subgroups could be identified. A group of pervasively passive patients, reporting less daily activities and perceive more limitations in daily life functioning compared to the other subgroup of relatively active patients. In addition, Prins et al[6], who studied the effectiveness of cognitive behavioural therapy (CBT) in patients with CFS, found that the individual level of daily physical activity predicted the treatment outcome. Passive patients showed hardly any improvement after CBT. Therefore CBT protocols were adjusted for subgroups of patients (passive patients versus relatively active patients) in order to increase effectiveness of the CBT. In the Netherlands, these tailored CBT protocols for relatively active and passive patients are used frequently. In these clinical diagnostic and therapeutic protocols[6,7], relatively active patients are assumed to be more physically active, spend less time resting and show infrequent bursts of activity followed by extreme exhaustion during the day and between days (high level of fluctuations of activities). Passive patients with CFS are assumed to stay at home more often, not to walk long distances and lie down most of the day[6,7]. Nowadays CBT often incorporates a gradual increase in physical activities. In the CBT protocol for the passive patients, physical activities will be increased from the beginning of therapy. The relatively active patient is first taught to practice at a baseline activity level without bursts of activity in order to stabilize the level of activities and prevent extreme exhaustion. After stabilization has been reached, activities will be increased gradually. According to Prins et al[8] passive patients do not recover when they receive the CBT protocol for active patients. Therefore it is important to categorize patients correctly, as differences in physical functioning guides treatment content. Experts in CBT advise to categorize patients with the use of an actometer[6,7]. In clinical practice an actometer or other actual activity monitoring system is usually not available because they are too expensive, time-consuming, complex to analyze and difficult to interpret. Questionnaires on daily physical activity are used instead of the actometer but are still lacking validity[9].

Which method is the most valid for categorization is still unclear and needs further investigation. Currently therapists categorize patients using the definitions in the CBT protocol[6,7]. Although categorization of patients is often used in clinical practice, the assumed differences in physical functioning between relatively active and passive patients, as described in clinical protocols, have never been confirmed by measuring the actual daily life activities using an activity monitor. In patients with chronic low back pain (CLBP), it was found that a subgroup of avoiders, who seem to closely resemble the passive patients, had significantly higher disability levels, a lower perceived daily life activity level, and lower daily uptime compared to a subgroup of persisters[10]. However, no differences in the actual daily life activity level and fluctuations of activities over time could be found. In the CBT protocols for CFS[6,7] experts on CBT state that a patient's perception on physical activity is often distorted by cognitions regarding activity resulting in a discrepancy between what people say and what they actually do. Therefore, it is important to get insight in the patients' actual level of physical functioning as well as their perceived level of physical functioning, in both subgroups.

Hence the first aim of the present study is to evaluate the differences in actual physical functioning between subgroups, i.e. whether passive patients with CFS have a significantly lower actual total physical activity level, spend less time awake and out of bed (daily uptime), spend more time resting, and show less activity fluctuations compared to relatively active patients with CFS. The expert opinion, as this is the most commonly used form, will be used to categorize the patient. A second aim is to evaluate the differences in perceived physical functioning between subgroups, i.e. whether passive patients are significantly more impaired and have a lower perceived daily life activity level compared to relatively active patients with CFS.

METHODS

This study is part of a multi-centre randomized controlled trial (FatiGo) in which the effectiveness of two treatment approaches, multidisciplinary rehabilitation treatment (MRT) and CBT, are compared in patients with CFS[11]. Primary aim of the FatiGo trial is to compare the effectiveness of both outpatient rehabilitation treatment approaches on fatigue severity and quality of life in patients with CFS. The study protocol has been approved by the Research Ethics Committee of Rotterdam in the Netherlands (number 2008/22). Trial-registration: Current Controlled Trials ISRCTN77567702. In order to evaluate the difference in physical functioning between relatively active and passive patients with CFS, baseline data from 60 patients with CFS who were randomized CBT between 1 December 2008 and 28 January 2011 were analyzed.

Participants

The patients with CFS referred to Revant Rehabilitation Centre Breda, Rehabilitation Centre Blixembosch in Eindhoven, Reade Rehabilitation Centre in Amsterdam and Adelante Rehabilitation Centre in Hoensbroek between November 2008 and January 2011 were asked to participate in the trial. Patients were included if the following criteria were met: (1) CDC-94 criteria for CFS, (2) The subscale on severity of fatigue of the Checklist Individual Strength should be higher or equal to 40, (3) participant agreed to participate in a treatment aimed at changing behaviour, (4) age between 18 and 60 years, (5) able to speak, understand and write the Dutch language. Patients with any other medical condition which can explain the presence of chronic fatigue, a psychotic, major or bipolar depressive disorder, dementia, anorexia or bulimia nervosa, alcohol and/or drug abuse, severe obesity, pregnancy, previous or current CBT or MRT for their CFS or living more than 1 h travelling time away from the nearest participating rehabilitation centre, were excluded from the study. Patients should be able to attend therapy for at least three half days a week. A physician in rehabilitation medicine checked the in- and exclusion criteria. All patients signed the informed consent form.

Procedure

After inclusion, baseline assessment was performed and patients were asked to fill in the CIS[12,13], the Sickness Impact Profile 8 (SIP8)[14,15] and Short-Form 36 (SF-36)[16]. The research assistant instructed the patient to wear the activity monitor on the right upper arm over the triceps muscle during seven consecutive days. The different outcomes variables for actual and perceived physical functioning are shown in table 1. After baseline assessment, patients were randomly assigned to CBT or MRT. Because the CBT protocol is different for passive and relatively active patients with CFS, the CBT therapists were trained before the trial started to categorize the patients. Only patients from the CBT group were included in the analysis of the present study, because in MRT, the protocol is not different for subgroups of patients, and patients were therefore, not categorized by their therapists. Only data from baseline assessment of the FatiGo trial[11] were used in the present study.

Table 1. Outcome variables of actual and perceived physical functioning as used in the present study

Actual (activity monitor)	Perceived (self-report questionnaire)
Physical activity (PA)	Physical activity, CIS activity
Daily uptime	Physical functioning, SF-36
Duration of rest	Functional impairment, SIP8
Fluctuations between days (RMS-day)	Physical impairment, mobility (SIP mobility)
Fluctuations within days (RMS-15)	Physical impairment, walking (SIP walking)

Classification of patients

During two to three intake sessions, the CBT therapist categorized the patient by questioning the patient about his/her daily activities, using the week list of activities, which the patient had filled in during the week he or she was wearing the activity monitor. Furthermore, the CBT therapists had access to the results of the baseline questionnaires and they were free to use the information in their judgement when categorizing. None of the questionnaires had cut-off scores for categorization of patients with CFS into subgroups. The therapists had access to the results of the questionnaires on depression and anxiety (Hospital Anxiety and Depression Scale)[17], quality of life (SF-36)[16,18], fatigue severity (CIS)[12,13], psychological symptoms (Symptom Check List-90)[19], self-efficacy (Self-Efficacy Scale-28)[13], causal attributions (Causal Attribution List)[20] and the impact of disease on both physical and emotional functioning (SIP8)[14,15]. The CBT therapists were instructed to categorize the patient by using the following definitions of relatively active and passive patients with CFS as have been recommended in literature[6,7].

Relatively active patients with CFS are patients who fluctuate in their activities and often have problems with balancing their activities and rest during the day. They often force themselves to stay active, do not accept they are tired and carry on to finish the task. Most relatively active patients are still (partly) working. For passive patients with CFS their fear that activity enhances symptoms is regarded essential. Therefore, passive patients are most of the day physically inactive. They do not go out, do not walk long distances and lie down most of the day. Most passive patients with CFS are also not working.

Measures

Patient characteristics

Age, sex, onset of complaints, work status and perceived fatigue on the CIS[12,13], were measured during baseline assessment.

Perceived physical functioning

The perceived physical functioning was measured in terms of a) perceived physical activity, b) functional impairment, and c) perceived physical functioning as part of a patient's health-related quality of life.

Perceived physical activity

The perceived physical activity was measured using the activity subscale of the CIS. This subscale has 3 items. Each item is scored on a 7-point Likert scale. A higher score indicates less physical activity. Psychometric research has indicated that the CIS and the CIS subscales have satisfactory reliability and validity[5, 20,21].

Functional impairment

Functional impairment was measured using eight subscales of the SIP8. The following subscales were weighted and summed into a total score (range 0-6160): home management, mobility, alertness behaviour, sleep/rest, walking, social interactions, work and recreation and pastimes. The two subscales, mobility and walking are presented separately because they yield only physical activities. A higher total score or a high subscore means more functional impairment. Psychometric research has indicated that the SIP and his subscales are reliable and valid[14,15].

Perceived physical functioning as part of a patient's health-related quality of life

The physical functional subscale of the SF-36 was used to measure perceived physical functioning. The SF-36 is a questionnaire on health-related quality of life. The physical functioning subscale has 10 items. Every subscale of the SF-36 is transformed into ratings on a scale ranging from 0 (limited in all activities) to 100 (able to carry out vigorous activities). Validity and reliability of every subscale is high[16].

Actual physical functioning

A multi-sensor armband of SenseWear Pro Armband (BodyMedia, Inc., Pittsburgh, PA) was used to measure the actual level of physical activity during 24 h a day. The armband has an integrated two-axial accelerometer and registers, amongst others, the peak acceleration (in counts) of every minute in two directions (longitudinal and transversal axis). A count is a measure of frequency and intensity of acceleration and deceleration[22]. The armband is a reproducible and accurate measure in subjects with chronic illness who have moderately functional limitations[23]. In order to obtain seven complete registration days, the subjects were asked to put on the armband before midnight of the first measurement day, wear it on seven consecutive days and take off the armband on day 8 in the morning. Patients were asked to take off the armband only during swimming or bathing. To analyze the actual physical functioning, at least five valid measurement days, including one weekend day, had to be available[10,24,25]. A valid or complete measurement day was defined as a day in which the monitor registered counts during a period of at least 1142 min which is 80% of a standard measurement day[26]. Incomplete measurement days with less than 1142 min were discarded. MATLAB software (The Math Works Inc., Natick, Mass) was used for data processing. After filtering the data to reduce signal noise, MATLAB merged the peaks of every minute of the two acceleration axis (following the theorem of Pythagoras) into one signal. Missing signals, when patients took off the activity monitor were replaced by the mean peak acceleration per minute of that day for that particular patient to avoid underestimation of the subject's activity level. An algorithm was designed to identify daily uptime. After

identification of daily uptime, MATLAB was able to calculate physical activity levels, fluctuations in activity over time and duration of rest during daily uptime.

Daily uptime

Daily uptime was defined as the duration (in minutes) a patient is awake and out of bed. The period a patient was awake and out of bed, was set equal to the period between the first and last activity count that exceeded the predefined threshold of 40 counts per minute[10].

Physical activity (PA)

PA was expressed as the total sum of counts registered per day during daily uptime.

Activity fluctuations during the day

To study changes in activity over time during daily uptime, activity counts of 15 consecutive minutes were summed. The difference score between PA of 15 min and the PA of 15 min before were calculated. The difference score was differentiated once, after which the root mean square values were calculated (RMS15)[10].

Activity fluctuations between days

To study activity fluctuations between days during daily uptime, a Root Mean Square score for activities between days (RMS-day) was calculated. The difference score between PA of one day related to the PA of the day before were calculated. The same root mean square procedure as RMS-15 was used to measure the RMS-day.

Duration of rest

Duration of rest is defined as the percentage of daily uptime a patient is at rest. Sitting, lying down and sleeping are activities with 0-200 counts per minute and they were defined as rest. The total time a patient was at rest during daily uptime were summed and divided by the daily uptime.

Data analysis

Statistical analyses were performed using SPSS software version 20 (SPSS Inc., Chicago, III). Data were presented as median scores with interquartile ranges. The passive patient group is small (N = 12), therefore differences between subgroups in (actual and perceived) physical functioning were analyzed using non-parametric Mann-Whitney-U tests. Differences between subgroups in gender, onset of complaints and job status were tested by Fisher's Exact Test since these variables are binary or ordinal. For all analysis, a P-value equal or lower than 0.05 was considered to be significant. Effect sizes

were measured by dividing the standardized test statistics by the root of the total number of participants.

RESULTS

Sixty patients were randomized to CBT and their data were used in the analyses of the present study. Forty-seven patients were categorized as relatively active and thirteen patients were categorized as passive patients. All patients filled in the CIS, SF-36 and the SIP8 questionnaires. Three patients were excluded because their activity monitor data did not include a minimum of five valid measurement days, including one weekend day, leaving 57 patients with complete data. Forty-five relatively active and twelve passive patients were included in the study. Data were checked for outliers. One patient travelled one day by plane, which resulted in an extreme score, and hence the data of that particular day was excluded from further analysis.

Patient characteristics

Table 2 presents the characteristics of the two subgroups. Age, sex, onset of complaints and perceived fatigue on the CIS were not significantly different between the two subgroups. Twenty-eight patients (64%) of the relatively active subgroup have a job in comparison to two patients (17%) of the passive subgroup (P = 0.007).

Table 2. Patient characteristics

	Relatively active (N = 45)	Passive (N = 12)	*U*	Z (r)	P-value
Male Female[a]	10 (22.2%) 35 (77.8%)	3 (25.0%) 9 (75.0%)			1.00
Age[b]	40.0 [31.0-49.5]	47.5 [26.8-54.0]	301.5	0.62 (0.08)	0.54
Onset of complaints[a]					
6-12 months	6 (13.3%)	1 (8.3%)			0.78
1-2 years	10 (22.2%)	4 (33.3%)			
2-5 years	9 (20.0%)	3 (25.0%)			
> 5 years	20 (44.4%)	4 (33.3%)			
CIS fatigue[b]	52.0 [47.5-55.0]	52.5 [49.3-54.8]	280.0	0.20 (0.03)	0.84
Work (yes/no)[a]	28/16	2/10			0.007

[a] Binary and ordinal variables are represented by the actual numbers and percentages and tested by the Fisher's Exact Test because 25% have expected count less than 5.

[b] Not normally distributed data are represented by medians [interquartile ranges] and tested by the Mann-Whitney *U* test. Z-score, effect size (r) and P-values are also presented.

Table 3. Results of the actual physical functioning

	Relatively active (N = 45)	Passive (N = 12)	*U*	Z (r)	P-value
Daily uptime (min)[a]	972.6 [935.9-1024.1	907.0 [851.8-907.0]	130.5	-2.73 (0.36)	0.006
Physical activity[a] (in counts x 10^3)	20.9 [18.0-23.6]	18.79 [14.1-21.0]	193.0	-1.51 (0.20)	0.13
Fluctuations					
RMS-15[b] (in counts)	107.8 [98.4-115.4]	110.5 [100.9-119.6]	309.0	0.76 (0.10)	0.45
RMS-day[a] (in counts)	39.5 [32.9-46.8]	53.2 [36.3-70.4]	372.0	2.00 (0.27)	0.05
Duration of rest[a] (% of daily uptime)	50.7 [41.2-57.8]	53.3 [41.8-66.3]	308.0	0.74 (0.10)	0.46

[a] Data are represented by medians [interquartile ranges] and tested by the Mann-Whitney *U* test *(U).* Z-score, effect size (r) and P-values are also presented; RMS-15, activity fluctuations during the day; RMS-day, activity fluctuations between days.

Daily uptime, physical activity, fluctuations and duration of rest

Table 3 presents the scores on actual physical functioning for the two subgroups. Relatively active patients with CFS have a significantly higher daily uptime of 972.6 min (IQR 935.9-1024.1) compared to 907.0 min (IQR 851.8-907.0) of the passive patients. The median fluctuation in activities between days for the relatively active patients was 39.5 counts (IQR 32.9-46.8) compared to 53.2 counts (IQR 36.3-70.4) for the passive patients (P = 0.05). Relatively active patients also seem to be more active but the difference between the subgroups was not statistically significant (P = 0.13). Differences in RMS15 were also not significant (P = 0.45). All differences had a small to medium effect size (0.10 to 0.36).

