About a quarter of cancer survivors suffer from chronic cancer-related fatigue (CCRF). CCRF has a considerable impact on a patient's life because it hinders in daily life activities and causes distress.

To improve the quality and accessibility of interventions for CCRF, this dissertation comprises the evaluation of two different Web-based interventions for reducing CCRF: a physiotherapist guided ambulant activity feedback (AAF) therapy encompassing the use of an accelerometer, and a psychologist guided online mindfulness-based cognitive therapy (eMBCT).

The following topics will be addressed:
1. The effectiveness of these interventions compared to an unguided active control condition receiving psycho-educational e-mails;
2. Specific and generic predictors and working mechanisms of these interventions;
3. Patient experiences with following these interventions.

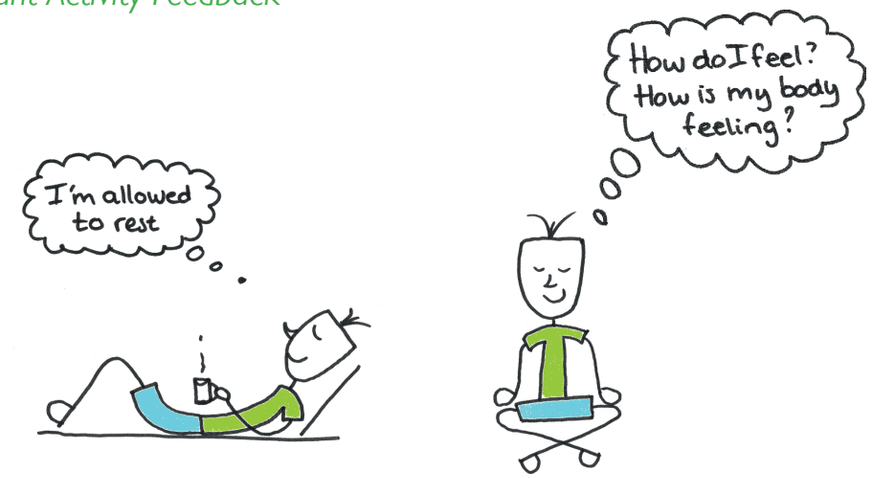
This project is called 'Fitter na kanker', and concerns applied research initiated by two research departments in clinical psycho-oncology practice centers in the Netherlands: the Helen Dowling Instituut (www.hdi.nl) and Roessingh Research and Development (www.rrd.nl).

Evaluating eHealth for chronic cancer-related fatigue

Fieke Bruggeman-Everts

Evaluation of two different Web-based interventions for chronic cancer-related fatigue

Online Mindfulness-Based Cognitive Therapy and Ambulant Activity Feedback



Fieke Bruggeman-Everts

Evaluation of two different Web-based interventions for chronic cancer-related fatigue

Online Mindfulness-Based Cognitive Therapy and Ambulant Activity Feedback

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EVALUATION OF TWO DIFFERENT WEB-BASED INTERVENTIONS FOR CHRONIC CANCER-RELATED FATIGUE

ONLINE MINDFULNESS-BASED COGNITIVE THERAPY AND AMBULANT ACTIVITY FEEDBACK

PROEFSCHRIFT

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Chapter 1

General Introduction

Chronic Cancer-Related Fatigue

Cancer-related fatigue (CRF) is defined as 'a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning' [1]. In the qualitative study of Wu et al. [2] CRF patients described their fatigue as not just being tired, but as a new sensation. It is described as an overwhelming depletion of energy, feeling like a 'rag doll', having an unusual need for rest, but resting or sleep is not refreshing. The unexpected sudden onset of fatigue and not being able to explain what is causing the fatigue is upsetting. Also the relationship with your body is changed. Feelings of becoming alienated from the body because it has let you down, are characteristic. The body has become a problematic object as it is incapable of functioning as it did formerly, resulting in distressing and depressing emotions of not measuring up, losing your identity. In approximately 30% of patients who have completed initial cancer treatment and who have no apparent evidence of active disease (cancer survivor), severe fatigue persists for months or even years [3]. This chronic cancer-related fatigue (CCRF), as we call it, has a considerable impact on a patient's life because of its interference with daily activities and because it hinders patients to participate optimally into the society and work. It is often accompanied with distress and affects the patients' mental health [1,4].

To illustrate, one of the patients in this study (mother of three children, in her early 40s) described fatigue as:

> *"Well, it is especially the kind of fatigue that arises very suddenly and is actually unpredictable when it comes. Sometimes I have had a busy day and then I don't have it, and sometimes it have quite an easy day and then at once, zip, bam boom, there it is. It is also a very strange paralyzing fatigue. Normal fatigue is when you sit down for a while, it is over, but this is never over. I still have it, now after 6 years I still have not discovered how I can make it better, or how to let it go away. It comes and goes."*

Models explaining CCRF and interventions

Since approximately the late 90's, there has been a growing interest in the wellbeing of cancer survivors. Nowadays, medical specialists recognize CCRF better and long term consequences of cancer diagnosis and treatment have become more familiar in society.

Several models are presented about the etiology of fatigue as a side effect of cancer treatment. The most accurate conceptualization of (C)CRF may be multidimensional or multifactorial. Different factors have been distinguished that are thought to be involved in severity of fatigue in cancer patients, such as cancer and its treatment (e.g. pain, appetite loss, difficulty swallowing, early menopause, lymphedema), psychological/behavioral factors (e.g. anxiety, depression, coping with chronic illness), comorbidities (e.g. heart failure, thyroid dysfunction, lung diseases), medication side effects (dry mouth, dizziness), sleep disturbances, poor physical condition [5,6]. For chronic cancer-related fatigue, Magnusson et al. [7] presented a multidimensional model which distinguishes between (1) experiences (loss of energy, malaise, psychological stress, feelings of sadness, dejection), (2) consequences (social limitation, affected self-esteem, affected quality of life), and (3) actions (coping). Concerning the actions or coping with fatigue, two different models can be distinguished:

- Stress coping model: CCRF is conceptualized as a result of prolonged stress due to cancer diagnosis and cancer treatment, and passive coping strategies [8,9].
- Energy balance model: CCRF is seen as a consequence of deconditioning and prolonged inactivity during cancer and its treatment. Secondary fatigue arises as a result of detraining and can lead to a downward spiral in physical energy [9,10].

Interventions for CCRF

Interventions that are based on an energy balance model are aimed at increasing level and/or balance in physical activity. They have shown to be effective in reducing fatigue [11–16] and roughly involve three types of interventions: exercise interventions [16], energy conservation interventions [14], or graded activity embedded in a Cognitive Behavior Therapy (CBT) protocol [17]. A change in perceptions about physical activity [18] and increase in self-efficacy [19] were found to play a role in reducing fatigue in cancer survivors, so there may not only be a physical component underlying the effect of these energy balance interventions.

Interventions based on a stress coping model aim at changing the behavioural and cognitive reactions of the patient. Psycho-oncological treatments that are based on these theories include, CBT and mindfulness-based cognitive therapy (MBCT) [20–22] and have been shown to help reduce CCRF in previous studies [23,24]. CBT follows the assumption that cancer or cancer treatment triggered fatigue, but that other factors cause the perpetuation of fatigue, such as poor coping with cancer and treatment, excessive fear of disease recurrence, dysfunctional cognitions regarding fatigue, dysregulation of sleep, dysregulation of activity, and low social support and negative social interactions [25]. The CBT protocol aims at changing these perpetuating factors and showed to be helpful in reducing fatigue severity in cancer survivors [17]. Mindfulness-Based Cognitive Therapy (MBCT) aims to change the patient's behavioral and cognitive reactions to cancer-related stressors, including fatigue itself and showed to help reduce fatigue in cancer survivors [26,27]. At the Helen Dowling Instituut (Bilthoven, the Netherlands) it is suggested that MBCT can help severely fatigued cancer survivors to become aware of their potentially maladaptive automatic responses (feelings, thoughts and behaviors) [20] through (1) exposure to fatigue sensations non-judgmentally, thereby reducing distress associated with fatigue through desensitization, (2) cognitively detaching from distressing thoughts and thereby not being overwhelmed by fear of cancer recurrence, (3) raising awareness to the present moment and thereby becoming aware of potentially maladaptive coping strategies and choose to act differently, (4) finding ways to relax through meditation exercises and thereby improving quality of sleep and rest, (5) accepting the present energy level and thereby reducing energy loss that would otherwise be spilled on trying to change, escape, or avoid fatigue [28,29].

Web-based interventions for cancer related-fatigue

Web-based interventions are interventions that make use of the Internet, but also other forms of technologies are possible, such as mobile devices, e-mail and telephone. They can serve as an addition to the provision of face-to-face interventions [30–32], either in combination with face-to-face treatment (blended), or as stand-alone treatment. The Web makes treatment available for patients who are unable to travel to a healthcare institute, because of lack of energy or physical limitations. Also, Web-based interventions may be suitable for patients who seek treatment that is easy to integrate into daily life activities, as one can follow the program when and wherever preferred. When this study was initiated, no web-based interventions had shown to be effective other than a web-based tailored education program for

reducing fatigue in cancer survivors [33]. While recently in 2017, an online CBT protocol for breast cancer survivors has also shown to be effective for reducing fatigue [34].

At Roessingh Research and Development in Enschede, the Netherlands in 2012, a 9-weekly Web-based intervention called Ambulant Activity Feedback (AAF) was developed especially for CCRF patients to reduce fatigue [35]. Via the use of a measuring device of physical activity (accelerometer) which is connected to a smartphone (Personal Digital Assistant), the patient receives feedback on his or her physical activity level. The participant is supported by personal feedback from a physiotherapist who corresponds to the patient via e-mail or telephone. AAF attempts to balance and/or increase physical activity using this physical activity feedback system.

An online version of Mindfulness-Based Cognitive Therapy (eMBCT) guided by a psychologist was developed for reducing CCRF in 2010 [29]. On a personal webpage, the CCRF patients could download mindfulness exercises, write down their experiences and correspond with their personal psychologist who was experienced in practicing and teaching mindfulness. eMBCT attempts to teach the participant to use a detached perspective as a skill to prevent the escalation of automatic negative thinking patterns in order to reduce fatigue.

In this dissertation, we chose to use the term Web-based interventions when describing both AAF and eMBCT, as it best describes these two interventions in one term. eHealth (preventive, promotive or curative healthcare with the use of electronic means), mHealth (eHealth delivered with the use of mobile devices), and Telehealth (care delivered over a distance) [36], are less suited as these terms can be too ambiguous or yet too specific.

Aim of the study

The overall aim of the study *More fit after cancer* (in Dutch ‘Fitter na kanker’, hereafter referred to as the FNK-trial) was to study the effectiveness, effect predictors, and working mechanisms of AAF and eMBCT in comparison to a minimal active control condition that consisted of emails with psycho-education about CCRF (3-arm Randomized Controlled Trial). In addition, patient experiences with doing AAF and eMBCT were investigated. The findings are expected to improve the quality and accessibility of Web-based interventions for cancer survivors who suffer from CCRF.

WHAT IS KNOWN:

* CCRF is a serious and growing problem, for which easy accessible interventions are needed.
* Physical activity interventions as well as psychological interventions specifically aimed at reducing CCRF are effective.

WHAT THIS STUDY ADDS:

* Knowledge about the effectiveness of two different types of home-based interventions for CCRF.
* Knowledge about specific and general working mechanisms of these interventions to optimize treatment for CCRF.
* Knowledge about what patients found helpful and hindering aspects of the interventions and to what extent the interventions matched to their needs
* Advice on how to improve these two interventions

Outline of the dissertation

In chapter 2, the results of a pilot study of eMBCT for CCRF is presented, with a pre-post measurement of fatigue severity of patients who applied for eMBCT at the Helen Dowling Instituut. In chapter 3 the FNK-trial design is presented. This trial design paper was published before analyzing the data, and this increases our transparency or our scientific doings. This is in line of the Open Science movement [37], which strives to make science more transparent during the research process. In chapter 4, we present a study on the psychometric qualities of a mindfulness questionnaire, in order to study mindfulness as a working mechanisms. In chapter 5, we present the results of the effectivity (fatigue severity and mental health) of both AAF and eMBCT compared to patients in the active control group receiving psycho-education. To increase our knowledge on how change in AAF and eMBCT may be established, we investigated in chapter 6 which previously hypothesized constructs were found as a predictor or working mechanism for a reduction of fatigue severity. And finally, in chapter 7, we report on patients experiences (qualitative study) of patients after following AAF and eMBCT.

In the discussion section (chapter 8) we summaries all results, put these results in a bigger picture and reflect on this dissertation. This results in answering questions like: What can we learn from this dissertation (take home message)? Did these interventions match to the needs of the participants? Do the quantitative results match the qualitative results? And also some reflection on the study design: Was this a good way of evaluating these interventions? And how could these interventions be improved?

Setting

This study concerned applied research initiated by two research departments in the Netherlands, namely the Roessingh Research and Development, a rehabilitation center in Enschede, and the Helen Dowling Instituut, a clinical psycho-oncology practice center in Utrecht/Bilthoven. This project is funded by Alpe d'Huzes/KWF foundation.

Frequently used abbreviations and definitions of this dissertation

AAF = ambulant activity feedback

CBT = cognitive behavior therapy

CCRF = chronic cancer-related fatigue

CIS-FS = Fatigue severity subscale of the Checklist Individual Strength

CRF = cancer-related fatigue

eHealth = preventive, promotive or curative healthcare with the use of electronic means

eMBCT = online mindfulness-based cognitive therapy

LGM = latent growth modeling

MBCT = mindfulness-based cognitive therapy

PE = psycho-education

Web-based interventions = interventions that make use of the Internet, but also other forms of technologies are possible, such as mobile devices, e-mail and telephone.

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Chapter 2

Web-Based Individual Mindfulness-Based Cognitive Therapy for Cancer-Related Fatigue – A Pilot Study

Based on:

Bruggeman-Everts, F.Z., Van der Lee, M.L. & De Jager Meezenbroek, E. Web-based individual Mindfulness-Based Cognitive Therapy for cancer-related fatigue — A pilot study. *Internet Interv*. 2, 200–213 (2015)

Abstract

Background: Severe fatigue may persist for many years in cancer survivors and has a considerable impact on a patient's life. This condition is called Cancer-Related Fatigue (CRF). Mindfulness-Based Cognitive Therapy has shown to significantly reduce CRF in cancer survivors. Internet-delivered interventions can be valuable for fatigued patients who are not able to travel to a healthcare institute because of the lack of energy and/or physical limitations. Therefore, we have developed a web-based, therapist guided individual 9-week Mindfulness-Based Cognitive Therapy (eMBCT) aimed at diminishing CRF.

Objective: The aim of this study was to evaluate the efficacy of eMBCT in a clinical setting in reducing fatigue severity and distress in cancer survivors.

Methods: This pilot study was based on data from severely fatigued cancer survivors who applied for eMBCT between 2009 and 2013. Our primary outcome measure was the change in self-reported web-assessed fatigue severity, measured with the Fatigue severity subscale of the Checklist Individual Strength before (baseline) and one month after (post-assessment) eMBCT. The secondary outcome was distress (HADS) and the proportion of participants that showed clinically relevant improvement on fatigue severity. Patients' satisfaction with using eMBCT and reasons for non-adherence were studied. Intention-to-treat analyses were performed using multiple imputations to deal with data loss at post-assessment. All patients had to be severely fatigued at baseline (≥ 35 on the fatigue severity subscale of the Checklist Individual Strength), were > 18 years old, had no history of psychosis or current Major Depressive Disorder, finished their last cancer treatment at least six months ago (mixed cancer types), and were not in the terminal phase of illness. Patients were recruited offline as well as online.

Results: Two-hundred fifty-seven patients (age range 22-79 (M = 50.2, SD = 10.7), 76% women, 44% breast cancer, most had had surgery, chemo- and/or radiotherapy) met our inclusion criteria. Paired samples t-tests showed that fatigue severity was significantly reduced post-assessment (t (18) = 13.27, p < .001, Cohen's d: 1.45 as well as distress (t (46) = 7.66, p < .001, Cohen's d: 0.71). Thirty-five percent (n=89) was clinically relevant improved

at post-assessment and 62% (*n* = 159) adhered to treatment. This study had a completion rate of 1.5 and a registration rate of 2.3.

Conclusion: These findings suggest that individual eMBCT may be effective in reducing fatigue in cancer survivors. A randomized controlled study with a large sample and longer follow up is needed to demonstrate the effectiveness of eMBCT for CRF.

Introduction

Background

Fatigue is a common side-effect of cancer and its treatment [1–3]. Cancer-related fatigue (CRF) is defined as a distressing persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning [4]. In about one third of cancer survivors fatigue may persist for months or even years after cancer treatment [5–9]. Fatigue is known as one of the most prevalent and distressing long-term consequences of cancer [10–13]. It is associated with high levels of depression and anxiety [14–16], and has an impact on patient's ability to reintegrate into everyday life [17]. It is estimated that in the Netherlands alone, at least 156.000 cancer survivors are suffering from fatigue [6,18]. This number is expected to rise in the next decades, as the number of people surviving cancer is increasing [18].

The etiology of CRF is complex and multidimensional [19], as it most likely involves physiological, biochemical and psychological systems [20]. Most commonly identified factors that contribute to CRF include 1) tumor-related factors and complications (e.g. anemia, pain, appetite loss, stress), 2) treatment side effects (e.g. tissue damage due to cytostatica, or radiation, medication side effects), 3) comorbid medical condition (e.g. thyroid dysfunction, diabetes mellitus, chronic obstructive pulmonary disease) 3) exacerbating comorbid symptoms (sleep disturbance, deconditioning, chronic pain) and 4) psychosocial factors (coping with illness, anxiety, depression) [19,21].

In the National Comprehensive Cancer Network (NCCN) guidelines for CRF [4] psychosocial interventions are recommended for CRF both during active cancer treatment, as well as after treatment. These interventions are aimed at changing inefficient coping strategies [4,22], thus

changing the behavioral and cognitive reactions of the patient to cancer-related stressors including fatigue itself [23–25]. Mindfulness-based cognitive therapy (MBCT) has shown to be effective in reducing severe fatigue in cancer survivors in a randomized controlled trial [25]. Mindfulness-based interventions have been found to have a positive effect on psychological and physiological symptoms in cancer survivors [26–29]. Baer [30] proposed that mindfulness skills can lead to symptom reduction and behavior change through exposure, cognitive change, self-management, relaxation and acceptance. In figure 1 the proposed mechanisms by Baer are presented, and applied to CRF by the authors.

Figure 1: How MBCT may help [30] – Applied to cancer-related fatigue by the authors.

I. Exposure	The ability to observe fatigue sensations non-judgmentally is believed to reduce distress associated with fatigue through desensitization.
II. Cognitive change	The practice of mindfulness may lead to changes in one's attitude towards one's thoughts. Fatigue-related thoughts like: "I am useless, feeling so fatigued all the time" are 'just thoughts' rather than reflections of truth or reality. Patients are stimulated to cognitively defuse from these thoughts.
III. Self-management	Through the practice of mindfulness a patient can learn to raise awareness to the present experience and becomes aware of potentially maladaptive coping strategies (e.g. irritation in social contact, catastrophizing about fatigue, being overactive, or being too inactive). By raising awareness people are able to choose a more helpful coping strategy.
IV. Relaxation	By raising awareness to bodily sensations such as muscle tension, autonomic arousal, and racing thoughts, mindfulness exercises may lead to relaxation. Relaxation has a beneficial effect on quality of sleep and rest.
V. Acceptance	Mindfulness meditation includes acceptance of fatigue-related thoughts, feelings, urges, or other bodily, cognitive and emotional reaction. In that way the patients can save energy which is otherwise spilled on trying to change, escape, or avoid fatigue.

Web-based Mindfulness-Based Cognitive Therapy for cancer survivors

Internet-delivered psychosocial interventions can serve as an addition to existing face-to-face interventions [31–33]. It makes treatment available for patients who are unable to travel to a healthcare institute, because of lack of energy or physical limitations. Also, internet interventions may be suitable for patients who seek treatment that is easy to integrate into daily life activities, as one can follow the program when and wherever preferred. We have developed a web-based individual MBCT aimed at alleviating CRF called eMBCT. The eMBCT is characterized by personal contact with one assigned therapist via e-mail and

follows the same protocol as face-to-face MBCT for CRF (see Appendix A) [25]. MBCT is originally delivered in a group format. Individual MBCT can be beneficial for patients who are reluctant to treatment in a group, for instance because they fear being confronted with stories of fellow patients. Individual MBCT has been shown to be effective in reducing depression in patient with diabetes [34]. As far as we know, this pilot study is the first to investigate a web-based individual MBCT for CRF.

Development of eMBCT

In the development of eMBCT, we originally adopted the 9-week face-to-face MBCT protocol for CRF [25], and made the following adaptations: We re-designed the reader with a professional lay-out, and added a written introduction which was originally given in the group face-to-face. The weekly reader was divided in paragraphs, describing each psycho-educational theme separately, and thereby improving readability. We transformed the audio files from the face-to-face MBCT to digital MP3 files. We created new MP3 files for the exercises 'eating with awareness' and 'walking meditation', as these exercises were originally done in the group in the face-to-face MBCT. We illustrated the yoga exercises in the reader so patients could easily copy the yoga postures.

We designed a website (www.mindermoebijkanker.nl [35]) with the help of an ICT company called Studio2 [36] (see Appendix D for screenshots). The 9-week protocol, the readers, MP3 files, and log boxes were implemented on a password-protected webpage on the website. In the log boxes patients could write down their experiences with doing the exercises. An e-mailbox was implemented on the webpage, so patients could securely correspond with their personal therapist, and receive feedback on their log files. An extensive intake procedure containing state and trait questionnaires was designed and put on the webpage. See Material and methods section for more information about setting and intervention.

Five fatigued cancer patients, who had previously followed face-to-face MBCT for CRF [25], volunteered to follow the first version of eMBCT and gave feedback about user friendliness and usability. Following their feedback, we added MP3 files of the same exercises (male voice, female voice, and shorter versions) so patients could choose which exercise they preferred. We added an option to print out the log files and e-mail correspondence with the therapist. We improved navigation on the webpage and enlarged the log boxes. An online

forum was suggested to share experiences with mindfulness, and to help continue practicing after the intervention had finished. Though, as the costs of a moderator would not be compensated by the health insurance companies, we instead referred to a website for the patient to find mindfulness meetings nearby.

Aim of this study

The aim of this study was to evaluate the efficacy of eMBCT in a clinical setting in reducing fatigue severity and distress in cancer survivors.