Perceived physical activity, physical functioning and functional impairment

Table 4 shows the results of the perceived physical functioning. Relatively active patients had a score of 16.0 (IQR 13.0-18.5) on the activity subscale of the CIS which means they perceive a higher physical activity compared to the passive patients who had a score of 18.0 (IQR 16.0-20.8). However, the difference was not statistically significant (P = 0.10). On the physical functioning subscale of the quality of life questionnaire, passive patients scored significantly lower 45.0 (IQR 36.3-55.0) compared to relatively active patients who had a score of 60.0, (IQR 45.0-72.5). Furthermore, passive patients reported to feel significantly more impaired in their mobility as they scored 133.5 (IQR 6.0-213.5) on the SIP mobility compared to a score of 41.0 (IQR 0.0-97.5) of the relatively active patient (P = 0.01). There were no significant differences in functional impair-

ment (P = 0.19) and impairment in walking (P = 0.35). All differences had a small to medium effect size (0.12 to 0.34).

Table 4 Results of the perceived physical functioning

	Relatively active (N=45)	Passive (N=12)	*U*	Z (r)	P-value
Physical activity (CIS activity)	16.0 [13.0-18.5]	18.0 [16.0-20.8]	353.5	1.65 (0.22)	0.10
Physical functioning (SF-36)[a]	60.0 [45.0-72.5]	45.0 [36.3-55.0]	152.5	-2.31 (0.31)	0.02
Functional impairment (SIP8)[a]	1160.0 [630.5-1642.0]	1417.0 [973.3-2579.0]	337.5	1.32 (0.18)	0.19
SIP walking	35.0 [0.0-69.5]	67.5 [0-137.0]	315.5	0.93 (0.12)	0.35
SIP mobility	41.0 [0-97.5]	133.5 [66.0-213.5]	396.0	2.55 (0.34)	0.01

[a] Data are represented by medians [interquartile ranges] and tested by the Mann-Whitney *U* test (U). Z-score, effect size (r) and P-values are also presented.

DISCUSSION

The aim of the present study was to evaluate the differences in actual and perceived physical functioning between relatively active and passive patients with CFS using the expert opinion to categorize the patients. Significant differences were found in daily uptime, activity fluctuations between days, perceived physical functioning (SF-36) and perceived functional impairment of a patient's mobility (SIP mobility).

In accordance with the description in CBT protocols[6,7], the relatively active patients have higher daily uptimes, which means they are longer awake and out of bed compared to passive patients. It might be that they finish their activities despite their fatigue as a characteristic of overactivity, which was also suggested for subgroups of patients with other chronic, medically unexplained, complaints. Huijnen et al[10] also found a longer daily uptime in a subgroup of patients with CLBP who persist in their activities compared to an avoiders subgroup. Our results are in line with the ideas of Van Houdenhove et al[27], who found support for the hypothesis that high 'action-proneness' and an associated 'overactive' lifestyle may be one of the factors that play a predisposing, initiating as well as perpetuating role in CFS. A higher daily uptime can be a sign of overactivity. However, another possible explanation of the difference in daily uptime is that a larger proportion of the relatively active patients were still working. It is plausible that having a job obligates them to go out of bed at predefined wake up times. Patients who do not have jobs can afford themselves to stay in bed longer and let themselves be more guided by their fatigue.

Although passive patients were found to be less physical active and spend more time resting, these differences were not statistically significant. These results are in accordance with the results of two studies among patients with CLBP[10,28] who did not find differences in the actual daily life activity level between subgroups of patients ei-

ther. A possible reason for not finding significant differences between the subgroups might be the fact that patients were only included in the FatiGo trial if they were able to travel to the rehabilitation centre and able to attend therapy for three half days a week. Homebound patients, who have an extremely low level of physical activity[29], were not included in the trial because they were unable to attend therapy. The differences found between subgroups could have been caused by the disparity in the number of relatively active and passive patients. Matching these patient numbers and including homebound patients is recommended for future research.

When evaluating the fluctuations during the day as differences between consecutive time frames of 15 min, no differences were found between both subgroups. This is in accordance with the findings of Huijnen et al[10] who did not find differences in fluctuations between subgroups in patients with CLBP. When evaluating fluctuations between days, passive patients fluctuate more in their activities compared to relatively active patients. Since 64% of the relatively active patients have jobs, it is possible that patients who are working have a more stable pattern of activities because the job obligates them to do the same activities every day. Since not every job causes a stable pattern of activities, future studies should, next to work status, measure the fluctuation of activities during working hours. This makes it possible to distinguish fluctuations in activities related and not related to the job. It is also possible that the social environment and the support a patient receives, might partly explain the fluctuations during the day and between days. Patients may fluctuate less if they receive help from their environment. In this study social support and social environment were not measured. In future research it is worthwhile measuring professional activities, social context and social support a patient receives to get insight in the reasons for fluctuations in a patient's activity level. The assumption that relatively active patients with CFS fluctuate more in their activities during the day could not be confirmed. There might be a discrepancy between the perception of the patient and the actual measure of fluctuations in activity. It is possible that relatively active patients perceive more fluctuations in their physical activities, while a higher level of fluctuations in activity measured by the activity monitor was not found. Future studies should focus not only on the actual fluctuations in activity measured by an activity monitor but also in the perceived fluctuations in activity measured by self-report questionnaires. Another explanation for our findings can be the method we have used to assess fluctuations of activities. Different methods for measuring fluctuations of activities exist. Other examples of methods might be to extend the 15 min-timeframe, as used in the current study, to a longer timeframe for calculating the RMS values or to measure fluctuations between parts of the day by calculating differences in total physical activity between morning, afternoon and evening. To date, different methods for assessing fluctuations in activities[10,30] have never been compared and consensus on which method is the most valid is lacking. Future studies should compare different methods in order to find the most valid and reliable method for measuring fluctuations in activities.

On the perceived physical functioning, passive patients reported to feel more impaired in their mobility (SIP mobility) and showed lower scores on physical functioning (SF-36) compared to the relatively active patients. This is in accordance with the theory that underlies the CBT protocols[6,7], the results of Van der Werf et al[2] and Wiborg et al[29] showing higher functional impairment scores in passive patients. Although perceived physical functioning is lower in passive patients, the actual physical activity level does not show the same pattern when compared to the relatively active patient. There seems to be a discrepancy between the perceived level of physical functioning and the actual daily life activities. It is essential for future research to measure actual and perceived physical activity at the same time-period in order to further investigate this discrepancy. The discrepancy between what the patient perceives and the actual physical activity during daily life might be of greater importance when individualizing treatment than making subgroups solely based on the perceived or actual physical activity level. Whether this optimized individualized treatment also results in higher effectiveness of the provided treatment has to be established. On the other hand these results can also be due to selection bias because the CBT therapists had access to the results of these questionnaires when categorizing the patients.

The current study has some limitations that need to be addressed. Although the characteristics of our sample appear to be similar to those reported in other studies reporting physical activity in patients with CFS[2,8] the generalizability of our findings might be limited due to the relatively small number of participants in the passive group. More research is needed with a larger number of patients. As in previous studies[2], our study shows that approximately 25% of the patients are categorized as passive and 75 % relatively active. Furthermore, some doubt can be cast upon the methods used for categorizing the patients. The activity monitor, self-report questionnaires, expert opinion or a combination of these methods can all be used to categorize the patient. Another, more simple measurement, is the step counter, which is cheap, practical and easy to use, but needs to be validated if assessment of the physical activity level in patients with CFS is strived to be assessed. In a study of Scheeres et al[9] three methods for categorization (the Activity Pattern Interview, International Physical Activity Questionnaire or the CFS-Activity Questionnaire) were compared. According to the authors, none of the instruments could really be called satisfactory. In the present study we used the expert opinion to categorize the patient, which is mostly used in clinical practice. More research is needed to define the best way to categorize the patient and to define clear definitions or cut-off scores when using self-rated questionnaires in order to categorize the patient. In addition, for future research it is also recommended to evaluate other potential differences between patients with CFS used to categorize patients in subgroups that may further improve the treatment outcome. Since post-exertional malaise is a potential core symptom responsible for much of the debilitation in patients with CFS, it is worthwhile analysing the difference in actual and perceived physical function-

ing in patients with or without this symptom and tailoring treatment based on this symptom[31].

Following the results of this study only a few differences were found between relatively active and passive patients with CFS in both actual as well as perceived physical functioning. The differences had small to medium effect sizes. It is possible that not every patient can be categorized as relatively active or passive because they have characteristics of both subgroups.

CONCLUSION

A clear difference in actual and perceived physical functioning between relatively active and passive patients with CFS as judged by their therapists could not be found. Discrepancies exist between the patient's perception and the actual measure of physical functioning. Individualizing treatment based on the discrepancy within patients with CFS might be worthwhile. Furthermore, more research is needed with a greater number of participants to form a consensus on how to categorize patients, validate this categorization and tailor treatments based on the categorization in order to increase the effectiveness of treatment.

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6

Treatment expectations influence the outcome of multidisciplinary rehabilitation treatment in patients with CFS.

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Vos-Vromans DCWM, Huijnen IPJ, Rijnders LJM, Winkens B, Knottnerus JA, Smeets RJEM. Treatment expectations influence the outcome of multidisciplinary rehabilitation treatment in patients with CFS.

ABSTRACT

Objective. To improve the effectiveness of treatment in patients with chronic fatigue syndrome it is worthwhile studying factors influencing outcomes. The aims of this study were (1) to assess the association of expectancy and credibility on treatment outcomes, and (2) to identify baseline variables associated with treatment expectancy and credibility.

Methods. 122 Patients were included in a randomized controlled trial of whom 60 received cognitive behavioural therapy (CBT) and 62 multidisciplinary rehabilitation treatment (MRT). Expectancy and credibility were measured with the credibility and expectancy questionnaire. Outcomes of treatment, fatigue, and quality of life (QoL) were measured at baseline and post-treatment. Multiple linear regressions were performed to analyse associations.

Results. The effect of expectancy on fatigue and the physical component of the QoL after treatment was significant for MRT, whereas in CBT no such associations were found. The overall effect of expectancy on the mental component of QoL was not significant. For credibility, the overall effect on fatigue and the physical component of QoL was not significant. For the mental component of QoL the interaction with treatment was significant for credibility. However, the effects within each group were not significant.

In the regression model with expectancy as dependent variable, only centre of treatment appeared significantly associated. In the equation with credibility as dependent variable, centre of treatment, treatment allocation and depression were significantly associated.

Conclusions. For clinical practice it seems to be important to check the expectations of the patient since expectations influence the outcome after MRT.

INTRODUCTION

Cognitive behavioural therapy (CBT) has shown to be an effective, evidence based treatment for patients with chronic fatigue syndrome (CFS)[1]. Recently, a new, innovative multidisciplinary rehabilitation treatment (MRT) has been developed and compared with CBT in a randomized controlled trial (RCT). The results of this RCT showed MRT was more effective in reducing fatigue severity at long-term compared to CBT[2]. To understand the working mechanisms of these interventions and to find out how to increase their effectiveness, it is important to study factors that influence the outcome of treatment. A factor that might influence important treatment outcomes, such as fatigue and quality of life (QoL) is the expectancy of the patient. Expectations or predicted expectations are what the patient believes will occur after following treatment[3]. Heins et al (2013)[4] were the first to investigate whether outcome expectations contribute to the reduction in fatigue during CBT for patients with CFS. 25% of the variance in post-treatment fatigue was jointly explained by outcome expectations and agreement between therapist and patient on the content of treatment and how to achieve the patient's goals[4]. It is postulated that these factors exert their positive effect through a change in fatigue perpetuating factors. In patients with chronic low back pain, similar results were found regarding the influence of expectations on the outcome. Expectations explained 1-8% of the variance in the equation of four different outcome variables after CBT, namely: motor behaviour, pain coping and control, negative effect and QoL[5]. Whether expectations influence the outcome after MRT in patients with CFS needs to be evaluated. If expectancy and/or credibility are related to the outcome, interventions could be designed to increase these concepts which eventually also will increase treatment outcome.

Another factor, which might influence treatment outcome is credibility. Credibility is how believable, convincing and logical the treatment seems to the patient. In patients with chronic low back pain, credibility was a significant predictor for global perceived effect in patients following a rehabilitation treatment, which combined active physical therapy with CBT[6]. In patients with CFS, the association between credibility and outcome of treatment has never been studied before.

If expectations and credibility are associated to the final outcome it is important to know what other factors are associated with expectations. Age, internal control over symptoms, self-efficacy, depression, duration of complaints and severity of symptoms have been proposed as factors influencing expectations before treatment[6-8]. Whether these factors influence the expectancy or credibility in patients with CFS referred for treatment needs to be studied.

The purpose of this study was two-fold: First, to assess the association of patients' treatment expectancy and credibility on the outcome of treatment (change in fatigue severity and quality of life), and whether these associations are different for MRT and

CBT respectively. Second, to study the effect of age, centre of treatment, type of treatment allocation, self-efficacy, depression and duration of complaints at baseline on treatment expectancy and credibility.

METHODS

This study is part of the FatiGo trial, a multi-centre, pragmatic two-arm RCT (ISRCTN77567702) of which the methods and results are described previously[9]. The main aim of the FatiGo trial was to analyse the difference in treatment effect between MRT and CBT for patients with CFS. In summary, the main results of the RCT reveal that MRT is more effective than CBT in reducing fatigue at 52 weeks. At baseline, patients from the MRT had mean fatigue score of 51.47 (SD 5.08) compared to 51.05 (SD 5.09) in CBT. At follow-up, patients from MRT scored 33.84 (SD 14.33) compared to 40.05 (SD 12.79) in CBT. The estimated difference in fatigue between the two treatments was -5.69 (95% CI -10.62 to -0.76; P = 0.02) at 52 weeks. Estimated differences between groups are calculated using linear mixed models with centre, treatment allocation, time and time by treatment allocation as covariates (unstructured covariance). At baseline, patients from MRT had a mean observed MCS of 46.57 (SD 9.23) and PCS of 30.59 (SD 7.93). In CBT, baseline scores were 44.38 (SD 9.02) and 32.60 (SD 7.78) for MCS and PCS, respectively. At 52 weeks follow-up quality of life scores were 51.10 (SD 10.22), and 40.19 (SD 11.29) for MCS and PCS in MRT. For CBT scores were 49.88 (SD 9.16) for MSC and 36.67 (SD 10.40) for PCS. Patients showed an improvement in quality of life over time but between-group differences were not statistically significant[2].

Participants

Patients with complaints of chronic fatigue referred to Revant Rehabilitation Centre in Breda, Rehabilitation Centre Blixembosch in Eindhoven, Reade Centre for Rheumatology and Rehabilitation in Amsterdam and Adelante Rehabilitation Centre in Hoensbroek between December 1st, 2008 and January 31st, 2011 were asked to participate. Inclusion criteria were: met the US Centers for Disease Control and Prevention (CDC-94) criteria for CFS[10]; Checklist Individual Strength (CIS)[11] fatigue subscale score of 40 or more (range is 8-56); willing to participate in a treatment aimed at changing behaviour; aged between 18 and 60 years; comprehended the written and verbal Dutch. Patients were excluded if they suffered from a medical condition explaining the presence of chronic fatigue, had a psychotic, major or bipolar depressive disorder, dementia, anorexia, bulimia nervosa, alcohol and/or drug abuse, a body mass index ≥ 45, or were pregnant. Patients, who had already received CBT or MRT for CFS, or had to travel more than 1 h to the nearest participating rehabilitation centre were also excluded. The multistage inclusion process is more fully described elsewhere[9].

Outcomes

Assessment of outcomes took place before treatment (baseline), 26 weeks (post-treatment) and 52 weeks after start of treatment (follow-up). Fatigue severity was measured by the CIS fatigue subscale (eight items scored on a 7-point Likert scale, range 8-56, lower scores indicate less fatigue)[12]. Previous assessment of measurement properties suggests adequate reliability and validity[13].

Health-related QoL was measured by the Short-Form 36 (SF-36)[14]. The SF-36 consists of eight subscales (range 0-100, higher score indicate better quality of life). The SF-36 subscales can be summed to provide in a physical component summary score (PCS) and a mental component summary score (MCS)[15]. Psychometric properties of the SF-36 are satisfactory[16]. Depression was measured with the Symptom Check List-90 (SCL-90)[17] subscale depression and self-efficacy with the Self-Efficacy Scale (SES)[12].