Materials and methods

Patients

Participants in this pilot study had to meet the following inclusion criteria: they (a) were a cancer survivor (all cancer types included), meaning either they had cancer but were not in the terminal phase of illness, or had suffered from cancer in the past (b) had completed their last cancer treatment at least six months before the start of eMBCT (hormonal treatment excluded); (d) were older than 18 years; (e) scored ≥ 35 on the severity of fatigue subscale of the self-report Checklist Individual Strength (CIS) at baseline [37]; (f) had no history of psychosis or current Major Depressive Disorder. If patients followed any other form of psychological care for fatigue or changed their medication considerably during the eMBCT, this was registered at post-assessment (self-report). Patients who reported they had cancer recurrence or started a cancer treatment during the study were excluded from analysis. Co-morbid somatic diseases that were a possible cause for fatigue were no exclusion criterion, but were registered during the study (self-reported).

Recruitment

We informed medical doctors about the eMBCT via articles in relevant magazines, and informed patients directly by newsletters of patient associations, and via advertisements on relevant websites in the Netherlands (see Appendix B for advertisement).

Setting and intervention

Patients were referred to the Helen Dowling Instituut (a health care institution, specialized in psycho-oncology, then situated in Utrecht, the Netherlands) by medical doctors and all costs were compensated by health insurance. The intervention was given by eleven therapists (see Appendix C for case volume), who had at least two years of experience with face-to-face MBCT for cancer patients. They were trained in giving the nine-week eMBCT protocol (see Appendix A) and attended supervision bimonthly. Patients registered for eMBCT via the website www.mindermoebijkanker.nl [35]. They filled in the fatigue severity subscale and were given immediate automated feedback on their fatigue severity. In case their scores indicated severe fatigue, patients could register for eMBCT. After registration, patients were asked to agree on the general usage conditions and fill in the intake questionnaire on their personal password-protected webpage. Then, their personal therapist gave feedback on the intake and judged whether eMBCT would be suitable for them. If the therapist had doubts about whether eMBCT was adequate care for the patient, the therapist contacted patients via telephone for inquiry. To start the intervention, patients could log on to their personal password-protected webpage where they could download MP3 files with exercises, read written information about a specific mindfulness theme each week in the weekly reader, and to correspond with their personal therapist via e-mail (see Appendix D for screenshots). Patients were asked to practice the mindfulness exercises six days a week for half an hour, and to document their experiences in their personal log on their webpage. On an agreed day of the week, the therapists replied to this weekly log, thereby guiding the patients through the nine-week program. The therapist encouraged the patient to try out the new mindfulness exercises and also do some of the exercises of the weeks before (see Appendix A). From week 7 on participants could choose which exercises they preferred, and in week 9 they created their own program. The therapist provided the patient with personal support in doing the exercises, and creating a mild and open awareness for thoughts, feelings and behaviors. Patients could continue with the next week's session after they had registered their experiences with each exercise in their log of the previous week. Patients were stimulated to follow the nine-week intervention within the nine weeks period. In case of holidays or illness they could pause for a week or more in consultation with their therapist. At the end of each week patients answered eight questions about their wellbeing using the outcome rating scale [38], so the therapists could monitor their patients closely. In case a patient reported a drop in wellbeing, the therapist contacted the patient for inquiry, to investigate if (additional) help was needed from their general practitioner or other health professionals nearby. An evaluation

questionnaire was sent by e-mail four weeks after the intervention (see Data collection). The therapist replied to this evaluation questionnaire for one last time, and encouraged the patient to continue practicing after the intervention had finished.

Data collection

On their personal webpage, patients filled in questionnaires concerning fatigue severity and distress before (baseline intake) the nine-week intervention. One month after the intervention (post-assessment), patients were sent an invitation via e-mail to fill in the post-assessment questionnaire via a password secured online questionnaire. IP addresses were used to distinguish post-assessment questionnaires between patients. Patients were able to review and modify their answers through a 'back' button. All items of the fatigue severity and distress questionnaires were mandatory. Regarding satisfaction with eMBCT, all patients were send an evaluation questionnaire post-assessment. The data were collected in a clinical setting, and was approved by the ethical board of the Helen Dowling Instituut. In the general usage conditions, patients agreed on their answers to the questionnaires being used for research purposes.

Measures

Primary outcome variable: Fatigue severity

Fatigue severity was assessed with the fatigue severity subscale of the Checklist Individual Strength (CIS) [37]. The subscale fatigue severity consists of eight items, each scored on a 7-point Likert scale and demonstrated acceptable to excellent reliability [39] and internal consistency [40]. In this study, Guttman's λ_2 [41,42] for the CIS subscale fatigue severity was .75 at baseline and .93 at post-assessment. Patients with a score of $\geq$ 35 on this subscale are considered to suffer from severe fatigue [24,39]. The CIS has been used to assess fatigue in cancer survivors [24,43,44]. It closely resembles the Multidimensional Fatigue Inventory [45,46], which is often used internationally for measuring CRF. We chose the CIS, because a clinical cut off point for severe fatigue is available for Dutch cancer survivors [24].

Secondary outcome variables: distress, clinically relevant improvement, satisfaction

Distress is a common symptom in cancer patients, and is often associated with fatigue severity [5,47,48]. Therefore distress was used as our secondary outcome measure and was assessed with the Hospital Anxiety and Depression Scale (HADS) [49]. The HADS is a self-report

questionnaire that comprises 14 items measuring feelings of generalized fear and depressive symptoms. The HADS is considered a reliable and valid instrument in medical patients and is sensitive to change [50,51]. A Dutch validation study showed good reliability [52]. Le Fevre et al. [53] showed that $\geq$ 20 on the total scale is a good cut off point to screen for depression in cancer patients. In this study, Guttman's λ_2 [41,42] for the HADS was .85 at baseline and .85 at post-assessment. We calculated the percentage of clinically relevant improved patients at post-assessment on fatigue severity. Also, we calculated how many patients were less fatigued, how many patients did not respond to treatment, and how many patients reported more fatigue after treatment [54]. Concerning patients' satisfaction with eMBCT, we asked adherent patients about their opinion on the duration of, the amount of homework, and what grade they would give their therapist on a scale from 1-10. Adherent patients were asked about what they thought had helped them most and what they would like to see improved about eMBCT. Non-adherent patients were also asked what they would like to see improved about eMBCT, and were asked for their reason to stop using the intervention. The post-assessment questionnaire for non-adherent patients was shorter than adherent patients, as we expected that a long evaluation questionnaire would not be filled in by non-adherers, leading to loss at post-assessment. A patient was considered adherent if he or she had followed at least 70% of the intervention. We chose 70%, as we expect that by week 6 patients have experienced enough content of the intervention to could benefit from it [55].

Patient characteristics

Demographic and medical information (marital status, age, gender, work status, education, cancer type, medicine use, treatment, time since treatment) was collected at baseline via self-report.

Control variables

At post-assessment patients registered important changes that could have influenced their fatigue over the last four months, such as changes in medication, following another treatment for fatigue, divorce, starting a new medical treatment, or cancer recurrence.

Statistical analysis

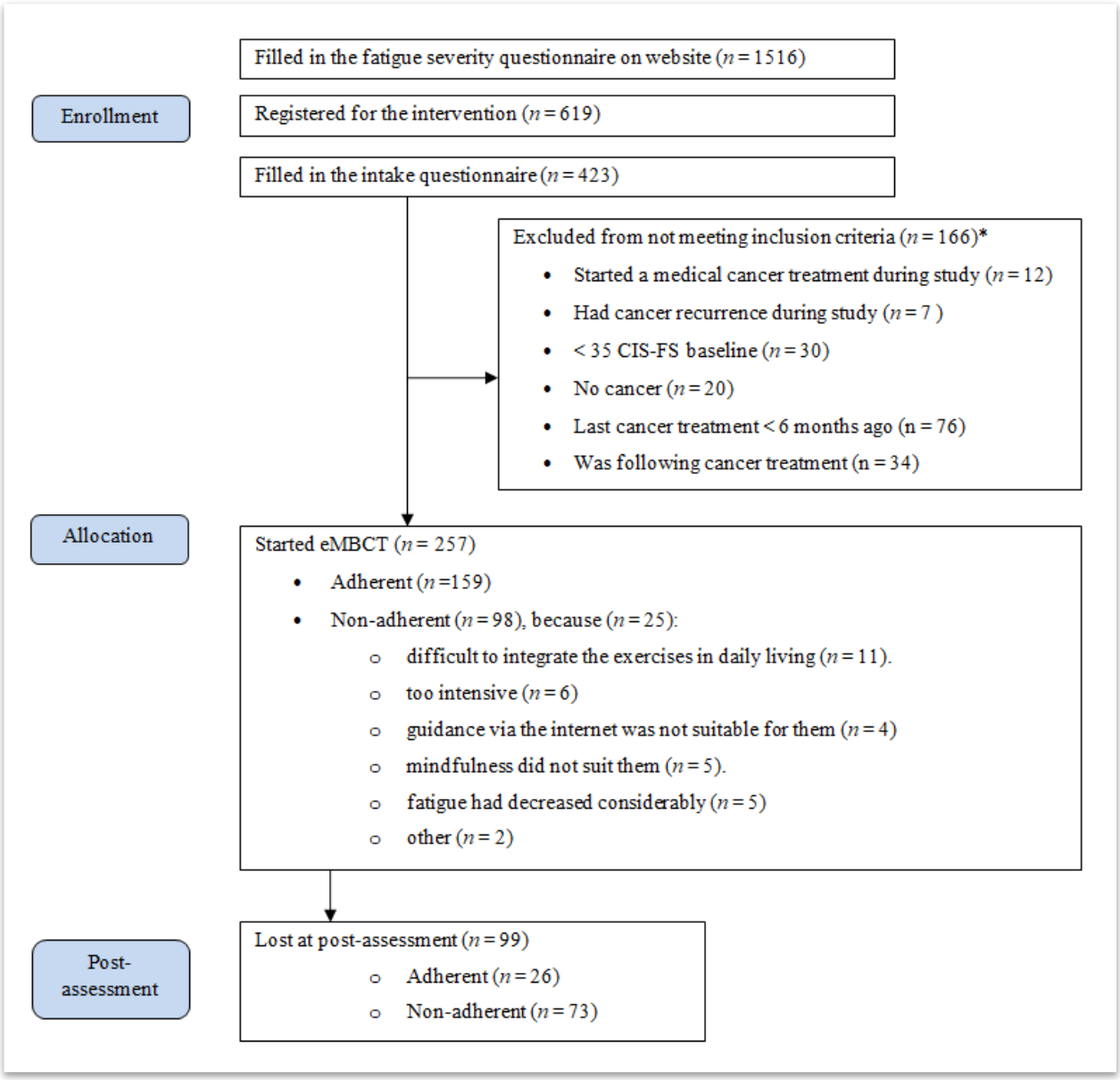
A paired samples *t*-test was used to investigate changes on the primary outcome CIS fatigue severity subscale, and secondary outcome HADS, both between baseline and post treatment. We used multiple imputation algorithms (Predictive Mean Matching) to deal with missing

values at post-assessment [56,57]. Firstly, we performed an intention-to-treat (ITT) analysis including both adherent and non-adherent patients. Secondly, we analyzed change scores for only adherent patients. To measure the effect size for the dependent samples *t*-test analyses, Cohen's *d* was calculated as followed: Cohen's *d* = mean difference / standard deviation of the difference [58]. Significance level was set at $p \leq .05$. To assess clinical relevance in fatigue severity change, a patient was considered clinically improved if the following two conditions were met: 1) the reliable change index (RCI) should be more than 1.96 [59], and 2) the post score should be within the normal range, that is a score < 1 standard deviation above the mean of a normative group [60], i.e. a score < 30.4 on CIS fatigue severity subscale. Moreover, we used the RCI to calculate the number of patients who were less fatigued (RCI > 1.96), did not respond to treatment (RCI between 1.96 and -1.96), and who were more fatigued after treatment (RCI < -1.96). The demographic, medical history and outcome variables were described using frequency and descriptive statistics. To see if there were differences at baseline between non-adherent and adherent patients, we checked the following characteristics using *t*-tests and χ^2-tests: depression (HADS ≥ 20), fatigue severity at baseline, prognosis, marital status, age, gender, employment, education, cancer type, medicine use, treatment type, previous experience with meditation, and time since cancer treatment. Analyses were performed using SPSS Version 19 for Windows package (SPSS Inc, Chicago, IL).