Expectancy and credibility

Expectancy and credibility were measured with the Dutch version of the Devilly and Borkovec credibility and expectancy questionnaire (CEQ)[6,18]. The CEQ has three items to measure expectancy and three to measure credibility. Items were scored on a scale from 1 (not at all) to 9 (very much) or a scale from 0% (not at all) to 100% (very much), percentage rating scores were linear transformed to a 1 to 9 rating[6]. Separate scores were calculated for expectancy and credibility, each ranging from 3 to 27, with a higher score indicating higher expectation or higher credibility. Expectancy and credibility were assessed two weeks after start of treatment, after the treatment rationale was explained. In MRT, the physical therapist asked the patient to complete the CEQ, in CBT, the psychologist or cognitive behavioural therapist did so. After completion the patients were asked to return the questionnaire in a sealed envelope. To maintain confidentiality and to avoid socially desirable answers, the patients were told not to share their responses with the therapist.

Interventions

After baseline assessment, patients were randomly assigned to MRT or CBT. In MRT, gradual reactivation, pacing, mindfulness, body awareness therapy, normalising sleep/wake rhythm and social reintegration are combined with CBT. The biopsychosocial model is the basis of therapy, suggesting that multiple factors (physical, mental and social factors) may lead to the development and persistence of CFS[19]. MRT was patient tailored, based on addressing the modifiable factors thought to be related to the precipitation and perpetuation of the CFS. MRT was provided by an interdisciplinary team consisting of a physical therapist, occupational therapist, psychologist, social worker and consultant in rehabilitation medicine. CBT is a psychotherapeutic approach where

perpetuating cognitions and behaviours such as high physical attributions, decreased physical activity, low level of sense of control, focusing on physical sensation and perceived lack of social support are the focus of the intervention[20]. CBT is a monodisciplinary treatment given by a psychologist or cognitive behavioural therapist.

Analyses

Numerical variables were presented by means (SD), where numbers (%) describe categorical variables. The difference between treatment groups were analysed using independent-sample *t*-test for numerical variable and Chi-square test for categorical variables.

To measure the role of expectancy and credibility on the effectiveness of the treatment, multiple linear regression analyses were used with the post-treatment scores (at 26 weeks after start of treatment) of fatigue severity and the physical and mental component summary score of QoL as outcomes. The analyses were performed in three steps: 1) a model with age, centre of treatment, baseline scores of the outcome, treatment allocation and expectancy and credibility as explanatory variables. 2) Same variables as step 1, but also including the interaction between expectancy and treatment allocation and credibility with treatment allocation to determine whether expectancy or credibility were significantly different for MRT compared to CBT, 3) same variables as step 2, but without the interaction terms that are clearly non-significant ($P > 0.10$). Previous studies[21-25] in patients with CFS showed that depression, self-efficacy and duration of complaints were associated with outcome of treatment. In a sensitivity analysis, depression, self-efficacy and duration of complaints were entered in the final model to analyse whether these factors influence the final model.

To analyse whether treatment expectancy and credibility were associated with different variables at baseline, multiple linear regression analyses were performed with expectancy or credibility as the dependent variable. Age, centre of treatment, treatment allocation, fatigue severity, depression, duration of illness and self-efficacy were entered in the model as explanatory variables.

For all explanatory variables, the association with the outcome was presented by the regression coefficient (B), the corresponding 95% confidence interval (CI) and P-value. In every step of the analyses as described above, there was a check for high collinearity (VIF > 10). A P-value ≤ 0.05 was considered statistically significant. All analyses were performed using IBM SPPS for windows (Version 20.0, Armonk NY: IBM Corp.).

RESULTS

Baseline characteristics

Overall, 364 patients were referred to the participating rehabilitation centres with a major complaint of fatigue. The most common reasons for exclusion were unwillingness to participate (54 patients), not meeting the CDC-94 criteria (34 patients), and other diagnosis explaining the presence of fatigue or fatigue was not the primary complaint (34 patients). Finally, 60 patients completed the baseline assessment and were randomized to CBT and 62 to MRT. In the MRT group 57 (95%) patients completed the CEQ and 56 (90%) patients in CBT, one further patient in each group did not fill in the expectation part of the CEQ. Fifty-nine (98%) patients in MRT completed CIS and 55 (89%) completed the CIS in CBT at post-treatment. Fifty-eight (97%) patients completed the SF-36 (MCS and PCS) post-treatment in MRT and 55 (89%) patients in CBT. Table 1 displays the baseline characteristics of the study sample only including the patients with either expectancy or credibility data or both (N = 113, 93%). These patients were included in the final analyses. The mean expectancy score was 17.46 (SD 4.37) for MRT and 16.77 (SD 5.26) for CBT. The mean credibility score of 22.39 (SD 3.41) for MRT was significantly higher than the mean score of 19.43 (SD 4.01) for CBT. The MCS in MRT (47.03, SD 8.86) was also significantly different compared to CBT (43.72, SD 8.66). There were no other significant differences in patient characteristics between the treatment groups at baseline.

The influence of a patient's treatment expectancy and credibility on the effectiveness of treatment

The overall effect of expectancy on fatigue appeared to be clearly non significantly between MRT and CBT (P = 0.07), and therefore as planned, separate analyses per treatment were performed. The effect of expectancy on fatigue appeared to be significant for MRT (B = -1.52, 95% CI -2.39, -0.66, P = 0.001), whereas it was not significant for CBT (B = -0.47, 95% CI -1.35, 0.41, P = 0.29). The effect of credibility on fatigue was not significantly different for the treatment groups (P = 0.61) (see table 2). In addition, the overall effect (without analyzing separate treatment groups) of credibility was also not significant (B = -0.39, 95% CI -1.40, 0.62, P = 0.45).

For the physical component of QoL, similar results were found, i.e. a significant interaction for expectancy (P = 0.03) and no significant interaction with treatment group for credibility (P = 0.40). The effect of expectancy on the physical component was significant for MRT (B = 1.15, 95% CI 0.49, 1.81, P = 0.001), whereas it was not significant for CBT (B = 0.24, 95% CI -0.43, 0.91, P = 0.48). For credibility, the overall effect on the physical component was not significant (B = 0.49, 95% CI -0.28, 1.25, P = 0.21).

Table 1. Patient characteristics

		MRT (N = 57)	CBT (N = 56)
Demographic			
Age (yr)		39.3 (10.1)	39.9 (12.1)
Gender, N (%) female		47 (82.5)	45 (80.4)
Education (at referral)			
	Low	35 (61.4)	35 (62.5)
	Middle-high	21 (36.8)	20 (35.7)
	Missing	1	1
Work status, N (%)			
	Work	13 (22.8)	16 (28.6)
	Work, but partial sick leave	7 (12.3)	8 (14.3)
	Work, but full sick leave	15 (26.3)	14 (25.0)
	No work	21 (36.8)	18 (32.1)
Duration of fatigue			
(at referral), N (%)	½ - 1 year	3 (5.3)	7 (12.5)
	1-2 years	13 (22.8)	14 (25.0)
	2-5 years	19 (33.3)	13 (23.2)
	> 5 years	22 (38.6)	22 (39.3)
Baseline			
CIS, fatigue		51.19 (5.20)	51.50 (4.17)
QoL, PCS		30.97 (7.87)	32.50 (7.67)
QoL, MCS		47.03 (8.86)*	43.72 (8.66)*
Self-efficacy		17.70 (2.71)	17.52 (2.89)
Depression		28.74 (8.56)	31.89 (9.11)
Two weeks after start of treatment			
Expectancy		17.46 (4.37)	16.77 (5.26)
Credibility		22.39 (3.41)*	19.43 (4.01)*

Values are presented as means and standard deviation or percentage at baseline or at referral; MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy; CIS, Checklist Individual Strength, QoL, PCS, physical component summary scale of the health-related quality of life; QoL, MCS, Mental component summary scale of the health-related quality of life; * significant difference between MRT and CBT (P-value < 0.05).

The results for the mental component of QoL showed that the interaction with treatment group was significant for credibility (P = 0.048) and not significant for expectancy (P = 0.51). However, within each treatment condition no significant associations between credibility and the mental component could be found (credibility: B = 0.93, 95% CI -0.05, 1.92, P = 0.06 in MRT group, B = -0.14, 95% CI -0.81, 0.52, P = 0.67 in CBT group.

Similar results were obtained in the sensitivity analyses, i.e. including symptoms of depression, self-efficacy and duration of complaints as explanatory variables in the models.

Pre-treatment associations with credibility and expectancy

Pre-treatment associations with expectancy and credibility appear in table 3. Centre of treatment was significantly associated with expectancy. Patients receiving treatment in rehabilitation centre Blixembosch (B = -2.25, P = 0.05), Reade (B = -3.44, P = 0.009) or Adelante (B = -4.27, P = 0.001) had lower expectations on the outcome of treatment compared to Revant. Other variables in the equation were not significantly associated with expectancy. For credibility, Adelante rehabilitation centre (B = -2.17, P = 0.03), treatment allocation (B = -3.46, P < 0.01) and depression (B = 0.09, P = 0.04) were significantly associated. Patients allocated to CBT and patients treated in Adelante rehabilitation centre (versus Revant) had a significantly lower credibility score compared to patients allocated to MRT. Patients with a higher degree of depression at baseline reported a significantly, but only slightly higher credibility score.

Table 2. Effect of expectancy and credibility on fatigue severity, and physical and mental component of the quality of life

Model steps	Outcome variables								
	Fatigue severity			Physical component, QoL			Mental component, QoL		
	B	P	CI	B	P	CI	B	p	CI
Step 1									
Age	0.05	0.63	-0.16 to 0.26	-0.001	0.99	-0.16 to 0.16	-0.05	0.44	-0.18 to 0.08
Treatment	-2.36	0.37	-7.62 to 2.89	2.35	0.25	-1.64 to 6.35	0.91	0.59	-2.43 to 4.24
Centre 1	6.64	0.03	0.71 to 12.57	-3.30	0.16	-7.88 to 1.27	-3.01	0.11	-6.68 to 0.67
Centre 2	7.47	0.03	0.66 to 14.29	-5.64	0.04	-10.89 to -0.39	-3.76	0.08	-8.02 to 0.50
Centre 3	9.59	0.01	2.90 to 16.27	-4.93	0.06	-10.11 to 0.25	-4.06	0.07	-8.37 to 0.26
Dep. var. at T1	0.82	0.001	0.33 to 1.30	0.64	0.00	0.41 to 0.87	0.40	0.00	0.22 to 0.58
Expectancy	-1.01	0.004	-1.69 to 0.33	0.71	0.01	0.18 to 1.23	-0.15	0.48	-0.57 to 0.27
Credibility	-0.06	0.91	-1.02 to 0.91	0.21	0.58	-0.53 to 0.94	0.14	0.64	-0.47 to 0.75
Step 2									
Exp x treatment	-1.25	0.07	-2.58 to 0.09	1.16	0.03	0.14 to 2.17	-0.27	0.51	-1.10 to 0.55
Cred x treatment	0.53	0.61	-1.52 to 2.58	-0.68	0.40	-2.27 to 0.91	1.31	0.05	0.02 to 2.60
Step 3									
Expectancy							-0.09	0.67	-0.51 to 0.33
MRT	-1.52	0.001	-2.39 to -0.66	1.15	0.001	0.49 to 1.81			
CBT	-0.47	0.29	-1.35 to 0.41	0.24	0.48	-0.43 to 0.91			
Credibility	-0.39	0.45	-1.40 to 0.62	0.49	0.21	-0.28 to 1.25			
MRT							0.93	0.06	-0.05 to 1.92
CBT							-0.14	0.67	-0.81 to 0.52

Outcome variables are measured at 26 weeks after treatment. Values presented are the regression coefficient (B's) and 95% confidence interval's (CI) in the equation. P-values for the separate variables are from the *t*-tests in the equation. All VIF < 10.

QoL, quality of life; Dep. var. at T1, dependent variables at baseline; MRT, multidisciplinary rehabilitation treatment; CBT, cognitive behavioural therapy.

Table 3. Effect of patient characteristics on expectancy and credibility as outcome variables

		Expectancy		Credibility	
		B	CI	B	CI
Age		0.012	-0.07 to 0.09	0.001	-0.06 to 0.07
Centre	Blixembosch	-2.25*	-4.47 to -0.03	-1.02	-2.72 to 0.68
	Reade	-3.44**	-5.99 to -0.89	-1.57	-3.58 to 0.44
	Adelante	-4.27**	-6.77 to -1.76	-2.17*	-4.14 to -0.20
Treatment allocation		-1.38	-3.14 to 0.39	-3.46**	-4.84 to -2.09
Fatigue severity		0.07	-0.12 to 0.26	0.14	-0.01 to 0.29
Self-efficacy		0.12	-0.20 to 0.44	0.22	-0.03 to 0.47
Depression		0.06	-0.05 to 0.17	0.09*	0.003 to 0.17
Duration of complaints	1-2 years	0.39	-3.02 to 3.79	0.53	-2.15 to 3.21
	2-5 years	-2.94	-6.28 to 0.41	-1.21	-3.82 to 1.41
	> 5 years	-2.60	-5.85 to 0.64	-1.36	-3.92 to 1.20

Values presented are the regression coefficient (B's) and 95% confidence interval's (CI) in the equation. P-values for the separate variables are from the *t*-tests in the equation *, P-value < 0.05; **, P-value < 0.01. All VIF < 10.
Revant Rehabilitation centre, MRT and 0-1 year of complaints are the reference categories for Centre, Treatment allocation, and Duration of complaints respectively.

DISCUSSION

The first aim of the present study was to evaluate the influence of expectancy and credibility on the outcomes fatigue severity and QoL after MRT and CBT. The second aim was to evaluate whether expectancy and credibility are associated with age, treatment allocation, centre of treatment, self-efficacy, depression and duration of complaints at baseline.

Expectations regarding outcome of treatment were associated with the effect on the severity of fatigue and the physical component of QoL after treatment. In addition, different effects of expectancy on both outcomes were found for MRT compared to CBT. A higher expectancy at the beginning of treatment is associated with a lower fatigue and a higher physical QoL score after treatment in patients allocated to MRT, whereas no significant association between expectancy and fatigue or physical component of QoL could be found in the patients who received CBT. It is possible that the rationale of MRT is more in line with what patients think will help them in achieving a positive result. Higher expectations and a higher agreement on the content of therapy might result in patients being more engaged and compliant to treatment, resulting in a better outcome. Although there was a difference in credibility between MRT and CBT as described in the baseline characteristics section of the results, credibility did not significantly influence the studied outcomes after treatment. It is possible that credibility does

not have a direct positive effect on the outcome, but credibility might influence the expectations of a patient which in turn influences the outcome of treatment. This is in line with the results of a study of Hardy et al[26] who stated that outcome expectations might develop, at least in part, from how credible a treatment seems.

Since higher expectations seem to improve the outcome of treatment it is worthwhile studying how expectations can be enhanced. One method for enhancing expectations is proposed by Mertens et al[27]. They suggest to provide a pre-treatment in which motivational interviewing is used to address motivation, expectation and beliefs before treatment starts in order to increase the expectations and the final outcome of treatment in patients with chronic low back pain. Results of this study will reveal if pre-treatment influences the expectation of a patient and thereby increases efficacy of treatment. Whether this method influences expectancies in patients with CFS needs to be studied.

No significant associations between expectations and outcomes were found in patients receiving CBT. These results are contradictory to the results of Heins et al[4] who found that expectations are one of the factors influencing treatment outcome in patients with CFS. In that study, all patients were referred to CBT and accepted the referral. In the present trial, patients accepted the referral but they knew they could be randomized to MRT or CBT. Since patients in the study of Heins et al[4] all accepted the referral to CBT, they may have been motivated and confident about CBT, which might have influenced the results. In the present trial, expectations before randomization might be different for MRT and CBT. Although explained to the patient that both treatments are effective, it is possible that patients initially preferred MRT or CBT. This preference might have influenced the expectations and final results of the trial. It would be interesting to study the expectations before and after the first contact with the therapists to determine if and how expectations change during the first contact with the therapists. Another explanation of the difference in results between the study of Heins et al[4] and the present trial is that different measurements for expectations were used. Expectations on functional limitations, as used in the present trial might be different from expectations regarding decrease of, or coping with symptoms and expectations of recovery after treatment, which were used in the study of Heins et al[4]. It would be interesting whether and how these expectations differ in patients following MRT or CBT.

In both treatments, expectancy and credibility did not significantly influence the mental component of the QoL. This might be due to the fact that patients were asked whether they think or feel the treatment will reduce functional limitations caused by the fatigue. They were not asked about their expectations regarding their mental health after treatment. It remains unclear whether expectations will change when the term 'functional limitations' is substituted by another term like 'mental health'. Future research is

needed on this topic. Functional limitations are probably more related to the physical component of the QoL score.

Since expectations interact with treatment with regard to fatigue, it is important to investigate which baseline factors might influence these. In this study, no statistically significant associations were found between expectations and age, treatment allocation, fatigue at baseline, self-efficacy, depression or duration of complaints. A clear explanation for this could not be found. The finding that treatment allocation was not significantly related to expectancy can be explained by the fact that both treatments aimed at recovery and in both treatments the same effort was paid to explain the rationale of treatment. The definition of recovery given by the therapists was finding a new balance in overall functioning of a patient and not experiencing disproportionate fatigue. This definition was the same in both treatments. Centre of treatment was significantly associated with expectations and credibility. Patients receiving treatment in other than the reference centre Revant had lower expectations of the outcome of treatment. In Revant, higher expectations were seen in both the MRT and CBT group compared to other rehabilitation centres. This could be explained by the fact that in Revant, therapists were more experienced in coaching patients with CFS and were possibly more capable in explaining the rationale of the treatments. They might also be more convinced (by positive experiences in the past) that MRT or CBT will work for the patient.

This positive vision of the therapist regarding treatment outcome might also have influenced the patients' expectations. This is to some extent in line with the findings of Westra et al[28] who found that more effective therapists were characterized by higher client outcome expectancies and treatment credibility in patients receiving CBT for a generalized anxiety disorder. However, which therapeutic skills are most valuable in increasing expectations and credibility in patients with CFS needs to be evaluated in future research. Furthermore, treatment allocation, centre of treatment and depression are significantly associated with credibility. It might be that patients experiencing physical complaints prefer MRT, as in this treatment approach specific attention is paid to the physical components of their complaints for instance by the physical therapist. A rather surprising result was the association of depression with credibility. A higher degree of depressive symptoms is associated with slightly higher credibility. The fact that patients with psychotic, major or bipolar depression were not included in the trial should be taken into account when interpreting this association. Future studies should reveal whether including a more depressed population alters the association with credibility.

This trial has a number of strengths and limitations. In particular internal validity is high due to robust randomization and concealed allocation procedures, protocol publication/registration and pre-specification of primary outcomes and analytic methods. The

trial also has some limitations. CEQ has never been validated in the CFS population. Since there were no other expectancy questionnaires available, which were validated for this patient group, a questionnaire was chosen which was used frequently in other patients with chronic illness[5,6,27]. Future research should be aimed at validating the CEQ for patients with CFS. Furthermore, patients were not able to choose their preferred treatment. This might have influenced the expectations of treatment. In clinical practice, patients are often able to choose their preferred treatment, and therefore generalizability of the study is limited. On the other hand, treatments for patients with CFS are scarce and patients are often not able to choose their preferred treatment, since there are not available in their direct environment. Another limitation is the fact that expectancy and credibility were measured two weeks after start of treatment. The first two weeks of treatment are intended to be an intake or observational phase in which the rationale of treatment is provided, but it is possible that the contact of the therapists with the patients changed the expectations. On the other hand, having patients fill out the CEQ after this explanation of the rationale enables them to do so with a better impression about the aims of treatment.

In conclusion, expectancy influenced the severity of fatigue and the physical component of the health-related quality of life after MRT. Credibility did not significantly influence the outcomes in MRT or in CBT. Expectancy was not significantly influenced by baseline factors age, depression, duration of illness, or treatment allocation, but was influenced by centre of treatment. For future research it seems to be important to study how to increase expectations in order to increase the effectiveness of treatment.

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Conflict of interest statement

None of the authors has any conflicts of interest.

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7

General discussion

GENERAL DISCUSSION

CBT is seen as one of the most effective and evidence-based treatments for patients with CFS[1,2]. Less attention has been paid to multidisciplinary rehabilitation treatments using different interventions to increase the effectiveness of treatment. In Revant, multidisciplinary rehabilitation treatment (MRT) for patient with CFS belongs to the standard care supply. Although used in Revant, MRT, as described in chapter 2, has never before been evaluated in a randomized controlled trial (RCT). The effect of MRT had only been evaluated in a pilot study among 36 patients with CFS. Results were promising showing a significant decrease in fatigue and functional impairments after treatment. Another small uncontrolled study in a Dutch rehabilitation setting evaluating a similar multidisciplinary rehabilitation treatment showed a significant decrease in fatigue severity, impairments and increase in physical functioning[3]. To study the effectiveness and cost-effectiveness of MRT in comparison with CBT, the FatiGo trial was designed. The primary aim of the trial was to assess the differences in treatment effect (change between baseline and 26 and 52 weeks follow-up in fatigue severity and quality of life) between MRT and CBT in patients with CFS. As an integral part of the study the cost-effectiveness from a societal perspective was evaluated.

In this general discussion, first the main results presented will be interpreted. In addition, knowledge will be integrated and discussed in relation to the current scientific evidence. Then methodological considerations are formulated followed by the clinical implications, suggestions for implementation and future directions of research. Finally, overall conclusions will be drawn.

INTERPRETATION OF FINDINGS

Effectiveness of treatment

In chapter 3 the results of the multicenter RCT were described. During the trial the primary outcome fatigue severity was measured five times, namely at baseline, after 4 and 14 weeks of treatment, at 26 weeks (end of treatment) and at 52 weeks (follow-up). It was concluded that MRT is more effective in reducing fatigue severity compared to CBT at 4, 14 and 52 weeks after start of treatment. At 26 weeks there was no statistically significant difference between MRT and CBT. In both treatments fatigue severity decreases, with a more rapid decline in MRT compared to CBT from baseline to 14 weeks. Even more important is the fact that after 26 weeks, fatigue increases again in the patient group receiving CBT, while the effect in the MRT group remains at a lower level resulting in a statistically significantly lower level of fatigue at 52 weeks of the MRT group compared to CBT. So, the effect in MRT seems more sustainable at long-term

with a decrease of 34% of fatigue severity in MRT (baseline versus 52 weeks follow-up) compared to 22% in CBT. The Cohen's d of the difference between MRT and CBT is 0.46, indicating a medium effect. At 52 weeks 49% of the patients in MRT group had a CIS fatigue subscale score of less than 35 compared to 26% of the patients receiving CBT. A score of 35 is often used as a cut-off score to decide whether the patient improved[3,4].

Although important for clinical practice, only few studies compared CBT with other treatment approaches for patients with CFS. To our knowledge previous studies compared CBT with psychological approaches, (graded) exercise or adaptive pacing therapy[1,2,5,6]. CBT and graded exercise therapy were found to be the most effective treatments for patients with CFS. The effect of rehabilitation treatments for adult patients with CFS comparable to MRT, were mainly studied in uncontrolled studies[3,7]. Since the trial presented in this thesis was the first to compare MRT with CBT and showing that MRT is more effective in reducing fatigue at long-term, it is important for the management of patients with CFS in the future.

A possible explanation for the results of the primary outcome fatigue is that in MRT special attention is paid to increase the patient's insight in the mutual interaction between biological, social and psychological factors of health. Not only by explaining these factors and their interactions to the patient, but also by doing exercises under close supervision of the therapists. During these exercises, negative thoughts, emotions and bodily symptoms are immediately discussed with the patient. Another important part of MRT is body awareness. As described in chapter 2, body awareness therapy aims at increasing awareness and consciousness of the body and its relation to psychological well-being. Body awareness was evaluated in a meta analysis by Courtois et al[8] and showed that body awareness interventions had positive effects on pain, depression, anxiety and depression in patients with fibromyalgia and in patients with chronic fatigue syndrome when compared with control conditions. More recently, body awareness is studied in a randomized comparative trial among patients with chronic whiplash associated disorders and showed to be more effective in increasing physical functioning, greater pain reduction and social functioning 3 months after end of treatment compared to exercise therapy[9]. As confirmed in several studies[8,10-12], patients with CFS often have an exaggerated focus on fatigue which will have a negative impact on fatigue perception and cognitive functioning. During body awareness therapy, patients are taught to increase the perception of normal body sensations, which might decrease the focus on fatigue[8,13]. In CBT the focus on fatigue is suppressed by advising the patient not to talk about fatigue and to ask family and friends not to ask the patient about the fatigue[14]. In MRT, fatigue is discussed, and explained as mentioned earlier. This might result in a better understanding of the symptoms of CFS and increased skills how to influence them, resulting in an increased confidence in the self. By increasing self-efficacy and confidence in the self, healthy behaviour is stimulated[13]. This healthy behaviour might eventually establish a longer lasting decrease in fatigue. This assumption regarding the working mechanisms of MRT, is supported by the results of the secondary

outcome self-efficacy. The level of self-efficacy is significantly higher in MRT compared to CBT at 26 and 52 weeks, which indicates that patients are more convinced they can positively influence their complaints.

Unlike fatigue severity and self-efficacy, there is no significant difference between MRT and CBT regarding health-related quality of life, functional impairments and psychological symptoms. Although the FatiGo trial was not designed to investigate the treatment effect within each treatment, a post-hoc analysis was executed showing that quality of life increased significantly, and functional impairments and psychological symptoms decreased significantly in both treatment groups when comparing baseline scores with 26 or 52 weeks follow-up scores. However, both treatments are equally effective in reducing the impairments and psychological symptoms and increasing quality of life. It is hypothesized that other, more interacting factors of the biopsychosocial model, as discussed in the introduction, might be influenced more by MRT compared to CBT. The importance of interacting factors is explained by Luyten et al (2012)[15] who introduced a mentalization based model for functional somatic disorders including CFS. This model proposes interacting factors and based on this model, treatment approaches are advised to focus on restoring these interacting factors. However, research regarding such treatments faces many challenges. One of the most important challenges is how to measure these interactions. As described in chapter 2, in MRT, body awareness therapy is used to increase the awareness of a patient regarding the relation between the body and the physical functioning, psychological well-being and social interaction. The challenge was to measure this specific interacting factor. At the start of the trial, an assessment instrument with sufficient clinimetric qualities was not available. Instead, only one concept of body awareness, the present-centred attention awareness, was measured in our study. Although improvement awareness within groups between baseline and follow-up measurements was present in both groups, a significant difference between MRT and CBT was not found. As described in chapter 3 there was only a tendency towards significance at 52 weeks with a higher attention-awareness in patients receiving MRT. Since the Mindfulness Attention and Awareness Scale (MAAS) only measures one concept of body awareness, this might explain our study results.

As mentioned in chapter 2, it was hypothesized that MRT is more effective in increasing quality of life compared to CBT because in MRT interventions are more likely to intrude on the different aspects of quality of life (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role-emotional and mental health). However, based on the results of this study, this could not be confirmed. It might be that MRT focuses on other than 'health-related' factors of quality of life, like coping to stress, social support and personal goals in life which are to a lesser extend measured with the SF-36. The personal goals of treatment were measured with the Patient Specific Complaints and Goals questionnaire (PSCG) and with the Improvement and satisfaction

questionnaire (EET). The goals of treatment are described as activities a patient wants to achieve during treatment. The results in chapter 3 showed that patients in MRT find themselves significantly more capable of doing the things they want to do after treatment compared to patients in CBT. From baseline to 52 weeks, patients in MRT increased 58% in reaching their personal goals compared to a 36% increase in reaching goals after CBT. Furthermore, the results of the EET also showed that significantly more patients in MRT found themselves improved in their daily activities and in dealing with problems compared to patients receiving CBT. Significantly more patients were satisfied with the results of treatment after MRT compared to CBT. It was expected that with a higher achievement of personal goals and a higher satisfaction with the results of treatment quality of life would increase. However this could not be confirmed by the results of the quality of life as measured with the SF-36.

It is possible that health-related quality of life does not change immediately after treatment but after a longer follow-up. In order to analyze such long-term effects of treatment it is worthwhile studying the outcomes for more than one year after start of treatment.

Similarly to quality of life, no differences in physical and non-physical attributions after treatment between MRT and CBT were found, indicating that there was no difference in how patients think about the etiology of their CFS and which factors attribute to the syndrome. The fact that both treatments do not focus on the etiology of the illness, might explain why the results were not significantly different. A rather surprising result of our trial was that there was no difference in physical activity in daily life between both treatments. Physical activity was measured with an activity monitor, which the patient wore for 7 consecutive days before, and after treatment, and at 52 weeks after start of treatment. Although patients gradually increased physical activity under close supervision of a physical therapist in MRT, the home exercises without supervision in CBT resulted in the same level of physical activity in daily life after treatment. It is remarkable that patients in MRT perceived they were more capable in doing the activities they wanted to (goals of treatment), but on the other hand their actual physical activity in daily life was not significantly higher compared to CBT. Similar, patients in MRT perceived a higher improvement in their daily activities (measured with the EET) but their actual physical activity measured in daily life was not significantly higher compared to CBT. The physical activity level measured by the activity monitor is a general level. Results do not reveal what a patient is actually doing or how the patient is doing the activities during the day. It is possible patients change the way they perform the activities, without increasing the actual physical activity level as measured by an activity monitor. Another explanation is that perceiving improvement as measured with a questionnaire and actual increase on daily activities as measured by accelerometers are different constructs. In the study presented in chapter 5, differences between perceived and actual physical activity level were studied using the baseline data of the FatiGo trial.

According to the CBT protocol therapists were advised to categorize patients in relatively active and passive patients. To find evidence supporting the existence of these subgroups, baseline data of the CBT group from the trial were used. The activity monitor data was used to assess actual physical functioning while perceived physical functioning was measured using the CIS, SF-36 physical functioning subscale and the Sickness Impact Profile 8. On the perceived physical functioning, passive patients reported to feel more impaired in their mobility (SIP mobility) and showed lower scores on physical functioning (SF-36) compared to the relatively active patients. The actual physical activity level measured with the activity monitor did not show a lower level of physical activity in the passive group. These results showed that in patients with CFS there seems to be a discrepancy between the perceived level of physical functioning and the actual daily life activities as measured by accelerometers. Major limitation of this study was the inclusion of a rather small number of patients in the passive group. Future research should include more patients to reach consensus on how to categorize patients, validate this categorization and tailor treatments based on the categorization in order to increase the effectiveness of treatment.

Cost-effectiveness of treatment

As described in chapter 4, the FatiGo trial evaluated the one-year cost-effectiveness from a societal perspective of MRT and CBT in terms of gains in quality-adjusted life-years (QALYs) and reduction in fatigue and gains in health-related quality of life. The most important conclusion was that there is a difference in the results of the cost-utility and the cost-effectiveness analyses. Using the QALY as an outcome measure CBT had a higher probability of being the most cost-effective treatment. These results are in line with other studies evaluating the cost-effectiveness of CBT[16-18]. However, when using the CIS fatigue or SF-36 as an outcome measure, MRT had a higher probability of being the most cost-effective treatment. Different sensitivity analyses were done to test how differences in costing and differences in effect measurements influence the outcomes. All sensitivity analyses gave the same results as the base-case analysis.

There are some considerations that need to be addressed regarding this topic. First of all, the Euroqol-5D-3L (EQ-5D-3L) was used to measure quality of life and to calculate utilities. The EQ-5D-3L showed a marginal incremental treatment effect for MRT. With a low incremental effect in the denominator and a high incremental cost in the nominator, the incremental cost-effectiveness ratio (ICER) is high. The question arises whether our findings reflect an absence of a clinically significant treatment effect or, alternatively, a lack of sensitivity of the generic EQ-5D-3L measurement to detect a clinically meaningful improvement in patients with CFS. Differences between generic health-related quality of life measures and disease-specific measures have been discussed in previous research[19-21]. In patients who are chronically ill, treatments like MRT often focus on improving autonomy and participation of a patient in society. Both domains are not

included in the EQ-5D-3L. Future studies should assess the extent to which differences in the EQ-5D-3L following treatment reconcile with improvements on disease-specific measurements for patients with CFS after treatment. Looking at the cost-effectiveness of treatment and taking improvement on fatigue as the primary outcome measure (using the criteria from the CIS fatigue subscale), the cost-effectiveness increases compared to using the QALY in these analysis. But the criteria for improvement are mostly based on statistical methods and not on the patients' own opinion. For further research, it is recommended to evaluate improvement based on important domains for the individual patient and also to get insight what society is willing to pay for an improved patient with CFS to facilitate cost-effectiveness analysis of treatments.