Results

Between October 2009 and February 2013 1516 people filled in the fatigue severity subscale on the website www.mindermoebijkanker.nl, of which 98% (*n* = 1485) scored ≥ 35 and thus were given the automated feedback that they could apply for eMBCT. Eventually, 619 patients registered for the intervention, out of which 423 filled in the intake questionnaire (see Figure 2 for flowchart). This gives a registration rate of 2.3 (ratio unique visits to website/registered) and a completion rate of 1.5 (ratio agreed to participate/finished survey). For this study, we had to exclude 169 patients, leaving 257 patients that were eligible and started the intervention. Of these, 38.1% (*n* = 98) were not adherent as they stopped using the intervention before completing 70%, including 15.6% (*n* = 40) that did not start the intervention after they had filled in the intake. On average, patients completed 70% of the intervention within 16 weeks. Demographic characteristics at baseline are presented in Table 1.

Figure 2: Flowchart



* Numbers do not add up as multiple exclusion criteria are possible

Table 1. Baseline characteristics of study participants (*n*=257).

Baseline characteristics	**M (SD)/%**
Age(years)	50.2 (10.7)
Women	76.3
Dutch nationality	97.7
Living with partner and/or children	69.6
Education	
Low	5.8
Middle	37.7
High	50.6
Employment[a]	
Paid job	54.5
Disability insurance act	29.2
Absenteeism from work	36.2
Cancer type[a]	
Breast	44.0
Blood bone marrow, Hodgkin	12.1
Digestive system	6.6
Reproductive organs	7.0
Head and neck	4.7
Other	8.1
More than one cancer type	11.3
Cancer recurrence	6.6
Heredity form of cancer	3.5
Lymph nodes affected	42.0
Metastases	16.0
Type of cancer treatment [a]	
Surgery	67.7
Chemotherapy	60.3
Radiotherapy	55.3
Hormonal therapy	28.4
Immunotherapy	7.8
Stem cell transplantation	2.7
No treatment: wait and see	0.8
Other	5.4
Suffer from co morbidity	27.2
Of these, percentage that suffers from two or more co morbidities	18.6
Co morbidity [b]	
Infection	20.7
Spine	13.4

Blood	9.8
Thyroid	8.5
Lung	8.5
Diabetes	7.3
CFS, ME	6.1
Pain, fibromyalgia	6.1
Fear or mood disorder	2.4
Psoriasis, eczema	2.4
Migraine	2.4
Other	12.4
Medicine use [a]	
Pain	24.1
Tension	7.0
Sleep	13.2
Antidepressants	10.1
For cancer	23.7
Time since last cancer treatment (years)	2.93 (3.29) (range 0.5 – 22)
Time since diagnosis (years)	3.44 (2.42) (range 0.08 – 22.75)
HADS ≥ 20 at baseline	26.46
Duration of fatigue	4.11 (1.29)
1 = 0-5 months	9.0
2 = 6 months – 1 year	22.6
3 = 1-2 years	24.9
4 = 2-5 years	26.8
5 = more than 5 years	14.8
Patient's own estimated prognosis	
Positive	56.8
Unclear, uncertain	17.1
Negative	2.3
I don't know	8.9
No experience with attention-focused exercises, such as meditation or yoga	31.1
Duration completing 70% of intervention (weeks)	15.53 (10.12) (range 7 – 64)
Non-adherent	38.1
Followed any other form of psychological care for fatigue at baseline	15.5
Changed medication considerably during the eMBCT	8.9

[a] Percentages do not add up to 100% because multiple options are possible; [b] Infection including Sarcoidosis, Bechterew's disease, Crohn's disease, Graves' disease, rheumatoid arthritis. Spine injury including whiplash and hernia. Lung diseases including fibrosis, asthma, bronchitis, emphysema. Blood including heart problems, high blood pressure, polycytemia vera. *Abbreviations*: M = Mean; SD = standard deviation

Multiple imputation of missing data using predictive mean matching and predictors of dropout

To select auxiliary variables for multiple imputation, we investigated differences between *dropouts* (patients who did not fill in the post-assessment questionnaire [55]) and non-dropouts, using independent samples *t*-tests and χ^2-tests. This showed that dropouts had been suffering from fatigue shorter (χ^2 (6) = 14.96, p = .021), had relatively lower education (χ^2 (2) = 15.71, p < .001), were more often men (χ^2 (1) = 3.846, p < .05), had less often breast cancer (χ^2 (1) = 5.00, p = .025), had 'other' cancer type more often (χ^2 (1) = 6.99, p = .008), had a less good prognosis (χ^2 (4) = 11.13, p = .025), suffered from comorbidity more often (χ^2 (1) = 5.52, p = .019), were less often occupied with household activities (χ^2 (1) = 4.96, p = .026), and reported a poorer quality of life at baseline (measured with one 10-point scale question: *How would you rate your quality of life?*) (t (164) = -2.64, p = .009). These variables were used as auxiliary variables for imputation fatigue and distress scores at post-assessment. The pooled mean of the imputed dataset consisting of 5 iterations, was used for the analyses.

The efficacy of eMBCT on fatigue severity and distress.

Paired samples *t*-test in the ITT analysis indicated that patients experienced less fatigue severity after the intervention than before the intervention, with a large effect size (see Table 2a). Analysis of adherent patients gave comparable results (see Table 2b). The proportion of clinically relevant improved patients in the ITT analysis was 34.9% (n = 89) and for the adherent patients 36.8% (n = 59).

Concerning our secondary outcome distress, paired samples *t*-test in the ITT analysis indicated that on average, patients experienced less distress after the intervention than before the intervention with a moderate effect size (see Table 2a). The number of patients who were less fatigued after treatment was 82.5% (n = 212). We found that 6.5% (n = 17) did not respond to treatment, and 11.0% (n = 28) was more fatigued after treatment.

Table 2a. Intention-to-treat analysis. Paired samples *t*-test results of baseline and post assessment fatigue severity (CIS fatigue severity subscale) and distress (HADS) of the imputed dataset.

		Baseline	Post assessment			
	n	*M* (*SD*)	*M* (*SD*)	*t*-test	*p*	Cohen's *d*
CIS-FS	257	46.53 (5.70)	33.89 (10.67)	t (18) = 13.27	< .001	1.45
HADS	257	15.48 (6.76)	10.90 (6.10)	*t* (46) = 7.66	< .001	0.71

CIS-FS= Checklist Individual Strength - Fatigue severity subscale; HADS= Hospital Anxiety and Depression Scale; *M* = mean (standard deviation)

Table 2b. **Adherent patients.** Paired samples *t*-test results of baseline and post assessment fatigue severity (CIS fatigue severity subscale) and distress (HADS) of the imputed dataset.

		Baseline	Post assessment			
	n	*M* (*SD*)	*M* (*SD*)	*t*-test	*p*	Cohen's *d*
CIS-FS	159	46.12 (5.52)	34.02 (10.70)	*t* (160) = 13.37	< .001	1.37
HADS	159	15.63 (6.66)	11.14 (5.75)	*t* (561) = 7.46	< .001	0.72

CIS-FS = Checklist Individual Strength - Fatigue severity subscale; HADS= Hospital Anxiety and Depression Scale; *M* = mean (standard deviation)

Satisfaction with eMBCT

Adherent patients who filled in the post-assessment questionnaire (*n* = 133) rated the guidance by the therapist with an average grade of 8.0 (*SD* = 1.2) on a scale from 1-10. Most of these patients found the duration of eMBCT (78.9%; *n* = 105), and the amount of homework adequate (66.9%; *n* = 89). Patients reported that doing the exercises (especially breathing, yoga, body scan and meditation), writing down their experiences (reflect on their thoughts, feelings and behaviors), and receiving feedback from their therapist (feeling supported, receiving mild, understanding feedback) were factors that were most helpful in eMBCT. Patients wrote that eMBCT had helped them by learning to accept their fatigue, recognizing which factors (situations, thoughts, feelings, behaviors) are energy giving or energy taking, letting go of energy consuming thoughts, recognizing their boundaries and pitfalls, managing communicating their boundaries with others, and accepting not being the same person as before the cancer and treatments. We asked both adherent as well as non-adherent patients to give their feedback on what they would improve about eMBCT. This

question was answered by 158 patients (25 non-adherent and 133 adherent). The majority (55.1%; *n* = 87) said the intervention did not need improvement. The following issues were suggested for improvement: a) *Usability of webpage*: Patients said it was difficult to navigate on the webpage, and the box for the log file was too small to write down long texts (*n* = 27); b) *Intensity*: Patients reported that they needed more time to do the 9-weekly intervention program, as the program was too intensive, both emotional, as well as due the many assignments they had to do (*n* = 21); c) *Guidance through the internet*: Patients said they had difficulty in explaining themselves in written words, and would prefer face-to-face contact with their therapist or contact by telephone (*n* = 8).

We asked non-adherent patients (*n* = 25) for their reason to stop using the intervention before completing 70%. Most patients stopped because they found it difficult to integrate the exercises in daily life (*n* = 11). The second most frequent reason was that the intervention was too intensive (*n* = 6). Other reasons were that fatigue had decreased or that a co-morbid illness had gotten worse, mindfulness or online help did not suit them, or that the intervention was not what they had expected.

Differences in demographics and baseline characteristics of adherent and non-adherent patients

In Table 3a and b the results of the *t*-tests and χ^2-tests are presented, with Cramér's *V* as a measure of strength of the correlation. Significant differences between adherent and non-adherent patients were found on several demographic characteristics. The group of non-adherent patients were more often depressed at baseline (χ^2 (1) = 23.44, $p < .001$, $V = .30$, were often more men (χ^2 (1) = 14.79, $p < .001$, $V = -.24$), and had lower education (χ^2 (2) = 7.97, $p = .019$, $V = -.18$). They had a paid job less often (χ^2 (1) = 4.46, $p = .035$, $V = -.13$), used sleeping medication less often (χ^2 (1) = 3.91, $p = .048$, $V = -.14$), and had no previous experience with mindfulness (χ^2 (2) = 11.30, $p = .004$, $V = -.18$). Depression at baseline has a moderate correlation, meaning there is a moderate association between depression at baseline and non-adherence. All other correlations were small.

Table 3a. Cross tabulation of adherence and demographics

Demographics	Adherence		χ^2	Cramér's V
	Adherent	Non-adherent		
Depressed (HADS ≥ 20)	40 (-2.4)	54 (3.0)	23.44 *	.30
Male gender	25 (-2.1)	36 (2.6)	14.79 *	.24
Living with partner	110 (-.1)	69 (.1)	0.04	.01
No paid job	61 (-.9)	46 (1.3)	4.46 *	.13
High education	92 (1.1)	38 (-1.5)	7.97 *	.18
Type of cancer treatment				
Surgery	113 (.6)	61 (-.7)	2.78	-.11
Chemotherapy	100 (-.6)	55 (-.6)	1.48	.08
Radiotherapy	91 (.4)	51 (-.5)	0.86	.06
Hormonal therapy	48 (.4)	25 (-.6)	0.75	.06
Immunotherapy	14 (.5)	6 (-.6)	0.65	.05
Other	10 (.5)	4 (-.6)	0.60	.05
Cancer type				
Breast	86 (.7)	43 (-.9)	2.92	.11
Blood bone marrow, Hodgkin	22 (.4)	11 (-.5)	0.41	.04
Digestive system	13 (-.2)	9 (.2)	0.07	.01
Reproductive organs	12 (-.9)	13 (1.1)	2.19	.10
Head and neck	9 (-.8)	10 (1.0)	1.77	.09
Good prognosis	99 (.6)	47 (-.8)	3.23	.12
Medicine use				
Pain	42 (-.3)	10 (.5)	0.52	.05
Tension	13 (.1)	5 (-.1)	0.01	.01
Sleep	29 (1.0)	5 (-1.5)	3.91 *	.14
Antidepressants	19 (.1)	7 (-.2)	0.05	.02
For cancer	44 (.1)	17 (-.1)	0.03	.01
No previous experience with meditation	40 (-1.5)	40 (1.9)	11.30 *	.24

* $p < .05$. Note: Adjusted standardized residuals appear in parentheses next to group frequencies.

Table 3b. Demographic means for adherence

	Adherence			
Demographics	Adherent	Non-adherent	*t*	*df*
CIS-FS fatigue at baseline	46.12 (5.52)	47.19 (5.95)	-1.47	255
Age	49.29 (9.89)	51.63 (11.81)	-1.71	255
Time since cancer treatment	35.13 (41.56)	35.18 (35.58)	-.01	150

Note: Standard Deviations appear in parentheses next to means. *df* = degrees of freedom

Discussion

Principal results

In this study, the efficacy of an individual internet-delivered mindfulness-based cognitive therapy for the treatment of cancer-related fatigue, called eMBCT, was investigated in a clinical setting (n = 257). As far as we know, this is the first study to evaluate an internet-delivered individual MBCT for CRF. Fatigue severity and distress significantly decreased from baseline to post-assessment, with a high effect size of 1.45 (Cohen's d). Intention-to-treat analysis showed that in 34.9% of the patients, fatigue severity was clinically relevant decreased, meaning they no longer reported fatigue complaints. In 82.5% of the patients fatigue decreased post-assessment, 6.5% did not respond to treatment, and 11.0% was more fatigued after treatment.

Adherent patients (61.9%) reported that eMBCT had helped learning (1) to accept their fatigue or being the same person as before the cancer and treatments (acceptance, see Figure 1), (2) recognizing and managing their boundaries and pitfalls (self-management), and (3) letting go of energy consuming thoughts (relaxation). Most patients were satisfied with eMBCT, though some made suggestions for improving the usability of the webpage, lowering the intensity of the intervention, and providing additional face-to-face contact or contact by telephone. Non-adherent patients said they stopped using the intervention because they found it difficult to integrate the intervention in daily life activities, and/or found the intervention too intensive. We found a moderate correlation between depression at baseline and non-adherence, therefore these patients may need to be cautiously monitored by the therapist during the intervention.

Strengths and limitations

As this study was based on data assessed in a clinical setting, our research design has several limitations. First of all, we used a design without a control group and therefore cannot control for other factors that could explain change in fatigue and distress other than the intervention. Second, a follow-up measurement is lacking. As fatigue is variable in time, a follow-up is essential for evaluating the long term effects of eMBCT. Third, the questionnaires were assessed by the same institute that provided the intervention, therefore social desirability may have influenced the results. The influence of social desirability may be less if another party would assess the pre- and post-data. Unfortunately 38.5% patients did not fill in the evaluation questionnaire, thus we could not find out their satisfaction with eMBCT. Monitoring adherent and non-adherent patients is essential to get a clear view on the overall patient's satisfaction with the intervention.

Comparison with prior work of others

As this is the first study to investigate online individual web-based MBCT for CRF, we will compare our results to other (online) mindfulness-based interventions, or other online interventions.

Our findings concerning the proportion of clinically relevant improved patients [59] is slightly greater than in group face-to-face MBCT for CRF (30%) [25], and individual face-to-face MBCT for depression in diabetes patients (26%) [34]. It is slightly lower than the 40% Boettcher et al. (2014) found in their online mindfulness-based intervention for lowering severity of somatic and cognitive anxiety symptoms in patients suffering from an anxiety disorder. Yun et al. [61] found that 56% of moderate to severely fatigued cancer survivors were clinically meaningfully improved after a web-based tailored education program. Though, they used a different fatigue severity inventory and used a different statistical method for clinically relevant improvement: they did not use the criterion that the post-assessment fatigue severity score was within the normal range. Thus their definition of clinically relevant improvement was less stringent than used in the current study and others [25,34].

Our non-adherence rate of 38.1% is within the found range of a meta-analysis of face-to-face mindfulness-based interventions for several disorders (anxiety depression, chronic pain, psoriasis) (3-40%, M = 25% (8.91) [30]. Though, our non-adherence rate is slightly higher

than the results of a meta-analysis of nine web-based cognitive behavior therapies for depression and anxiety (3-34%, *M* = 18%) [62]. Also, compared to studies investigating face-to-face mindfulness-based interventions [25,63] more patients were non-adherent in our study. It should be noted that the ease to access online interventions (such as the one evaluated in this study) may invite patients to apply, who would never usually consider accessing a psychological face-to-face intervention. Therefore online interventions may show higher non-adherence rates [55].

We need to learn from the feedback patients gave us on the use of eMBCT. We have created a new version of eMBCT in a new ICT environment, as quite a large sample suggested improving the usability of the webpage. We launched this new version in April 2013 and expect it to be more user friendly. Regarding the intensity of the intervention, we agree that eMBCT is an intensive course. The therapists encouraged the patients to practice at least half an hour a day for six days a week, try out the new mindfulness exercises and also do some of the exercises of the weeks before, but in the same time respect their own boundaries. Better informing the patients beforehand about the intensity of the program may help decreasing disappointment, stress and non-adherence rate. As the average duration of the intervention was 16 weeks, we consider spreading the protocol over a longer time period.

Conclusion

These findings indicate promising possibilities for eMBCT in treatment of CRF. This pilot study involved a large sample size, the found significant decrease in fatigue severity had a high effect size, and a substantial proportion was clinically relevant improved. The results of this study are therefore informative, and suggest that individual eMBCT may be effective in reducing fatigue in cancer survivors. A randomized controlled study with a longer follow up is needed to demonstrate the effectiveness of eMBCT. Moreover, it would be valuable to investigate for which CRF patient eMBCT may be helpful in decreasing fatigue severity, and how the decrease in fatigue severity is established. Investigating the written correspondence between the therapist and the patient, would be of great value in understanding the role of the therapist and a possible variation in outcome between therapists. Currently, we are investigating the newly designed eMBCT in a three-armed randomized controlled trial funded by Alpe d'HuZes/KWF fund [64]. This trial is registered in the Dutch Trial Registry, trial number 3483: www.trialregister.nl, and results are expected in 2016.

Appendices

APPENDIX A – eMBCT protocol

Overview of the eMBCT protocol with the specific mindfulness themes of each week [25].

Week 1: Theme: the automatic pilot, do not strive.

Information about the stress-coping model and the 'automatic pilot mode'. Introduction to 'eating with awareness' and 'body scan'. Homework: 'eating with awareness' and 'body scan'. Addition: psycho-education about coping with stress and fatigue and cancer-related fatigue. MP3 files: Body scan (32 min, woman)

Week 2: Theme: the body and the breath, do not judge.

Information about how to cope with pain and fatigue during the body-scan exercise and how to handle thoughts during the 'awareness of breathing' exercise. Homework: 'breathing exercise' and the 'body scan' and noticing thoughts and feelings at nice or happy moments. Addition: tips for a better sleep quality. MP3 files: Body scan with muscle tension, Jacoben (22 min. – man), Attention to your breathing (14 min.- woman)

Week 3: Theme: accepting boundaries, acceptance.

Recognizing unpleasant experiences. Becoming aware of how one deals with physical and emotional boundaries and cultivating acceptance. Three minute exercise focusing on breathing. Homework: 'yoga exercise', 'body scan', 'breathing exercises'. Addition: psycho-education about how to build up energy and condition after cancer. MP3 files: Yoga (32 min. – woman), Three minute breathing exercise (4 min. – woman)

Week 4: Theme: patience, attention.

Recognizing automatic negative cognitions, recognizing daily stress inducing experiences and their emotional impact, promoting free choice how to handle daily stress. Homework: 'sitting with awareness',' walking with awareness', alternated with previous learned exercises. MP3 files: Sitting meditation (47 min. – man), Sitting meditation (30 min. – woman)

Week 5: Theme: letting go, accept things as they are.

Learning how to cope with negative emotions through acceptation. Keeping a diary of negative emotions. Homework: 'accepting what is in the present ', alternated with previous learned exercises. MP3 files: Accepting what is in the present (23 min. – woman)

Week 6: Theme: dealing with thoughts and fear, trust.

Explanation how thoughts, behavior and emotions interact and how one can choose to stop automatic reactions. Physiology of fear. Fear of cancer recurrence. Dealing with loss. Homework: 'walking with awareness' and 'sitting with awareness', alternated with previous learned exercises. MP3 files: Silence (20 min)

Week 7: Theme: silence and compassion, loving kindness towards oneself.

Patients plan half a day with several awareness and compassion exercises at home in silence. MP3 files: Mountain (16 min. - woman), Lake (20 min. - woman), Lake (21 min. - man), Flower (15 min. - woman), Metta-meditation (36 min. - woman)

Week 8: Theme: seeing from a new perspective: taking good care of myself.

Participants make their own program of exercises and plan how they will continue the exercises without therapist feedback. Making a list of the top ten of helpful cognitions. Accepting stress as a part of life. Homework: practice your own program of exercises.

Week 9: Theme: from stress to inner strength.

Repetition of previous themes. Recommended literature

APPENDIX B – Advertisement (in Dutch)

We informed medical doctors about the eMBCT via articles in relevant magazines, and informed patients directly by newsletters of patient associations, and via advertisements on relevant websites in the Netherlands.

Minder Moe bij Kanker

behandeling via internet bij het Helen Dowling Instituut (HDI)

Vermoeidheid is één van de meest voorkomende klachten bij kanker.
Heeft u ernstige vermoeidheidsklachten? U kunt wat doen!
Volg negen weken de training en ervaar het verschil.

Hoe werkt het?
Extreem moe zijn, kan alles overheersen. Veel energie gaat ongemerkt verloren aan niet helpende emoties, gedachten en gedragspatronen. Wat is uw energielek? Tijdens de aandachtgericht Cognitieve Therapie (aCT) leert u zich bewust te worden van automatische reacties die uw vermoeidheid versterken. Onder behandeling van uw eigen therapeut gaat u aan de slag met een vrij intensieve therapie; hou rekening met een tijdsinvestering van driekwartier per dag. Door opdrachten, oefeningen en informatie leert u in negen weken effectiever om te gaan met uw energie.