In the MRT and CBT the healthcare costs, as part of the total societal costs, are mainly dominated by the costs for the intervention. In addition, future research is needed to study how interventions can be more cost-effective. It might be possible to offer parts of the treatment in groups of patients instead of individuals, which will decrease the costs of treatment. Additionally, costs of treatment might become lower when therapists are able to decrease the number of sessions when achieving a patient's personal goal earlier or when specific interventions are not needed to achieve a patient's goal. In clinical practice this is already the case, but due to the treatment protocols in this trial, in which a minimum hours of treatment is prescribed this was not an option. Whether treatment effect remains similar should be evaluated in future studies. Since the productivity costs are highest in the MRT group, it is also worthwhile looking at this part of the costs. In CBT returning to work is part of the protocol. In MRT returning to work is only included in the treatment if it identified a patient's goal. If not, returning to work is no part of the MRT procedure. In order to decrease the costs from a societal perspective, making 'returning to work' a fixed part of the MRT protocol might be useful. Whether this adaptation changes the cost-effectiveness of treatment needs to be evaluated in future research.

In conclusion, using the fatigue severity as primary outcome for the cost-effectiveness, MRT is more likely to be cost-effective compared to CBT. Taken the QALY, CBT is more cost-effective than MRT. To further improve interpreting cost-effectiveness analysis of treatment in patients with CFS it is important to clearly define criteria for improvement and how much money society is willing to pay for an improved patients. The results of the effectiveness study described in chapter 3 and the results of the disease-specific outcome in the cost-effectiveness study described in chapter 4, imply that MRT should be included in the guidelines for treatment of patients with CFS. In future studies it is worthwhile evaluating which patient characteristics are important in defining which treatment should be advised to a patient. As presented in chapter 6, expectations should be taken into account advising a patient.

In the next five paragraphs different methodological considerations will be discussed according the chronological phases of the trial, followed by the implications for clinical practice.

METHODOLOGICAL CONSIDERATIONS

Inclusion of patients

Until now, several case definitions for CFS have been published[22-25]. Main difference between the CDC-94 criteria and for example the latest International Consensus Criteria (ICC) is that the latter also include symptoms more related to dysfunction of neurological, immune and gastro-intestinal systems. In the present study the CDC-94 criteria, were used. At this time, these criteria are still advised in the guidelines for CFS of the Dutch foundation for quality in healthcare[26]. Recently some concerns have been raised on its selection of widely heterogeneous patients[27]. Hence, this topic will be discussed in the present paragraph in relation to the inclusion process of patients. Since there is no unique or set of biological markers for diagnosing CFS, the diagnostic process is, at this moment, mainly based on differential diagnosis. In guidelines different methods for this differential diagnosis are described[26,28] and used in daily practice. A recent study of Johnston et al[27] with a sample size of N = 45, patients fulfilling CDC criteria were compared with patients fulfilling the ICC criteria and a healthy population. It was shown that patients fulfilling the ICC criteria reported significantly greater disability, poorer social functioning, and 'cognitive' difficulties in comparison to the CDC-94 criteria group, indicating that this is a more severe group of patients. Although expected, differences in biomarkers from a blood sample could not be found between the two patient groups. The results of the study of Johnston suggest that the ICC identifies a distinct subgroup within patients complying with the CDC-94 criteria. It is unknown whether CBT and MRT have the same effect on both subgroups of patients. In the present trial the heterogeneity of the included patients might be present, but as we performed randomization it can be expected that heterogeneity is equally spread over CBT and MRT. Notably, some studies, for example in the study of White et al[6,29], analyses were repeated using different definitions for CFS and concluded that the main results did not change.

Other inclusion criteria for entering the trial were: a CIS fatigue subscale score of 40 or more, willingness to participate in a treatment aimed at changing behavior, age between 18 and 60 years, and comprehension of written and verbal Dutch. In contrast to some other studies[30,31] there was no cut-off score for impairments or disabilities. In our study 18% of the patients scored below the severe impairment-level of the Sickness Impact Profile 8 (SIP8), 700, which might have influenced the results of the trial. In clinical practice in rehabilitation medicine indication criteria for treatment are not as stringent as the inclusion criteria described for the trial. Therefore results of the clinical trial may deviate from results in daily practice. During the trial patients with symptoms of chronic pain and fatigue were asked what the most prominent complaint was. If the pain was the most prominent complaint, patients were seen as chronic pain patients and were excluded before entering the trial. Future research should also include these

patients to study the effectiveness of MRT in patients with a combination of chronic pain and CFS since the combination of symptoms is often present.

Many different underlying illnesses can explain the presence of fatigue. Therefore it is of utmost importance to exclude underlying illnesses. In the inclusion process the patient was asked to send the latest results on blood and urine laboratory research. As there were no Dutch guidelines at the beginning of the trial, we used the NICE guidelines for laboratory testing. Following these guidelines, if no blood or urine results (less than one year old) were available, the patient was asked to go to the general practitioner for further investigation. Before intake by the consultant in rehabilitation medicine, the consultant checked the results of the laboratory research. If these results were abnormal the patient was referred to a specialist in internal medicine. If no abnormalities were found, and the CIS fatigue subscale was 40 or more and no exclusion criteria were found in the referral letter the patient was invited for an intake by the consultant in rehabilitation medicine. During the intake all CDC-94 and other inclusion and exclusion criteria were checked. If the Hospital Anxiety and Depression Scale, depression subscore was 11 or higher, or the consultant needed a second opinion to decide whether a patient met the in- or exclusion criteria, an intake with a psychologist was planned. If psychiatric illness was suspected the patient was referred to the psychiatry department of the nearest hospital. Not every patient was referred to the psychologist before inclusion and the visit to the psychologist was not protocollized so it is possible that patients with psychiatric co-morbidities were included. Besides psychiatric co-morbidities, also somatic co-morbidities (like treated sleep apnea and hypothyroidism) were found in the included patients but they were evaluated by a specialist as insufficiently accounting for the complaint of chronic fatigue. Furthermore, in some regions in the Netherlands, the incidence of Q fever increased during the trial. As Q fever can cause similar symptoms as CFS, patients from high-risk regions were additionally tested for Q fever and excluded from the study in case of a positive diagnosis according to the laboratory research (for acute and chronic Q fever). In addition, there were patients diagnosed with Q fever in the past but after testing for Q fever before inclusion, they were diagnosed negative and these patients were included in the study.

In some cases the process of checking the diagnosis and other underlying illnesses and intake at the consultant in rehabilitation medicine took longer than expected. Mean duration between filling in the questionnaires at referral and baseline assessment was 90 days (SD 50.58). We hope with the arrival of the CBO guidelines there will be an improvement of this diagnosing process of patients with CFS.

A CIS fatigue subscale of 40 or more was seen as having extreme fatigue. Previous research also used a CIS fatigue of 35 or more. This might indicate that the included patients experience more fatigue compared to previous research. The level of fatigue at baseline (CIS fatigue around 50) is comparable with other studies[3,7,31] and therefore this seems highly unlikely. On the other hand, patients who were bedridden and unable to

go to the rehabilitation centre were excluded from treatment since treatment could not be given at home. Therefore, results of the study cannot be generalized to all patients with CFS. It should be mentioned however that the group of patients who are bedridden is, as Wiborg stated in his study[32], relatively low.

Interventions for CFS

One of the main limitations of the trial was the difference in volume of treatment. According to the protocol, patients in MRT received 44.5 h of treatment compared to 16 h of treatment in CBT. Both treatments were spread out over a period of 26 weeks. Since both treatments are currently recommended in the Netherlands for patients with CFS, we matched treatments as closely to 'usual practice' as possible to resemble the 'real world' in evaluating the effectiveness of both treatments. Thus while the difference in hours of attention given to the patient might have influenced the results, this represents current clinical practice. Changing treatment frequencies in MRT or CBT would mean comparing treatments, which are not the same as clinical practice which in turn will decrease the clinical application following the trial.

Since the costs per hour for MRT and CBT were the same, MRT, with a higher number of sessions, had the highest costs for the interventions. After the trial, a check was done measuring the direct contact time in both groups. MRT exceeded the protocollized contact-time more (mean = 54.6 h, SD 15.5) compared to CBT (mean = 16.9 h, SD 11.5) resulting in a further increase of costs for the MRT. It is hypothesized that when teams are more experienced in treating patients with CFS, they need less contact hours to work through the protocol and costs for the MRT intervention decreases. In the present trial this could be confirmed because patients included at the beginning of the trial received more treatment compared to patients included at the end of the trial, indicating that teams were more familiar with the protocol and were more dedicated to the protocol as they got more experienced in treating patients with CFS. Therapists from teams other than in Revant only practiced with one patient before starting the trial. In future research al longer period of practicing the protocol is advised to ensure full dedication to the protocol.

The difference in contact hours might partially influence the effectiveness of treatment. In CBT hours of treatment was found to be a significant positive predictor of effect size, explaining 14% of the variance in outcome[2]. This preliminary evidence that a dose-response relationship exists, could not be confirmed in other patient groups strongly related to patients with CFS. In a multi-regression analysis of trials on exercise for patients with low back pain Ferreira et al showed that hours of exercise were not associated with the effect sizes of pain or disability after treatment[33]. More research is needed on this topic in patients with CFS following CBT and MRT. Another factor influencing the effectiveness is that in MRT different interventions were used. In MRT, all interventions were described and instructed to the therapists but the therapists were

able to choose which intervention to use. The sequence and duration of the interventions were chosen by the therapists. With checklists the different interventions were monitored. Therapists were asked to fill in every used intervention. Duration of the interventions was not registered. In MRT it is unknown which intervention was most effective and most valuable for the patient in achieving his/her final goal. To explore this, another qualitative study was performed in which patients were asked, during a semi-structured interview in focus groups, what in their view was the most valuable intervention to achieve the treatment goal and to not feeling 'CFS-patient' anymore. In the near future the data of these focus groups will be analyzed and the results will be published in a peer-reviewed article. The results of the focus groups may increase our insight how MRT works and which interventions are most valuable to the patient and hopefully this information can be used to further increase effectiveness of treatment.

In rehabilitation treatments for patients with chronic pain, Acceptance and Commitment Therapy (ACT) is often included as an intervention[34-36]. Accepting the illness, doing activities despite complaints and living a valuable life are all elements of the ACT, which has led to an increased popularity in rehabilitation treatment in the Netherlands. At the beginning of the trial, ACT was in his infancy and not yet proven effective. During the last five years several studies evaluated ACT and found ACT to be an effective treatment[34-36] for patient with chronic pain. Another possible effective intervention for patients with CFS is graded exposure therapy, which is also proven effective in patients with chronic low back pain[34,37-39]. To further gain effectiveness of treatment for patients with CFS, it might be worthwhile studying ACT and graded exposure as possible interventions in MRT.

To further improve the effectiveness of treatment factors influencing the final outcome were studied. In chapter 6 expectancy and credibility were studied. As described in this chapter, higher expectations in MRT were associated with lower fatigue severity and higher quality of life at 52 weeks after the start of treatment. For clinical practice it is important to focus on the expectations of the patient in the beginning of treatment and to find ways to increase these expectations. As suggested by Greenberg[40] changing illness perceptions regarding the changeability of the syndrome from 'I am not able to change the fatigue' to 'I am able to influence the fatigue' changes expectations. Extensively explaining the rationale of CFS, discussing this with the patient and changing illness enhancing thoughts, might alter expectations regarding treatment. Another method for enhancing expectations is motivational interviewing proposed by Mertens et al[41]. They suggested providing a pre-treatment in which motivational interviewing is used to address motivation, expectation and beliefs before pain rehabilitation treatment starts in order to increase the expectations and the final outcome of treatment. Results of the study of Mertens[41] may reveal whether pre-treatment influences the expectation of a patient and thereby increases efficacy of treatment.

How to measure clinically relevant improvement.

As mentioned before, in MRT, the group mean level of fatigue severity decreased below the level of 35 points on the CIS fatigue subscale. Several researchers used this level to decide whether or not a patient improved[3,4]. White et al[6] defined a clinical useful difference as a combination of 2 points decrease on the Chalder fatigue questionnaire and an 8 points increase on the SF-36 subscale, while for example Tummers et al[42] used the reliable change index in combination with a score lower than 35 on the CIS fatigue subscale to measure clinically relevant improvement. So one can conclude that there is clearly no consensus on how to measure a clinically relevant improvement in patients with CFS. It remains unclear what is most important to the patient to improve on and how this should be evaluated. Research regarding this topic is lacking. As mentioned before, it would be interesting to study the working mechanism of treatment in patient with CFS. It is postulated to evaluate biological factors (like severity of fatigue), psychological factors (for example anxiety and depression), and social factors (for instance participation in society) besides interacting factors like body awareness and mentalization. Following this research it is important to study which factors are most important to the patient to improve during treatment.

Power

Two limitations should be mentioned regarding the calculation of the power in the trial.

At first, the power of the study was originally calculated to detect a clinically relevant difference regarding fatigue (3.0 points on the CIS fatigue subscale) between MRT and CBT. Previous studies have never studied the clinically relevant difference between treatments for the CIS fatigue subscale, so no validated information about this estimated value of 3.0 were available. Future research should study the clinically relevant difference of the CIS fatigue subscale, between and within treatment, in order to improve the design of future studies to analyze the effectiveness of treatments.

Secondly, we used two different primary outcome-measures, the CIS and the SF-36. The CIS was used to calculate the power of the study. Although not statistically significant, quality of life is slightly higher in MRT compared to CBT at 52 weeks. In theory it is possible that the number of patients was too low to find a statistically significant difference in quality of life measured by the SF-36.

Statistical methods

The intention-to-treat approach was used to analyze the data. Some researcher will argue that this method is not correct, since patients who withdrew from treatment or did not show up during a follow-up assessment were also included in the final analysis. However, similar to daily practice, there will always be patients declining from treat-

ment, which makes the intention-to-treat procedure an appropriate method for analyzing the data, also from a clinical point of view. Moreover, limiting the analysis to only those who completed all follow-up assessments might have resulted in serious selection bias.

IMPLICATIONS FOR CLINICAL PRACTICE

For MRT as well as CBT, protocols are available and consultants as well as therapists can be trained in delivering these treatments. Most therapists and consultants participating in the trial were experienced in treating patients with chronic pain, which to our opinion was of great value for the implementation of the protocols. Furthermore in MRT, in which different interventions can be used, it is important that therapists are in line with each other regarding the rationale of treatment and with the interventions used. It is important to supervise unexperienced therapists during the learning process of coaching patients with CFS. It is advisable to therapists who are new in coaching patients with CFS to intensively study the treatment protocol, practice the interventions, follow team meetings and have supervision moments with experienced therapists before starting with MRT in clinical practice.

Furthermore it needs to be addressed that only 34% of the patients referred to the rehabilitation centres (see chapter 3) were included in the trial. Due to a stringent multistage process of inclusion (see chapter 2) only those patients were included who fulfilled the inclusion criteria for CFS. In daily practice such stringent inclusion criteria are not used because they are time-consuming. Since we do not know the effects of treatment for patients not fulfilling these criteria it is important to start with the use of inclusion criteria mentioned in chapter 2 when treatments are being implemented in other rehabilitation centres. Whether excluded patients with CFS or patients with other complaints, like chronic pain, improve with MRT or CBT needs to be studied in the future.

CONCLUSIONS AND FUTURE DIRECTIONS

The results of this FatiGo trial provide new insight in treatment of patients with CFS and also identified a new focus for future research.

Main conclusions and future directions for research are summarized point by point.

- On the long-term MRT is more effective in reducing fatigue severity in patients with CFS compared to CBT while MRT and CBT are equally effective in increasing quality of life. Patients in the MRT group had a significantly higher level of self-efficacy and higher achievement of personal goals after treatment compared to CBT. Finally, patients were more satisfied with the results after MRT. Following these results, MRT

should be included in the guidelines for treatments for patients with CFS next to CBT. It is advised to implement MRT in more rehabilitation centres in order to make MRT accessible to more patients with CFS.
- Using the fatigue severity as primary outcome for the cost-effectiveness, MRT is more likely to be cost-effective compared to CBT.
- Taken the QALY calculated with the EQ-5D-3L as main outcome parameter, CBT is more cost-effective than MRT.
- Higher expectations positively influence the effect of MRT on the outcome severity of fatigue and the physical component of the quality of life. In CBT such associations were not found.
- A clear difference in actual and perceived physical functioning between relatively active and passive patients with CFS as judged by their therapists could not be found.

In the near future:
- To further gain effectiveness of MRT, interventions to increase the expectations of treatment should be developed and evaluated.
- To further gain effectiveness of treatment it is worthwhile studying whether ACT and graded exposure should be included in MRT.
- To further gain cost-effectiveness lowering the costs for MRT should be proposed and evaluated. Possibility of providing parts of MRT in groups or not including every discipline in the treatment should be evaluated next to including a standardized module of reintegrating into work.