Wie behandelen u?
Het valt niet mee om automatische patronen te wijzigen. Maar u doet het niet alleen. De aCT wordt begeleid door BIG geregistreerde therapeuten, die ruime ervaring hebben in het behandelen van kankerpatiënten en het geven van aandachtgerichte Cognitieve Therapie. En het werkt. Acht op de tien deelnemers is minder moe na afloop. Bij maar liefst de helft van de deelnemers van de internettherapie is na afloop van de therapie de vermoeidheid verdwenen. Zie ook het persbericht: > Internettherapie zeer succesvol

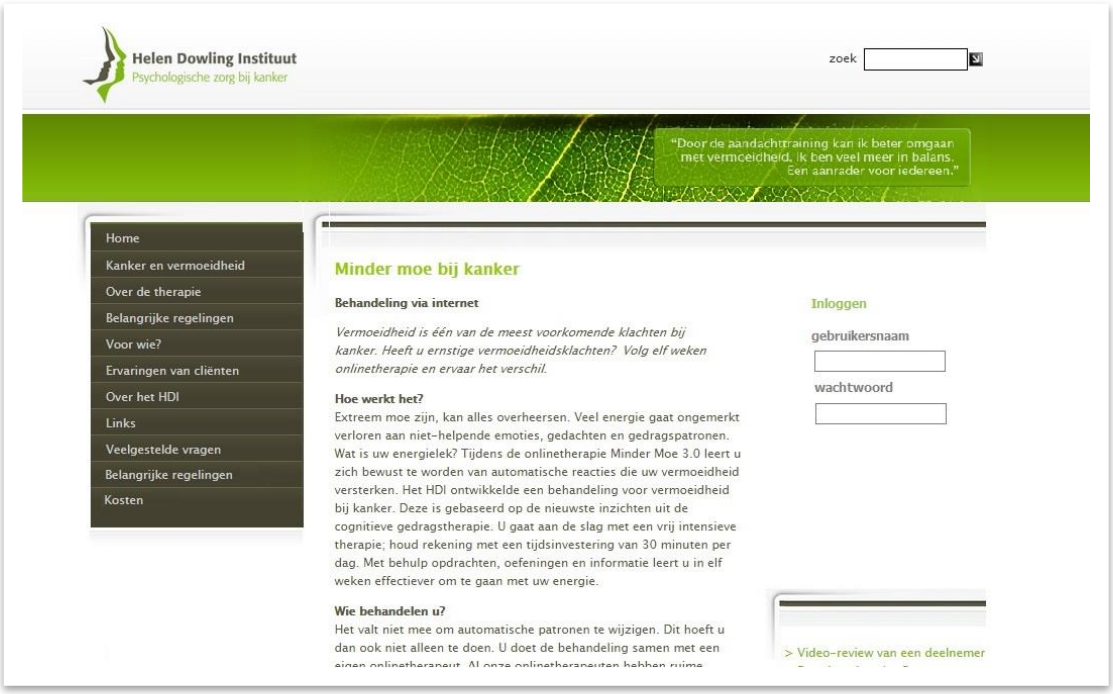
Wanneer kunt u starten?
Na de aanmelding volgt nog een online intake. Als uw therapeut de behandeling voor u geschikt vindt, kunt u direct starten en werken aan uw oefeningen wanneer het u uitkomt.

APPENDIX C - Case volume

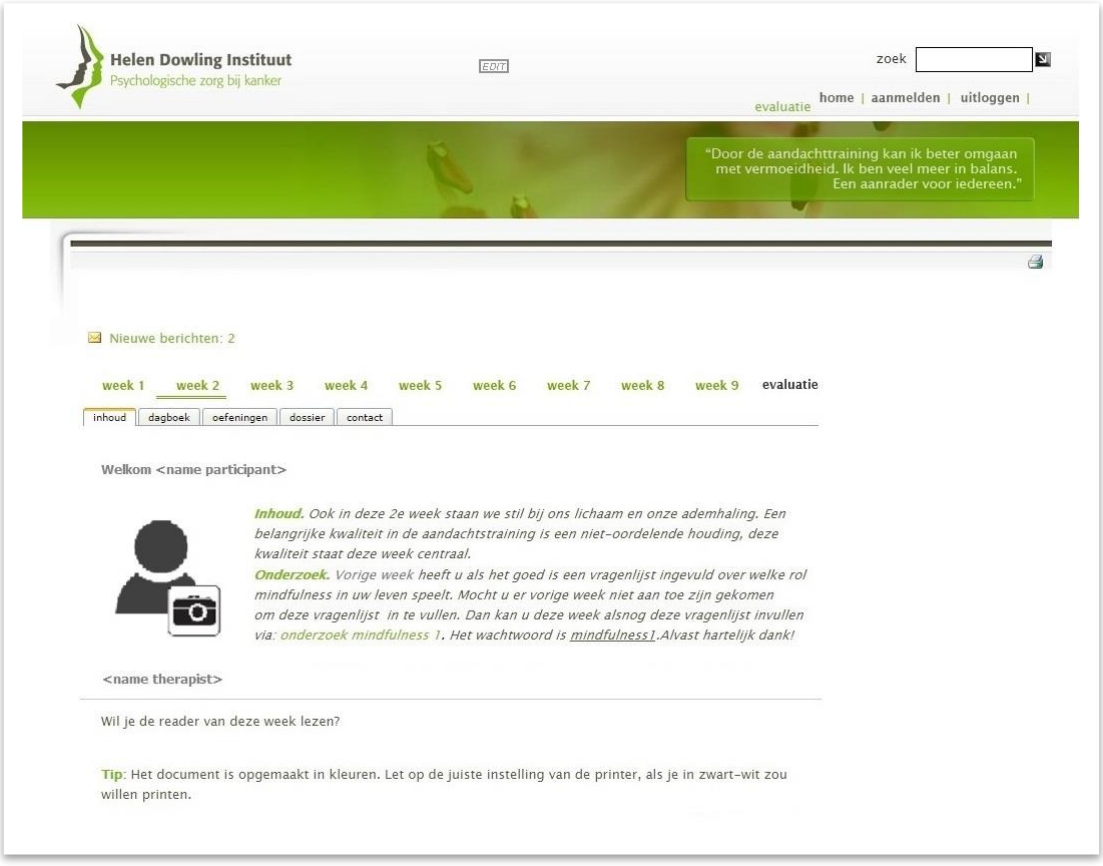
In this table the number of patients treated by each therapist is shown.

Therapist	Male/Female	*n*
Therapist 1	Female	3
Therapist 2	Female	6
Therapist 3	Female	20
Therapist 4	Female	16
Therapist 5	Female	6
Therapist 6	Female	47
Therapist 7	Female	61
Therapist 8	Male	46
Therapist 9	Female	35
Therapist 10	Female	14
Therapist 11	Male	2

APPENDIX D - Screenshots of eMBCT

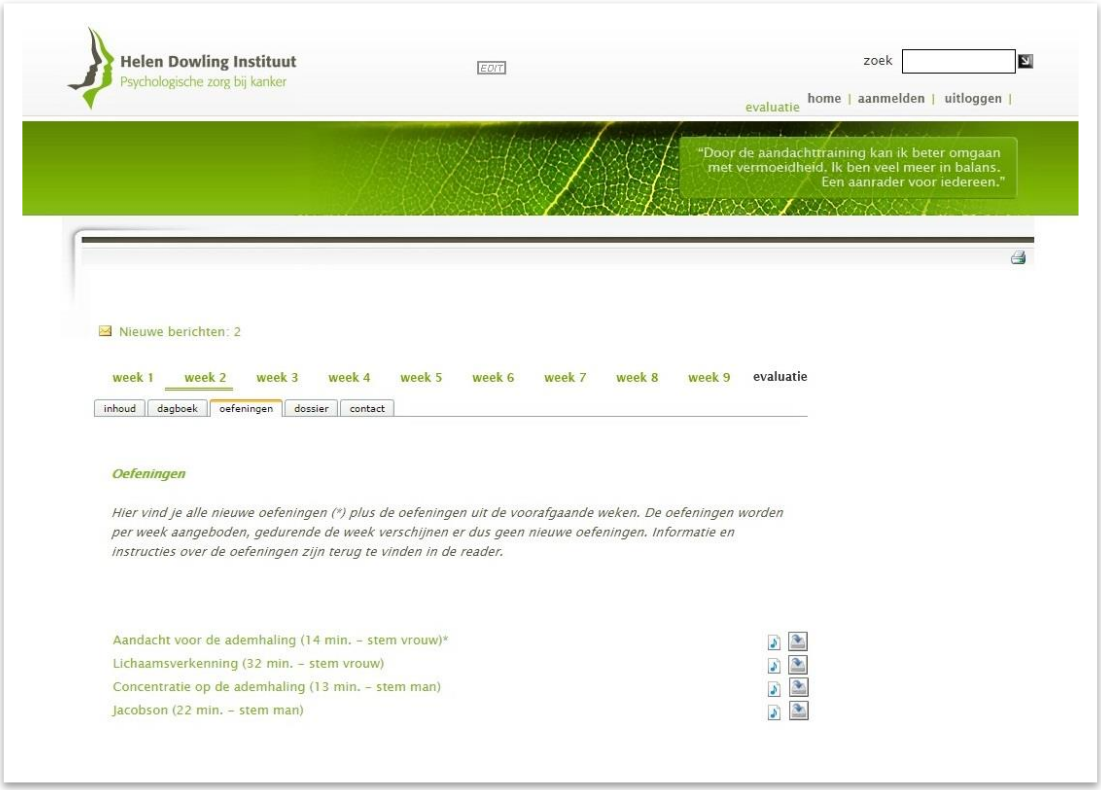


D.1

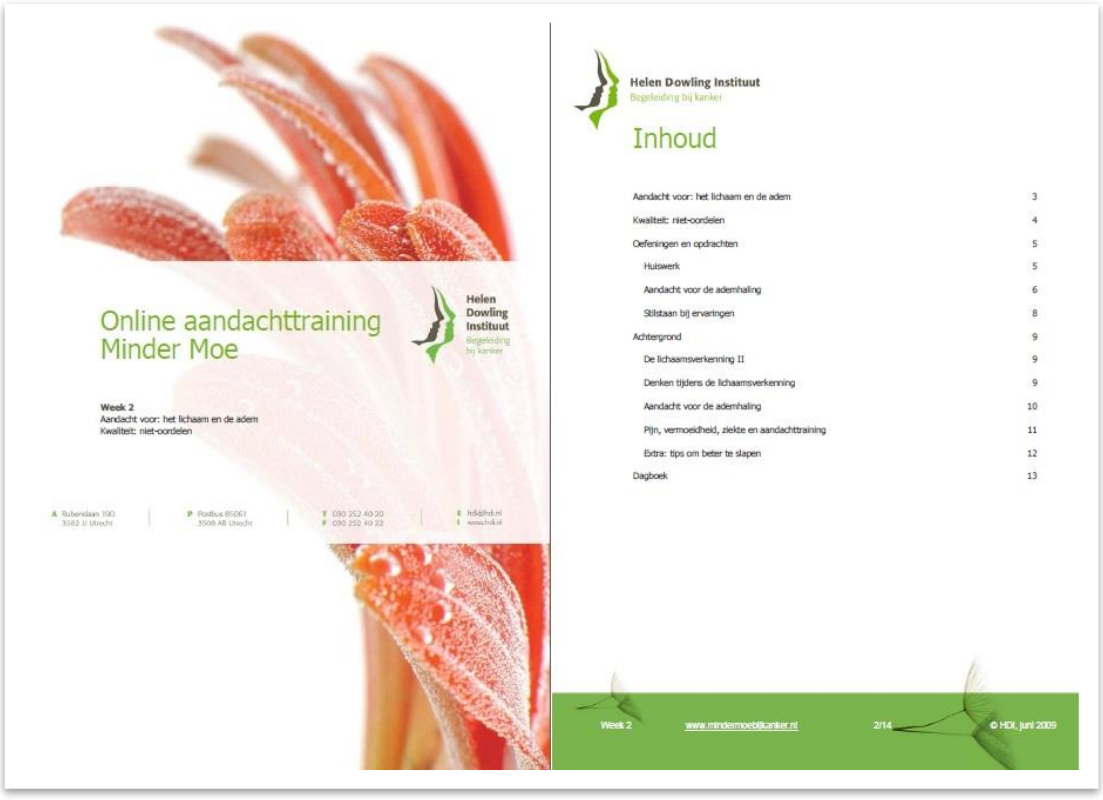


D.2

Figure D.1 and D.2. Patients could log in on their personal password-protected webpage (D.1). where patients were introduced to the new mindfulness theme by their therapist (D.2).

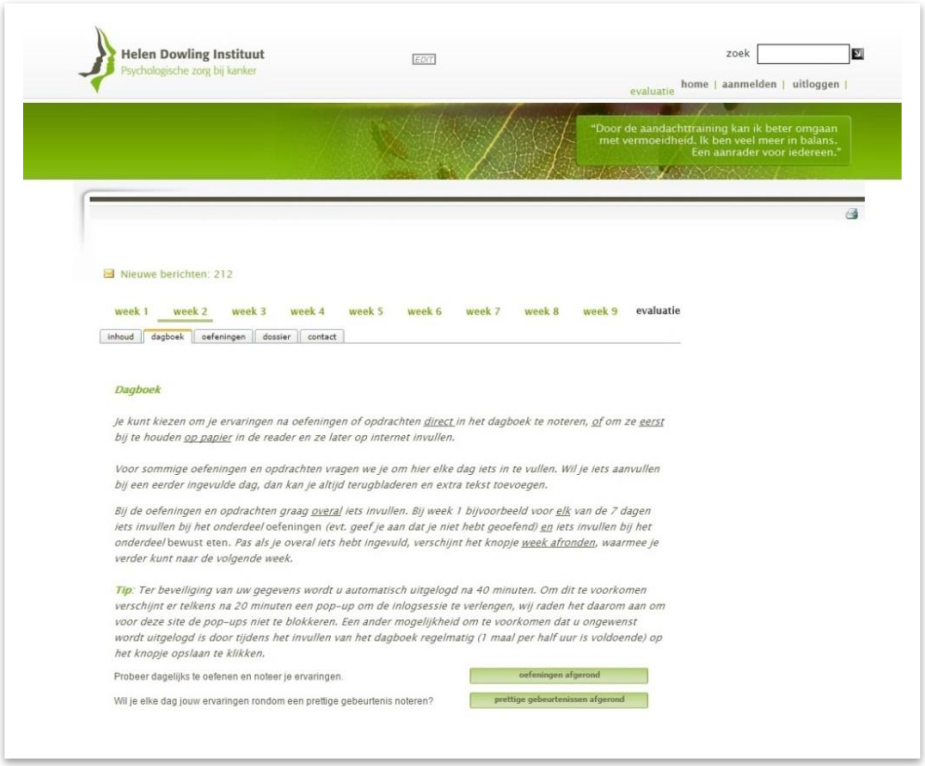


D.3

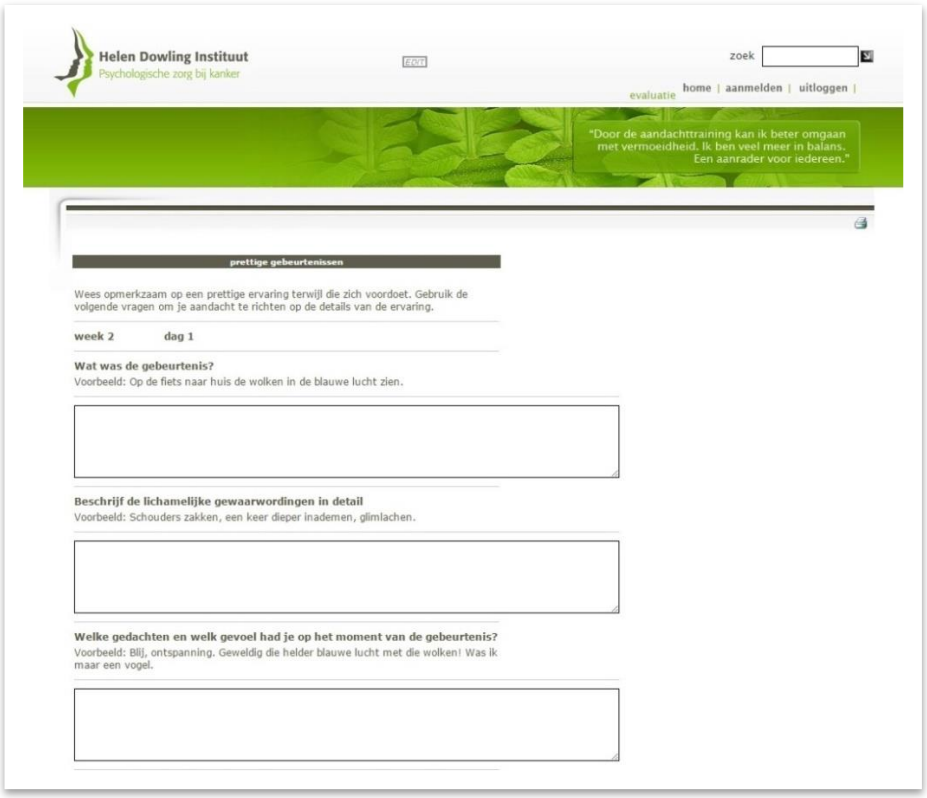


D.4

Figure D.3 and D.4. Patients downloaded mindfulness audio files (D.3), and downloaded written information following the specific mindfulness theme of the week (D.4).



D.5



D.6

Figure D.5 and D.6. On their personal log on their webpage, patients wrote down their experiences after doing the mindfulness exercises and reading the weekly information. On an agreed day of the week, the therapists replied to this log, thereby guiding the patients through the nine-week program.

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Chapter 3

Effectiveness, Mediators, and Effect Predictors of Internet Interventions for Chronic Cancer-Related Fatigue: The Design and an Analysis Plan of a 3-Armed Randomized Controlled Trial

Based on:

Wolvers, M.D.J., Bruggeman-Everts, F.Z., Van der Lee, M.L., Van de Schoot, R. & Vollenbroek-Hutten, M.M.R. Effectiveness, Mediators, and Effect Predictors of Internet Interventions for Chronic Cancer-Related Fatigue: The Design and an Analysis Plan of a 3-Armed Randomized Controlled Trial. *J. Med. Internet Res. - Res. Protoc.* **4,** e77 (2015)

Abstract

Background: Internet interventions offer advantages that especially cancer survivors who suffer from fatigue could benefit from. Given the growing number of such patients, Internet interventions could supplement and strengthen currently available health care.

Objective: This paper describes the design and analysis plan that will be used to study 2 Internet interventions aimed at reducing severe fatigue in cancer survivors: a mobile ambulant activity feedback therapy supported through a weekly e-mail by a physiotherapist and a weekly Web- and mindfulness-based cognitive therapy supported online by a psychologist. The data resulting from this trial will be used to (1) investigate the effectiveness, (2) investigate potential mediators of these interventions, and (3) explore participant characteristics that can predict the effect of these interventions.

Methods: A 3-armed randomized controlled trial is proposed that compares both Internet interventions with an active control condition that solely consists of receiving psycho-educational e-mails. The intervention period is 9 weeks for all 3 conditions. Six months after baseline, participants in the control condition can choose to follow 1 of the 2 experimental Internet interventions. Outcomes are measured in terms of fatigue severity, mental health, and self-perceived work ability. All are Web-assessed at baseline, 2 weeks after the intervention period, and at 6 and 12 months after baseline. Fatigue severity, mindfulness, physical activity, expectations and credibility of the intervention, therapeutic working alliance, sleep quality, and sense of control over fatigue are assessed 3 times during the intervention period for identifying mediators of the interventions. Recruitment is performed nationally throughout the Netherlands through patient organizations and their Web sites, newspapers, and by informing various types of health professionals. All participants register at an open-access Web site. We aim at including 330 cancer survivors who have finished curative-intent cancer treatment at least 3 months previously, and have been suffering from severe fatigue ever since. All cancer types are included. A detailed analysis plan is described to address the research questions, which allows for individual variation, and fully exploits the longitudinal design.

Results: Recruitment started in April 2013 and will proceed until April 2015.

Conclusions: This paper describes a systematic trial design for studying 2 different interventions for chronic cancer-related fatigue in order to gain insight into the effectiveness and mediators of the interventions. This design will also be used to identify predictors for the interventions' effect on fatigue. By publishing our hypotheses and analysis plan before completion of data collection, this paper is a first step in reporting on this trial comprehensively.

KEYWORDS: fatigue; cancer survivors; chronic disease; Internet interventions; mindfulness-based cognitive therapy; motor activity; behavior therapy; accelerometry; effect predictors; mediation; Bayesian statistics; latent growth analysis.

Introduction

Background

Behavioral interventions have shown to effectively relieve psychological and physical complaints in cancer survivors. However, the effect on the individual is less explicit, because patients differ greatly in the ways they experience and respond to such interventions. Therefore, when studying such an intervention, individual differences and temporal aspects need to be appreciated. This paper presents a detailed analysis plan for studying behavioral interventions that satisfies such needs.

The protocol of a 3-armed randomized controlled trial is described to study the effectiveness, mediators, and effect predictors of 2 different Internet interventions that share the same aim: reducing fatigue for cancer survivors. Due to its longitudinal design and multiple assessments during the intervention, the temporal development of relevant factors rather than pre-post differences can be studied. Latent growth analysis can be performed and mixture models can be run, which allow for individual variance in growth trajectories. Furthermore, full longitudinal mediation analyses can be performed on the most important potential mediators of both interventions, and differentiating effect predictors can be identified in order to allocate individuals to the most suitable intervention.

The goal of this paper is to present our trial design, hypotheses, and analysis plan. This paper will therefore be the basis for a number of papers that will present the results of the trial. We

will first provide brief background information on the research population, the relevance of Internet interventions for this population, and introduce the 2 Internet interventions that are the subject of this trial. Next, the importance of identifying mediating and predicting factors for the intervention effect is discussed. In the remaining sections, we give a detailed description of the trial's design, our hypotheses, and the analysis plan for handling the data that the trial will collect. The analysis plan is written in general terms, in order to facilitate the use of this strategy in other contexts, and to keep this paper focused. Consequently, the extended background of—and reasoning for—the specific hypotheses will be presented in future papers that will focus on the results of the proposed analyses.