In the mid-term future:
- To measure effectiveness of treatment it is important to clearly define improvement in patients with CFS.
- To improve the interpretation of cost-effectiveness analysis of treatment in patients with CFS it is important to investigate how much money society is willing to pay for an improved patient.
- To further gain insight in the working mechanism of MRT, potentially interacting factors like body awareness should be evaluated using valid, reliable and responsive assessment tools.

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8

Valorisation

INTRODUCTION

'How can I overcome my fatigue?', 'What is the best treatment for my illness?', and 'Where can I get this treatment?' are frequently asked questions from patients with CFS. As mentioned in the introduction of this thesis different treatments exist but patients and referrers are mainly interested in the best treatment. Although effectiveness studies have been done before, a comparison of different treatments is less common. This effectiveness study is aimed at studying which of two compared treatments is the most effective in reducing fatigue and increasing quality of life. This thesis presents not only the scientific value of the effectiveness of two different treatments for patients with CFS. In this chapter, also the societal value, i.e. the valorisation will be presented. Valorisation is transferring scientific knowledge to for example healthcare organizations, by making knowledge available and suitable for economic and social exploitation. It is the translation of knowledge into products, services, processes or new business. This chapter presents how the scientific knowledge can be transferred and utilized in society. At first, the relevance for patients and their families, therapists, medical specialists and health insurance companies, will be presented, followed by the examples of innovative activities and products.

RELEVANCE OF THE FINDINGS

Effectiveness and cost-effectiveness

Effectiveness studies provide scientific evidence on how effective treatments are. The results of this study reveal that in the long run MRT is more effective in reducing fatigue compared to CBT. This may facilitate the choice of treatment for the patient and the referrer. Unfortunately, the choice of treatment is not only depending on the effectiveness of treatment. Treatment should be available in the direct environment of a patient's home. Sometimes patients have to travel long distances to receive treatment. Long traveling hours might change the effectiveness of treatment since travelling is often an energy consuming activity. Implementation of MRT in more rehabilitation centres is therefore advised. Furthermore, health insurance companies are more willing to reimburse treatments that are proven both effective and less expensive, which facilitates the implementation of treatment in more rehabilitation centres or other healthcare organizations, making treatment available for more patients.

Differences between active and passive patients

To improve treatment it is worthwhile studying differences in patient (sub)groups in order to decide whether or not to tailor treatments on the basis of these differences to

improve effectiveness. A clear difference in actual and perceived physical functioning between relatively active and passive patients with CVS as judged by their therapists could not be found. However, this trial was the first to study differences in activity patterns between subgroups of patients classified by their therapists.

Expectancy and credibility

To further improve treatment effectiveness it is valuable to study factors influencing this effectiveness. Reading this study can increase the awareness of therapists and specialists on how expectations can influence treatment outcome. It might stimulate other researchers to study the impact of expectations before treatment. Increasing our insight in these influences can be important for decision making of treatment choice and for the communication between therapists and patients.

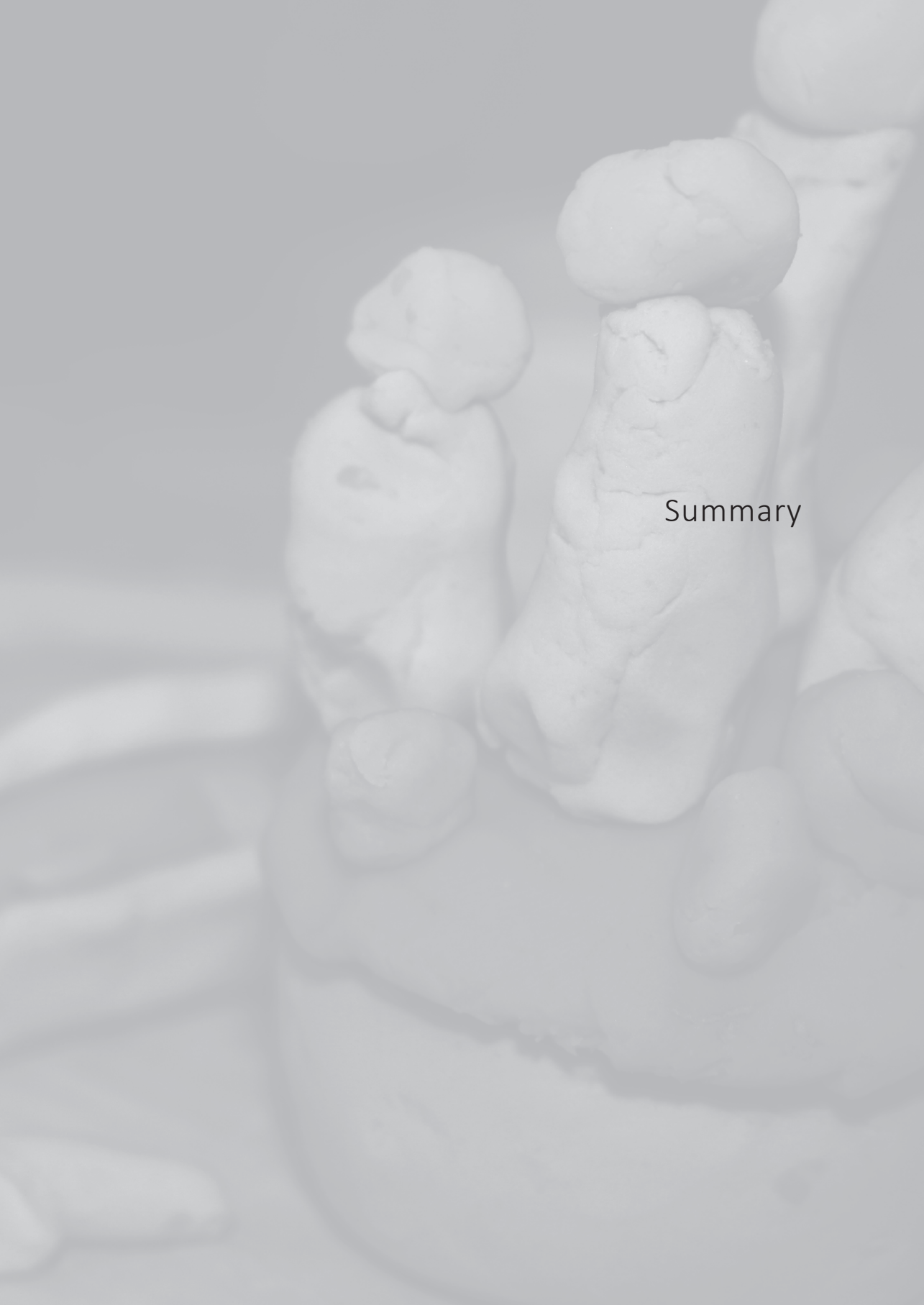
INNOVATIVE ACTIVITIES AND PRODUCTS

Before the start of the study Revant, Rehabilitation Centre Breda was the only rehabilitation centre offering treatments for patients with CFS in the southern districts of the Netherlands. During the preparation of the trial, rehabilitation teams of four different rehabilitation centres received training to deliver the interventions of the MRT protocol and psychologists received training to deliver CBT. Unfortunately, after the trial was ended, some rehabilitation centres have chosen not to include the MRT for patients with CFS in their standard care supply. At this moment many patients with chronic pain are referred to a limited number of rehabilitation centres resulting in long waiting lists. Since MRT for patients with CFS is often given by the same therapists who also deliver chronic pain treatment, the number of patients on the waiting lists will increase even further if patients with CFS are included in the standard care supply of the rehabilitation centre. Some rehabilitation centres have chosen to deliver the treatments but will not promote the treatment as this might increase these waiting lists so that they would not be able to start treatment within predefined normative waiting time (the so called 'Treeknormen'). These norms are time-guidelines defined by health insurance companies and healthcare suppliers. They contain a time period in which patients should receive healthcare if needed. Furthermore, the health insurance companies use fixed budgets for each rehabilitation centre. Introducing a new patient-group will interfere with the present groups, since the introduction of a new patient-group asks for redistribution of the budget. This makes it hard to introduce new patient-groups in rehabilitation settings. It is therefore recommended that health insurance companies increase the budget for rehabilitation centres that are willing to introduce a new evidence based rehabilitation program for patients with CFS. When increasing the number of centres to adopt the program, it is important to train the therapists to deliver the evaluated proto-

col as described in this thesis. Courses and supervision meetings should be organized to train the teams in delivering MRT. By training more therapists, patients with CFS can be spread over different locations and lower the burden on the waiting lists. Different CBT centres are already training CBT therapists to deliver CBT for patients with CFS in order to decrease the number of patients on their waiting lists. Less common is the training for MRT therapists. Before the trial, protocols of MRT and courses for MRT therapist were already well described and can now be used to train other rehabilitation teams. Training can increase the knowledge regarding CFS and treatment of CFS. Although plans for such a course are not yet realized, this can be a future product of this study. If more healthcare organizations are familiar with MRT, more patients can benefit from this effective approach. For the patients, traveling time to the nearest healthcare organization will decrease, which might increase the likelihood of an effective treatment since traveling is often seen as an energy consuming activity.

Furthermore, inclusion criteria for treating patients with CFS are well described in the trial. Using these criteria to refer patients will facilitate the process of referral to a rehabilitation centre. Diagnostic criteria and inclusion criteria should be introduced in different hospitals and in general practice centres to get more familiar with these criteria and facilitate the referral of the patients. This will also reduce the burden of the patients who are now sometimes referred to many different specialists in healthcare before arriving at the address where they can be effectively treated. Also the burden for the general practitioners will be reduced as nowadays they often see the patient repeatedly.

The above-mentioned products, services and processes are examples of how the scientific knowledge from this trial can be transferred and utilized in society. Focusing on two general aims: 1) Making treatment for patients with CFS as effective as possible and 2) making effective, evidence based treatment available to as many patients as possible. The patient should always be the starting point when decisions are to be made how to transfer knowledge into society.



Summary

In chapter 1, a general introduction is provided with an overall view on chronic fatigue syndrome (CFS), the different models explaining the perpetuation of CFS and different treatments. In the Netherlands, approximately 30.000-40.000 people suffer from CFS. Patients with CFS experience severe fatigue for more than 6 months. CFS leads to substantial limitations in occupational, educational, social and personal activities. Annual societal costs per patient with CFS are high, and underline the need to investigate new treatments and their benefits for the patient and society.

The etiology of CFS is unclear. Many immunological, viral, psychological and neuroendocrinological mechanisms have been hypothesized. There is a lack of conclusive evidence for all of these hypotheses. In order to understand and improve treatments, several researchers proposed a working mechanism model regarding the development and perpetuation of fatigue in patients with CFS. In 1998, Vercoulen presented a statistically tested model of CFS with different perpetuating factors. The model presents which factors perpetuate the fatigue and the impairments of patients with CFS. This model is often used as a theoretical framework of cognitive behavioural therapy (CBT). Another model, which was designed to describe health and illness, is the biopsychosocial model. The principle of the biopsychosocial model states that all issues relating to health are products of a complex interplay of biological, psychological and social factors. This model is often used in multidisciplinary rehabilitation treatments.

During the preparation of our trial, different pharmacological and non-pharmacological treatments have been studied in relation to CFS. Of all studied treatments, CBT and graded exercise therapy (GET) were found to be the most effective treatments at the time. Although proven effective, CBT and GET do not improve fatigue severity and quality of life for all patients. Further research was needed to improve the management of CFS. Revant developed a multidisciplinary rehabilitation treatment (MRT) which is based on the biopsychosocial model in which various precipitating, predisposing and perpetuating factors are hypothesized to interact, resulting in multiple pathways leading to the development and persistence of CFS. In MRT those components are addressed that are thought to be modifiable and have a strong relation with the precipitation, predisposition and perpetuation of the CFS. These components and the personal goals of a patient are the focus of the treatment. After identifying the modifiable components and the personal goals, treatment aims are determined and the interdisciplinary team provides an indication of how the interventions can be used to achieve the personal goals. MRT includes interventions of CBT, gradual reactivation, pacing, elements of mindfulness, body awareness therapy, normalising sleep/wake rhythm and social reintegration. At the time of development of MRT only few studies had reported results of a multidisciplinary approach in peer-reviewed scientific journals. Although treatments described seem to have some overlap, there still was a great variety among the studies regarding the content of rehabilitation treatments for patients with CFS which made it difficult to give an overall conclusion on the effectiveness of such rehabilitation treatments. Therefore, a multi-centre randomized controlled trial

(RCT) was developed to study the effectiveness of MRT compared to CBT. The main aim of the trial was to study which treatment, CBT or MRT, was the most effective and cost-effective in reducing fatigue and increasing quality of life in patients with CFS.

In chapter 2 the design of the trial is presented. A two-arm, pragmatic, RCT, which was performed in four rehabilitation centres in the Netherlands. After a multistage process of inclusion, patients were included if they met the inclusion criteria and were willing to participate in the trial. After inclusion, a baseline assessment was performed and patients were randomized to MRT or CBT. After 26 weeks of individual, outpatient treatment patients had the second assessment. For the follow-up assessment patients were asked to come back to the rehabilitation centre at 52 weeks after start of treatment. The primary outcomes, fatigue and quality of life were measured using questionnaires. Data was analysed using an intention-to-treat approach. Differences in treatment effects were analysed with mixed linear regression models.

Chapter 3 describes the results of the RCT. In the trial 122 patients were included, 62 patients were randomized to MRT and 60 to CBT. Eighteen patients (12 CBT, 6 MRT) withdrew from treatment. We tested the hypothesis that MRT is more effective in reducing fatigue severity and increasing quality of life compared to CBT at 26 and 52 weeks after start of treatment. It was concluded that MRT is more effective in reducing fatigue severity compared to CBT at 52 weeks after start of treatment. In both treatments fatigue severity decreases, with a more rapid decline in MRT compared to CBT from baseline to 14 weeks. At 26 weeks there is no significant difference between the groups. After 26 weeks fatigue increases again in the patient group receiving CBT, while the effect in the MRT group remains at a lower level resulting in a statistically significantly lower level of fatigue at 52 weeks of the MRT group compared to CBT. Although quality of life increases in both treatments, a statistically significant difference between the two treatments was not found at 26 or 52 weeks. Nevertheless the effect of MRT regarding fatigue seems more sustainable, resulting in a significant difference in fatigue severity at long-term. Additionally, self-efficacy and achievement on personal goals increased significantly more during the follow-up period in the MRT group than in CBT. Furthermore, statistically significant more patients in MRT were satisfied with the results of treatment compared to CBT. No significant differences between groups were found regarding the changes in attention and awareness, functional impairment, physical and non-physical attributions, psychological symptoms, physical activity and satisfaction with life. The RCT in chapter 3 provides evidence that MRT is more effective in reducing long-term fatigue severity than CBT in patients with CFS. Although implementation in comparable populations can be recommended based on clinical effectiveness, these findings should be replicated in another multi-centre trial.

Chapter 4 presents the economic evaluation of the RCT from a societal perspective. The societal costs (healthcare costs, patient and family costs, and costs for loss of productivity), fatigue severity, quality of life, quality-adjusted life-year (QALY), and cost-effectiveness ratios were measured over a one-year follow-up. Results show that MRT has a high probability of being the most cost effective, taking fatigue as primary outcome. The results of the cost-utility analysis, using the QALY, indicate that the CBT had a higher likelihood of being the most cost-effective. Different explanations are offered for finding the different results in cost-effectiveness and cost-utility analysis, one indicating that the generic quality of life measurement is not sensitive enough to measure differences between CBT and MRT. Since the societal costs in MRT are mainly dominated by the costs for the intervention it is needed to study how the intervention can be more cost-effective, for example by enabling the therapists to decrease the number of sessions when achieving a patient's personal goal earlier or when specific interventions are not needed to achieve a patient's goal.

In chapter 5 the differences in physical functioning between relatively active and passive patients with CFS were studied in the CBT group at baseline. In the CBT protocol therapists are advised to categorize patients into relatively active and passive patients. Treatment is tailored for these two subgroups of patients. To find evidence to support the differences between the groups, differences in actual (using an activity monitor) and perceived (measured by questionnaires) physical functioning were analyzed. No significant differences were found in the actual physical activity, duration of rest during the day or fluctuations in activities during the day measured by an accelerometer between relatively active and passive patients. Relatively active patients did have a significantly higher daily uptime and showed significantly less fluctuations in activities between days. Passive patients perceived a significantly lower level of physical functioning and felt more functionally impaired in their mobility compared to relatively active patients. Discrepancies seem to exist between the patient's perception and the actual measure of physical functioning. It is concluded that individualizing treatment based on the discrepancy within patients might be worthwhile but needs to be studied in the future.

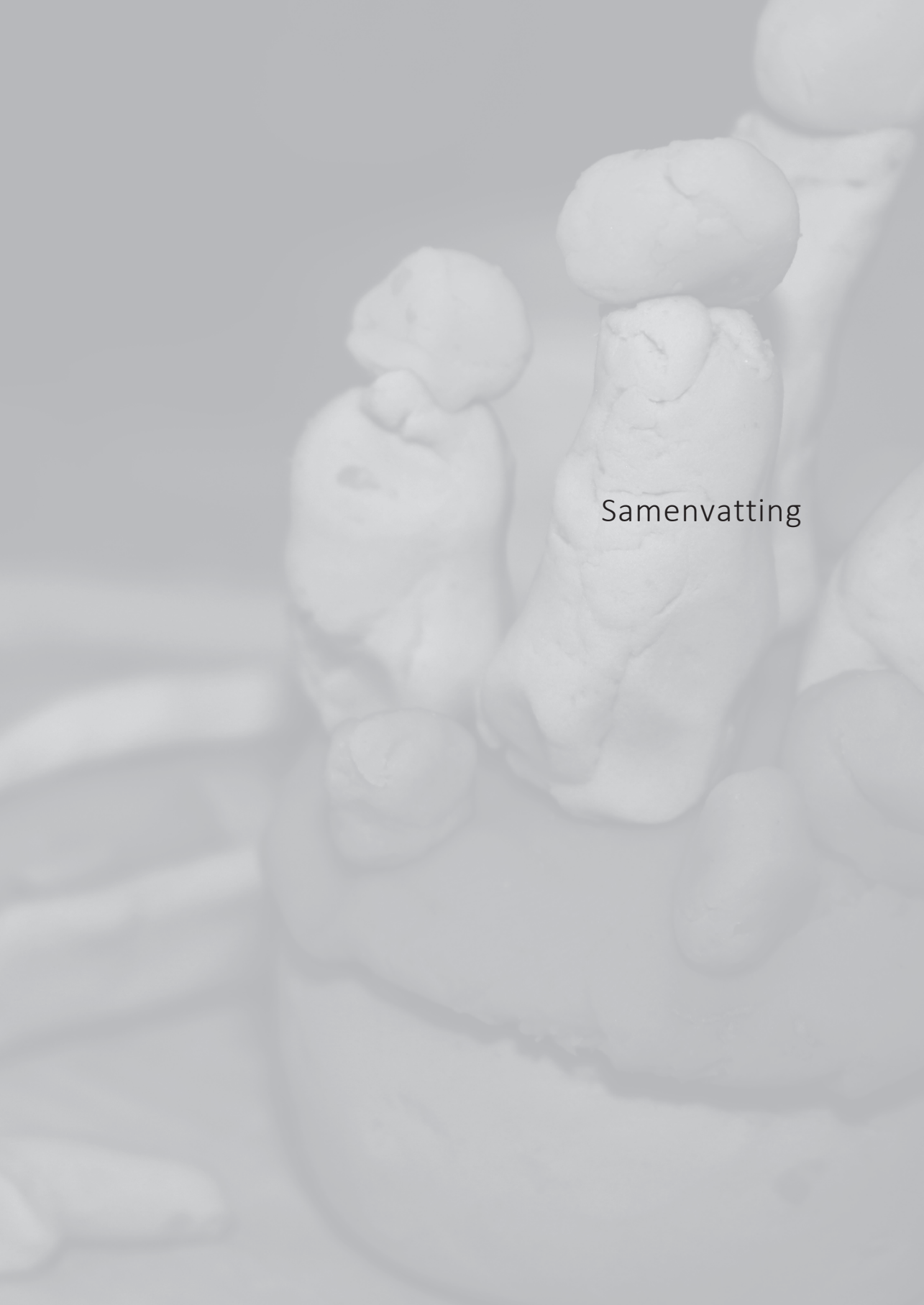
To improve the effectiveness of treatment in patients with chronic fatigue syndrome it is worthwhile studying factors influencing the outcomes. Therefore the aim of the study, described in chapter 6, was to assess the association of patients' treatment expectancy and credibility on the outcomes of treatment and whether this association is different for MRT and CBT. The effect of expectancy on the fatigue and the physical component of the quality of life (QoL) after treatment was significant for MRT. However, in CBT such associations were not found. The effect of expectancy on the mental component of QoL was not significant for either MRT or CBT. For credibility, the overall effect on fatigue and QoL was not significant. The results for the mental component of

QoL showed that the interaction with treatment was significant for credibility. However, the effects within each group were not significant. For clinical practice it seems to be important to check the expectations since expectations influence the outcome after MRT. More research is needed to study interventions to increase the expectations in order to increase effectiveness of MRT. The second aim was to study the effect of age, centre of treatment, type of treatment allocation, self-efficacy, depression and duration of complaints at baseline on treatment expectancy and credibility. Results showed that only centre of treatment appeared to be significantly associated with expectancy. For credibility, centre of treatment, treatment allocation and depression were significantly associated. Since centre of treatment was significantly associated with both expectancy and credibility, it seems that therapists and the way they explain the rationale of treatment influences the expectations of patients. However, which therapeutic skills are most valuable in increasing expectations and credibility in patients with CFS needs to be evaluated in future research.

Chapter 7 contains the general discussion in which the main findings of the thesis are presented. This trial provides evidence that at long-term, MRT is more effective in reducing fatigue severity in patients with CFS compared to CBT while MRT and CBT are equally effective in increasing quality of life. The probability of being the most cost-effective treatment is higher for MRT when taking the disease-specific outcome as primary outcome. This could not be confirmed by the cost-utility analyses using the QALY. Since the societal costs are mainly dominated by the costs for the intervention, in the near future it is necessary to study how the interventions can become more cost-effective. In the near future, MRT should be included in the guidelines for treatments for patients with CFS next to CBT. Furthermore, it is advised to implement MRT in more rehabilitation centres in order to make MRT accessible to more patients with CFS.

To further improve the effectiveness of treatment expectations should be measured and discussed with the patient since higher expectations are associated with a more positive outcome of treatment. Other future directions, limitations and possible clinical implications are discussed in chapter 7.

In chapter 8, valorisation is described. Benefits for the patient, referrers, therapists and consultants in rehabilitation medicine in- and outside the rehabilitation centres are described.



Samenvatting

In hoofdstuk 1 van dit proefschrift wordt een algemene introductie gegeven over het chronisch vermoeidheidssyndroom (CVS). In Nederland lijden ongeveer 30.000-40.000 mensen aan CVS. Er wordt gesproken van CVS als men ernstige vermoeidheid ervaart die langer dan 6 maanden duurt. CVS leidt vaak tot ernstige beperkingen in het uitvoeren van werk en/of opleiding, sociale en persoonlijke activiteiten. Hierdoor zijn de maatschappelijke kosten per patiënt met CVS hoog en dit onderstreept de behoefte aan onderzoeken naar nieuwe behandelvormen en de meerwaarde van deze behandelvormen voor de patiënt en de maatschappij.

De etiologie van CVS is nog steeds niet helemaal duidelijk. Er bestaan verschillende hypothesen, waarin immunologische, virale, psychologische en neuro-endocrinologische mechanismen worden beschreven. Om behandelmethodieken te begrijpen en te verbeteren, hebben verschillende onderzoekers werkingsmechanismen voorgesteld met betrekking tot de ontwikkeling en het voortduren van vermoeidheid bij patiënten met CVS. In 1998 presenteerde Vercoulen et al een model voor CVS met statistische onderbouwing. Dit model presenteert welke factoren de vermoeidheid en de ervaren beperkingen van patiënten met CVS in stand houden. Het model wordt vaak gebruikt als theoretisch kader voor cognitieve gedragstherapie (CGT). Een ander model, dat is ontwikkeld voor het beschrijven van het menselijk functioneren en het beschrijven van gezondheid en ziekte, is het biopsychosociale model. Het biopsychosociale model gaat ervan uit dat alle factoren die gerelateerd zijn aan gezondheid, een resultaat zijn van een complexe interactie tussen biologische, psychologische en sociale factoren. Dit model wordt vaak gebruikt als kader voor multidisciplinaire revalidatiebehandeling (MRT).

Voor de start van de onderzoeken gepresenteerd in dit proefschrift waren verschillende studies uitgevoerd naar het effect van farmacologische en niet-farmacologische behandelingen bij patiënten met CVS. Op dat moment bleek dat van alle onderzochte behandelingen, CGT en graded exercise therapy (GET) de meest effectieve behandelvormen waren. Hoewel CGT en GET bewezen effectief zijn, ervaren niet alle patiënten een vermindering in vermoeidheid en een verbetering van kwaliteit van leven. Dit pleitte voor aanpassing van het zorgaanbod in de keten en nader onderzoek naar het effect van behandelingen. Revant, het medisch specialistische revalidatiecentrum in Breda, ontwikkelde een multidisciplinaire revalidatie behandeling (MRT) welke is gebaseerd op de hypothese dat meerdere precipiterende, predisponerende en perpetuerende factoren met elkaar interacteren. Deze factoren kunnen per patiënt variëren waardoor verschillende hypothesen kunnen worden geformuleerd voor het ontstaan en het voortduren van CVS. In de MRT worden de componenten behandeld waarvan wordt gedacht dat deze veranderbaar zijn en welke een sterke relatie hebben met het precipiteren, predisponeren en perpetueren van CVS. Deze componenten en de hulpvraag van de patiënt vormen de focus van de behandeling. Na het identificeren van deze veranderbare componenten en de hulpvraag van de patiënt worden de behandeldoelstellingen bepaald. Het interdisciplinair team maakt een keuze voor welke interventies worden

ingezet om de doelstellingen van de patiënt te behalen. CGT, gedoseerde re-activatie, energiemanagement, elementen vanuit mindfulness, lichaamsgerichte therapie, het normaliseren van slaap-waak ritme en sociale re-integratie zijn interventies die binnen MRT ingezet kunnen worden. Tijdens de ontwikkeling van de revalidatiebehandeling werden slechts enkele wetenschappelijke studies gepubliceerd, die het effect van de multidisciplinaire aanpak onderzochten. Hoewel deze behandelingen enige overlap leken te hebben met MRT, bleken ze op inhoud toch vaak verschillend, waardoor het moeilijk was om een algemene conclusie te geven over het effect van deze revalidatiebehandelingen. Daarom is een gerandomiseerd controle onderzoek (RCT) ontwikkeld en uitgevoerd in vier revalidatiecentra. De hoofddoelstelling van de studie was te bepalen welke behandeling, CGT of MRT, het meest effectief en kosteneffectief is in het reduceren van vermoeidheid en in het verbeteren van de kwaliteit van leven bij patiënten met CVS.

Na de introductie in hoofdstuk 1, wordt in hoofdstuk 2 de opzet van het onderzoek beschreven. Voor de totstandkoming van dit proefschrift is een tweearmig, pragmatisch gerandomiseerd controle onderzoek, de zogenaamde RCT, uitgevoerd in vier revalidatiecentra in Nederland. Na een inclusie proces dat bestond uit meerdere fasen, werden patiënten geïncludeerd wanneer ze voldeden aan de inclusiecriteria en wanneer ze bereid waren om mee te werken aan het onderzoek. Na deze inclusie werd een baseline meting uitgevoerd waarna patiënten werden gerandomiseerd naar MRT of CGT. Na 26 weken individuele poliklinische behandeling werden patiënten voor de tweede keer gemeten. Patiënten werden 52 weken na start van de behandeling wederom gevraagd terug te komen naar de revalidatiecentra voor de lange-termijn vervolgmeting. De primaire uitkomstmaten waren vermoeidheid en kwaliteit van leven, beiden gemeten met vragenlijsten. De data werd geanalyseerd middels de 'intention-to-treat' methode. De verschillen in effect tussen de behandelingen werd bepaald met behulp van lineaire regressiemodel analyses.

Hoofdstuk 3 beschrijft de resultaten van de RCT. In het onderzoek werden 122 patiënten geïncludeerd, 62 werden gerandomiseerd naar MRT en 60 naar CGT. Achttien patienten (12 CGT en 6 MRT) zijn tussentijds met de behandeling gestopt. De hypothese, dat MRT meer effectief is dan CGT in het reduceren van de mate van vermoeidheid en het verbeteren van de kwaliteit van leven 26 en 52 weken na start van de behandeling, is getoetst. In beide behandelingen verminderde de vermoeidheid. Van baseline tot 14 weken na start van de behandeling, daalde de vermoeidheid bij patiënten in de MRT groep sneller in vergelijking tot CGT. Op 26 weken was er geen significant verschil meer tussen beide groepen. Vanaf 26 weken (direct na einde behandeling) nam de vermoeidheid weer toe in de groep die CGT heeft gehad, terwijl het effect in de MRT groep op het lagere niveau gehandhaafd bleef. Dit resulteerde uiteindelijk in een statistisch significant lager niveau van vermoeidheid voor de MRT-groep op 52 weken in vergelij-

king met CGT. Hoewel de kwaliteit van leven in beide groepen steeg, werd op deze uitkomstmaat geen statistisch significant verschil gevonden tussen beide groepen op 26 en 52 weken na start van de behandeling. Op langere termijn nam ook de mate waarin iemand zelf denkt invloed te kunnen uitoefenen op de klachten (self-efficacy) en het bereiken van persoonlijke doelen significant meer toe in de MRT-groep in vergelijking met de CGT-groep. Daarnaast waren significant meer patiënten uit de MRT-groep tevreden met het resultaat van de behandeling in vergelijking met CGT. Echter, geen significante verschillen tussen de groepen werden gevonden in de mate van aandacht voor dagelijkse bezigheden (attention and awareness), functionele beperkingen, fysieke en niet-fysieke attributies, psychologische symptomen, fysieke activiteit en tevredenheid over het eigen leven. Op basis van de resultaten beschreven in dit hoofdstuk kan worden geconcludeerd dat MRT effectiever is in het reduceren van vermoeidheid op lange termijn in vergelijking met CGT bij patiënten met CVS. Op basis van deze klinische effectiviteit is het aan te bevelen om MRT te implementeren in vergelijkbare groepen.

Hoofdstuk 4 presenteert de economische evaluatie van de RCT vanuit een maatschappelijk perspectief. Gedurende één jaar werden de maatschappelijke kosten (kosten voor de gezondheidszorg, patiënt- en familiekosten, kosten voor verlies van arbeidsproductiviteit), mate van vermoeidheid, kwaliteit van leven, voor kwaliteit gecorrigeerde levensjaren (quality-adjusted life-year) (QALY), en kosten-effectiviteit ratio's gemeten. Resultaten lieten zien dat MRT een hogere kans heeft om het meest kosteneffectief te zijn wanneer de vermoeidheid als primaire uitkomstmaat wordt gebruikt. De resultaten van de kosten-utiliteiten analyse, waarin de QALY werd gebruikt, geven aan dat CGT een hogere kans heeft om het meest kosteneffectief te zijn. Het verschil in resultaat tussen de kosteneffectiviteit en kosten-utiliteiten analyses kan op verschillende manier worden verklaard. Een mogelijke verklaring is dat de gebruikte generieke maat voor kwaliteit van leven niet gevoelig genoeg is om verschillen te meten tussen CGT en MRT.

Aangezien de maatschappelijke kosten in de MRT groep voor een groot deel bepaald worden door de kosten van de interventie, is het wenselijk te onderzoeken hoe de interventie meer kosteneffectief zou kunnen worden. Therapeuten kunnen mogelijk het behandeltraject eerder beëindigen, of het aantal sessies verminderen wanneer het doel van de patiënt eerder wordt behaald dan gepland of wanneer specifieke interventies niet nodig zijn om een vooraf gesteld doel van de patiënt te realiseren.

In hoofdstuk 5 wordt het verschil in fysiek functioneren tussen relatief actieve en passieve patiënten met CVS bestudeerd binnen de CGT-groep voor de start van de behandeling. In het CGT protocol worden therapeuten geadviseerd om de patiënten te categoriseren in relatief actieve en passieve patiënten. In de behandeling wordt per subgroep een ander protocol gevolgd. Om unieke kenmerken van beide subgroepen te identificeren, zijn verschillen in objectief (met activiteitenmonitor) gemeten en zelfgerapporteerde (gemeten met vragenlijsten) fysiek functioneren geanalyseerd. In te-

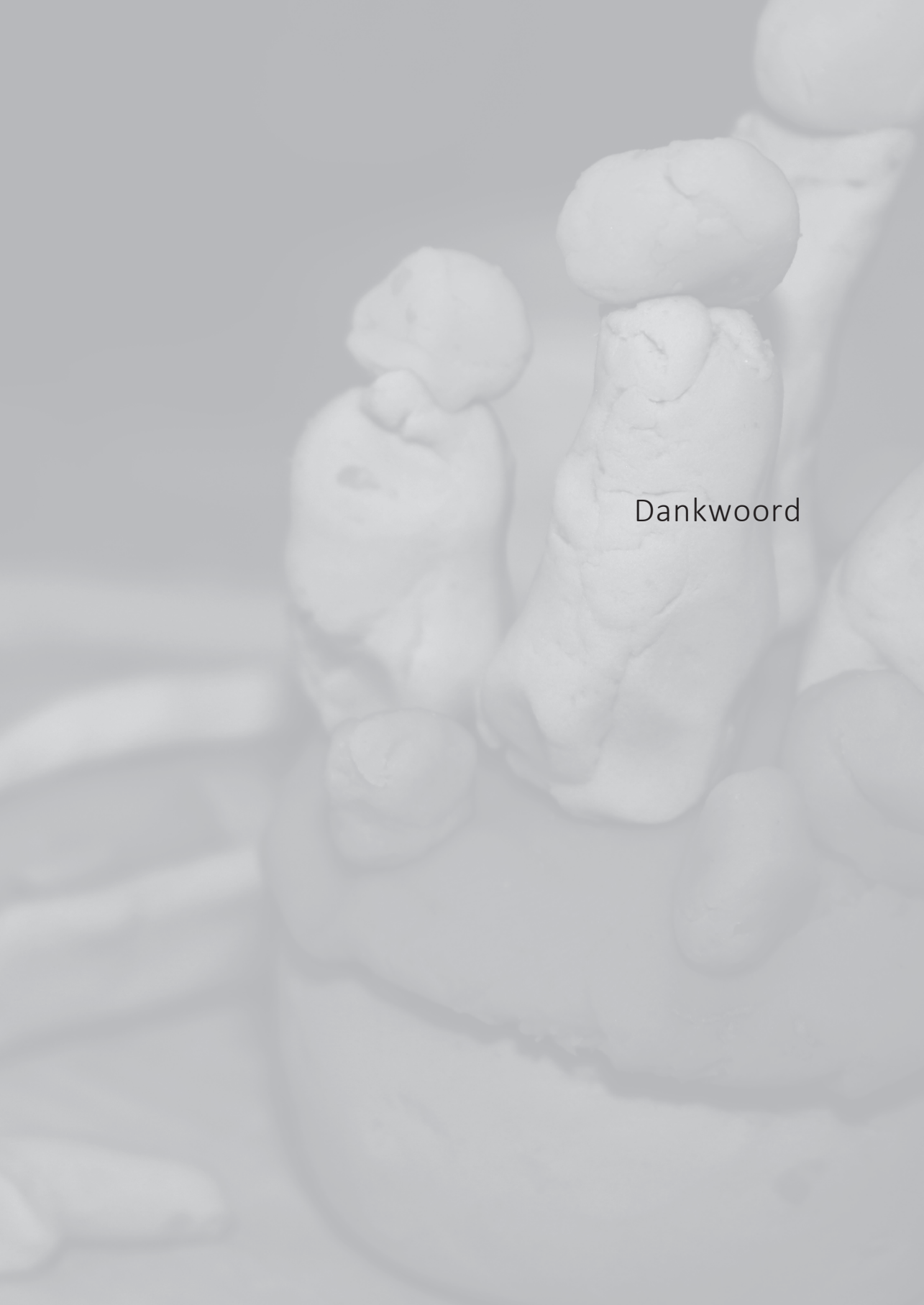
genstelling tot onze verwachting werden geen statistisch significante verschillen gevonden tussen relatief actieve en passieve patiënten in de daadwerkelijk objectief gemeten fysieke activiteit, duur van rust overdag en fluctuaties van activiteiten gedurende een dag. Relatief actieve patiënten hadden wel een significant langere dagduur (tijd tussen opstaan en gaan slapen). Ook lieten ze, echter anders dan we verwacht hadden, minder fluctuaties in activiteiten tussen de dagen zien. Passieve patiënten ervoeren een significant lager niveau van fysiek functioneren en voelden zich meer beperkt in hun mobiliteit in vergelijking tot de relatief actieve patiënten (gemeten met vragenlijsten). Discrepanties lijken te bestaan tussen de perceptie van een patiënt en het daadwerkelijk objectief gemeten fysiek functioneren. Dit zou een extra aandachtspunt kunnen zijn binnen het behandeltraject. In hoeverre aanpassing van het programma op basis van deze discrepantie het effect van de behandeling vergroot, moet in toekomstige studies verder worden onderzocht.

In hoofdstuk 6 wordt gekeken welke factoren van belang zijn voor het verder verhogen van de effectiviteit van de behandeling. In deze deelstudie werd de associatie van de behandelverwachtingen van de patiënt en de geloofwaardigheid van de behandeling op de uitkomst van behandeling geëvalueerd. Daarnaast werd bepaald of deze associatie verschillend is voor MRT en CGT. Binnen de MRT-groep was het hebben van een hogere verwachting geassocieerd met een grotere afname van vermoeidheid en een sterkere verbetering van de fysieke component van de kwaliteit van leven. Binnen de CGT-groep werden dergelijke associaties niet gevonden. Het effect van de verwachtingen op de mentale component van de kwaliteit van leven was niet statistisch significant verschillend voor MRT of CGT. Voor geloofwaardigheid van de behandeling, was het overall effect op vermoeidheid en kwaliteit van leven niet significant van invloed. De resultaten van de mentale component van de kwaliteit van leven lieten zien dat de interactie met behandelconditie significant was voor geloofwaardigheid. Echter, wanneer de groepen apart werden bekeken was het effect binnen elke groep niet significant. Voor de klinische praktijk lijkt het belangrijk om de behandelverwachtingen vooraf te beoordelen. Meer onderzoek is nodig om interventies te onderzoeken die verwachtingen verhogen en om na te gaan of deze verwachtingen uiteindelijk ook leiden tot een hoger effect van MRT. Het tweede doel van deze deelstudie was te bepalen of leeftijd, centrum, behandelinterventie, self-efficacy, depressie en duur van de klachten op baseline een effect hadden op de behandelverwachting en op de geloofwaardigheid. Resultaten lieten zien dat alleen “centrum” significant geassocieerd was met de behandelverwachting. Centrum, behandelinterventie en depressie waren significant geassocieerd met geloofwaardigheid. Omdat het revalidatiecentrum waar de behandeling werd gegeven significant geassocieerd bleek met behandelverwachting en geloofwaardigheid, lijkt het erop dat de therapeuten en de manier waarop ze de rationale van de behandeling uitleggen naar de patiënt, invloed kunnen hebben op de uiteindelijke verwachtingen van de patient. Echter, het is onduidelijk welke therapeutische vaardigheden het meest waardevol

zijn in het laten toenemen van deze verwachtingen en geloofwaardigheid van de aangeboden behandeling bij patiënten met CVS. Meer onderzoek over dit onderwerp is van belang om dit te achterhalen.

Hoofdstuk 7 bevat de algemene discussie waarin de belangrijkste resultaten van dit proefschrift worden gepresenteerd. Deze studie levert bewijs dat MRT effectiever is op de lange-termijn effecten in het reduceren van vermoeidheid bij patiënten met CVS in vergelijking met standaard CGT. MRT en CGT zijn beide even effectief in het verhogen van de kwaliteit van leven. De kans dat MRT meer kosteneffectief is dan CBT is hoger wanneer de ziekte-specifieke maat als primaire uitkomstmaat wordt gebruikt. De resultaten van de kosten-utiliteiten analyse, waarin de QAYL werd gebruikt, geven echter aan dat CGT een hogere kans heeft om het meest kosteneffectief te zijn. De maatschappelijke kosten werden namelijk hoofdzakelijk bepaald door de kosten van de interventie. Het is belangrijk na te gaan hoe de interventies goedkoper kunnen worden gemaakt. In de nabije toekomst is het aan te bevelen MRT op te nemen in de richtlijnen voor behandeling van patiënten met CVS naast CGT. Om MRT meer beschikbaar te maken voor de patiënten dient MRT geïmplementeerd te worden in meerdere revalidatiecentra. Om de effectiviteit van de behandeling te vergroten is het raadzaam om behandelverwachtingen te meten en te bediscussiëren met de patiënt, aangezien hogere behandelverwachtingen geassocieerd zijn met een positiever behandelresultaat. In hoofdstuk 7 worden verder de methodologische beperkingen en adviezen voor vervolg onderzoeken besproken, naast de mogelijke klinische implicaties die kunnen volgen uit de gepresenteerde studie.

In hoofdstuk 8 worden de mogelijkheden van maatschappelijke valorisatie van de resultaten van de beschreven studie weergeven. Voordelen voor de patiënten, verwijzers, therapeuten en revalidatieartsen binnen en buiten de revalidatiecentra worden beschreven.



Dankwoord

Na jaren kan ik nu het laatste hoofdstuk van mijn proefschrift afronden. Het was en is nog steeds een mooi traject waarin ik veel interessante mensen heb mogen ontmoeten, en met velen heb mogen samenwerken. Het is het hoofdstuk waarin ik mensen wil bedanken, die op wat voor manier dan ook hebben meegeholpen aan het onderzoek en het proefschrift wat nu voor u ligt. Een aantal personen wil ik hiervoor in het bijzonder bedanken.

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En die start gaat een lange tijd terug. De tijd waarin Revant nog Revalidatiecentrum Breda heette. Een tijd waarin Gijs Kuijpers nog werkte en samen met Hanneke Robben (psycholoog) een begin maakten met het schrijven van een behandelprogramma specifiek voor revalidanten met CVS. Het programma is uiteindelijk beschreven en geïmplementeerd. Ook werd een pilot uitgevoerd om het effect van deze behandeling te meten. Met subsidies kreeg de pilot uiteindelijk een vervolg: een RCT in vier revalidatiecentra in Nederland. Gijs, jij was in het begin de aandrijver van het project en ging op zoek naar revalidatieartsen en onderzoekers die het onderzoek mee vorm wilden geven. Nog steeds heb ik veel waardering voor je gedrevenheid in deze fase van het onderzoek. Jij bent degene geweest die ervoor zorgde dat meerdere revalidatiecentra mee gingen werken aan het onderzoek, waarvoor mijn dank. Zoals je je hart bij je revalidanten had liggen, zo legde je je hart ook in het onderzoek en ben je het tot na je pensioengerechtigde leeftijd blijven volgen. Snel kwamen we uit bij prof. dr. Marcel Post, als senior onderzoeker werkende bij revalidatiecentrum de Hoogstraat. Marcel dank voor je beoordeling en je adviezen in deze fase. Rond dezelfde periode werd door Gijs, Rob Smeets (destijds revalidatiearts bij Revalidatiecentrum Blixembosch, nu Libra geheten) benaderd.

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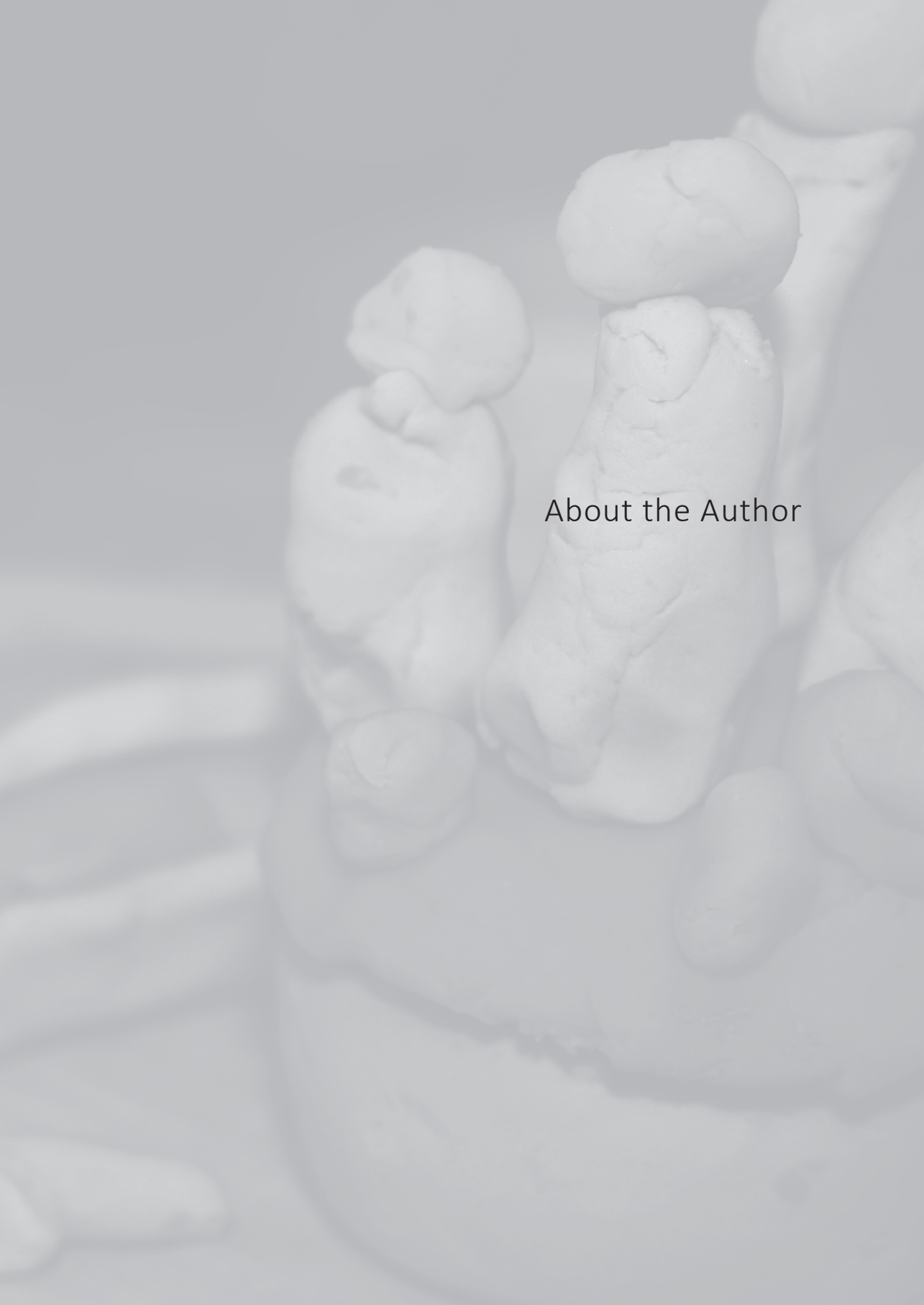

About the Author

Desirée Vos-Vromans was born on April 10, 1977 in Dongen, the Netherlands. After she obtained her 'VWO diploma' at the secondary school Cambreur college in Dongen in 1995, she started her study in Health Sciences at Maastricht University, the Netherlands. Thereafter, Desirée received her Master degree from Maastricht University (Maastricht, the Netherlands), in the domain of Movement Sciences in 1999. In 1999, she worked part-time as a research assistant in Rehabilitation Centre 'de Hoogstraat' in Utrecht, the Netherlands. Meanwhile she studied physical therapy at the HU University of Applied Sciences Utrecht. After her graduation in 2002, she started working at Revant, Rehabilitation Centre Breda as a physical therapist and coordinated several (scientific) research projects. In 2007, she was appointed as a PhD researcher at the Department of Rehabilitation Medicine of Maastricht University on the project FatiGo. The results of this project are presented in this thesis entitled 'Multidisciplinary rehabilitation treatment or cognitive behavioural therapy for patients with chronic fatigue syndrome: Comparison of treatment effects'.

During and after finishing her thesis she worked as a physical therapist at the department of neurorehabilitation at Revant, Rehabilitation Centre Breda.

Since 2004 she is happily married to Ronnie Vos. Together they have three children, Liza, Jelte and Emma.