Chronic fatigue and cancer

Cancer-related fatigue is defined as "a persistent, subjective sense of physical, emotional and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity, and interferes with usual functioning" [1]. It is one of the most prevalent and distressing long-term consequences of cancer [2], interferes with the activities of daily living, work ability [3] and maintenance of social relations, and consequently impacts patients' well-being [4]. As the number of cancer survivors in the Netherlands is expected to increase rapidly, with a growth of 50% in the 10-year prevalence between 2009 and 2020 [5], there is a strong need for effective and accessible treatments.

The etiology of cancer-related fatigue probably involves the deregulation of several interrelated physiological, biochemical and psychological systems [6]. There is no definite somatic explanation for the persistence of fatigue after cancer [7–9], and estimates of the proportion of cancer survivors who suffer from persistent fatigue vary widely [8,10]. However, research has shown that if fatigue continues three months after treatment, it is unlikely to decrease of its own accord [8]. The term chronic cancer-related fatigue (CCRF) will be used in this paper for severe fatigue that sustains for three months or longer after completing cancer treatment.

Management of chronic cancer-related fatigue

Currently, both pharmacological treatments and non-pharmacological treatments are applied to the effective management of CCRF; see the overview articles published by Ahlberg et al. [9] and Koornstra et al. [11]. Guidelines state that if no primary association can be found for

the persistence of fatigue with a somatic condition, behavioral interventions should also be considered [1]. The previously reported effects of non-pharmacological interventions on fatigue vary widely, as can be seen in the overview of recent meta-analyses in Table 1. Effect sizes tend to be higher when the intervention targets fatigue, and when increased fatigue was an inclusion criterion for the study. Not all studies that were included in the meta-analyses primarily targeted fatigue, therefore effect sizes might not be representative for nonpharmacological interventions that target fatigue.

Table 1. Ten recent meta-analyses considering non-pharmacological interventions for cancer patients that included off-treatment fatigue

***Meta*-analyses (off treatment)**	**Intervention type**	**ES (95% CI)**	**Fatigue reduced (*P*-value)**
Jacobsen 2007 (*k* = 4%)	Psychological	*d* = 0.10 (0.02 – 0.18)	Yes (<.05) [12]
Jacobsen 2007 (*k* = 29%)	Activity-based	*d* = 0.05 (-0.08 – 0.19)	n.s. [12]
Kangas 2008 (100%)	Psychological	WMES (r) = 0.51 (0.10 – 0.92)	Yes (.015) [13]
Kangas 2008 (100%)	Exercise	WMES (r) = 0.13 (-0.77 – 1.02)	n.s. (.784) [13]
Speck 2010 (100%)	Exercise	WMES (r) = 0.54 (0.19 – 0.90)	Yes (.003) [14]
Brown 2011(*k* = 54%)	Exercise	WMES (r) = 0.31 (0.22 – 0.40)	Yes [15]
Duijts 2011 (n = 31%)	Behavioral techniques	SMD (f) = 0.16 (0.08 – 0.23)	Yes (<.001) [16]
Duijts 2011 (n = 42%)	Exercise	SMD (r) = 0.315 (0.10 – 0.53)	Yes (.004) [16]
Cramp 2012 (100%)	Exercise	SMD = 0.37 (0.18 – 0.55)	Yes [17]
Tomlinson 2014 (100%)	Exercise	SMD (r) = 0.61 (0.33 – 0.88)	Yes [18]

Abbreviations: ES = Effect size; values are positive when the intervention was able to reduce fatigue more compared to the control condition. *k* = percentage of studies, *d* = Cohen's *d*, WMES = weighted means effect size, r = random effects, SMD = standardized mean difference, f = fixed effects, n = percentage of participants, n.s. = non significant.

Behavioral interventions are often based on energy balance models and/or stress coping models [12,19]. In energy balance models, CCRF is seen as a consequence of deconditioning and prolonged inactivity during cancer and its treatment. Secondary fatigue arises as a result of detraining and can lead to a downward spiral. In stress coping models, CCRF is conceptualized as a result of ineffective coping strategies and prolonged stress response [20]. Cognitive behavioral treatments that are based on these theories include physical activity interventions, exercise interventions [14,17,21,15,22], and mindfulness-based cognitive interventions [23–26] and have been shown to help reduce CCRF in previous studies [12,13]. However, all these interventions require the patient to travel to a health care facility, which can be a burden to the patient. Therefore, introducing effective interventions in a home-based setting could improve the health care options for this group.

Potential benefits of Internet interventions

Internet interventions offer advantages that cancer survivors who suffer from fatigue could especially benefit from. They have been found to be as effective as face-to-face therapies for a wide range of disorders, such as posttraumatic stress disorder, burnout or chronic stress, and depression [27–32]. Internet interventions have the ability to reach a wider range of patients compared to face-to-face interventions, especially severely fatigued patients, those with limited mobility, or patients in rural or even remote areas. Also, patients may benefit from the home-based setting of Internet interventions as these patients can practice more often, are less bound to the availability of care professionals, and can incorporate the intended behavioral change directly into their daily routine. Moreover, visiting a health care facility may no longer be desirable for some cancer survivors due to negative associations with the disease process or because they no longer want to be identified as a cancer patient and prefer the anonymity of their own environment.

Internet interventions for fatigue

Overview

In the Netherlands, to our best knowledge there are currently three Internet interventions that aim to reduce chronic fatigue: (1) an experimental mobile intervention aimed at changing physical activity behavior for participants with chronic fatigue syndrome [33], (2) the Web-based mindfulness-based cognitive therapy “Minder Moe Bij Kanker” [34], and (3) a Web-

based cognitive behavior therapy for severely fatigued breast cancer survivors, which is the subject of the current CHANGE study (trial registration NTR4309) [35].

This paper describes the design and analysis plan that studies the first two of these Internet interventions in a randomized controlled trial. Each of these two interventions is described below.

Mobile activity management intervention: ambulant activity feedback therapy (AAF)

The ambulant activity feedback therapy (AAF) is a mobile intervention that utilizes an ambulant activity coaching system, supported weekly by a physiotherapist through e-mail [33]. The activity coaching system has been developed by Roessingh Research and Development (Enschede, The Netherlands) and consists of a smartphone and an accelerometer (Appendix A) that communicate through BlueTooth [33].

In this intervention, the patient works to meet personal activity goals and subgoals that will be defined together with the therapist. The coaching system supports this process by showing real-time feedback about the accumulated activity of the patient relative to a personalized line of reference and tailored hourly feedback messages. Both the line of reference and the set of feedback messages of the activity coaching system can be adjusted by the therapist through a Web portal (see Appendix B). Patients also have access to a Web portal where they can monitor their past personal activity records. Consequently, patients are expected to gain insight in their activity pattern and on how to increase or balance their daily activity in a way that improves their energy levels. More information is given in Wolvers and Vollenbroek-Hutten [36].

Web-based mindfulness-based cognitive therapy: eMBCT

Mindfulness-based cognitive therapy (MBCT) adds elements of cognitive therapy to the mindfulness-based stress reduction program that was originally developed by John Kabat-Zinn [37]. The Helen Dowling Instituut (Bilthoven, the Netherlands) developed a nine-week Web-based, therapist-guided, individual MBCT (eMBCT) specifically designed to reduce CCRF [23]. On a personal Web-page, (see Appendix C), each patient can download audio files with mindfulness exercises and read information about a specific mindfulness theme each week. Patients write down their experiences of following the mindfulness exercises in a

log. On an agreed day of the week, the therapist replies to this log, thereby guiding the patient through the program. It is hypothesized that by learning to raise awareness of the present experience non-judgmentally and openly, the patient can become aware of potentially ineffective coping strategies that prolong stress and fatigue [38,39]. Patients learn to use a detached perspective as a skill to prevent the escalation of automatic negative thinking patterns. MBCT also teaches patients how to accept fatigue, physical limitations, or pain. The protocol of the eMBCT is discussed more extensively in the article by Bruggeman-Everts et al. [34].

Effectiveness

Our primary question is whether both interventions are effective in reducing fatigue. Therefore, both interventions will be compared to an active control group in a randomized controlled trial. The advantage of this design, as compared to a waiting-list control group, is that we can control for non-specific influences of the trial, such as receiving attention. Also, we expect that in an active control group, fewer participants drop out than in a waiting-list control group.

Usually, results of interventions are presented in terms of an average improvement of the relevant outcome measure. However, practice shows that individuals benefit differently from interventions [41]. Therefore, the proposed trial will aim to identify individual fatigue trajectories, since that seems to be more informative and helpful in improving health care provisions for CCRF-patients than just presenting averages.

Mediators

To optimize interventions in terms of efficiency and effectiveness, treatment-specific and nonspecific working mechanisms should be identified that account for each intervention's effect on fatigue. Knowledge about these mechanisms is an important prerequisite for improving the efficiency of interventions by shifting focus or shortening the intervention. Also, effectiveness can be increased by improving and tailoring the relevant items, subjects, or exercises, as well as improving the way these are embedded in the intervention. Therefore, the second objective of this study will be to identify the working mechanisms underpinning the interventions.

By using a three-armed randomized design, it is possible to study both treatment-specific (differentiating) and nonspecific working mechanisms. Also, by assessing important factors multiple times during the intervention, important time-specific information can be acquired.

Effect predictors

Although we expect that, in general, both interventions are effective, personal factors, medical factors, and demographics may determine the effect that each intervention has on fatigue [41]. We do not expect all individuals to benefit similarly from the interventions. Therefore, studying potential predictors of each intervention's effect will give us important input to inform both patients and caregivers and allow them to set reasonable expectations.

CCRF has a multifactorial character (eg, physical, cognitive, motivation); therefore, studying the effect predictors of two theoretically differing interventions simultaneously, might also reveal differentiating predictors for both therapies. By applying such knowledge carefully, the overall effectiveness of interventions that aim to reduce CCRF can be increased.

Methods

Design

A randomized controlled trial is performed including 3 parallel conditions: 2 experimental conditions (AAF and eMBCT) and a minimal intervention control condition. The intervention period is 9 weeks for all 3 conditions. Both experimental conditions are made as similar as possible in terms of time-investment and contact intensity with the therapist. Outcomes are self-reported and are Web-assessed at baseline (T0), 2 weeks post-intervention (T1), and at 6 months (T2) and 12 months (T3) after baseline. Figure 1 shows a schematic summary of the trial design.

The baseline assessment consists of 3 time-points: (1) T0a, the assessment to check eligibility; (2) T0b, the main baseline assessment taken after the eligibility check and informed consent, but naive of condition; and (3) T0c, directly after randomization for assessing the participant's credibility and expectancy about the condition. All participants are invited to fill out short questionnaires in weeks 1, 2, 3, 4, 6, and 9 (Mi) of the intervention period in order to study mediation of the interventions.

After T2, patients in the control condition are offered 1 of the 2 experimental interventions, again in a research setting. Please note that the first 4 participants of this trial were randomized to 1 of the experimental conditions for the second semester, but to minimize dropout, all other patients will be allocated based on their own preference. During this second intervention period, these participants will again be assessed in weeks 1, 2, 3, 4, 6, and 9 (Mi'), the second week after the intervention (T1'), and 6 months after the second allocation (T2'). Participants in the control condition that are preferentially allocated to eMBCT after T2 do not wear the accelerometer during the second semester. The protocol allows delay within the intervention period of a maximum of 2 weeks in case of, for example, illness or holiday. For all participants, the duration of their participation is approximately 12 months. Additional qualitative feedback will be obtained through explorative interviews with a subset of participants in the experimental condition shortly after T1 or T1'.

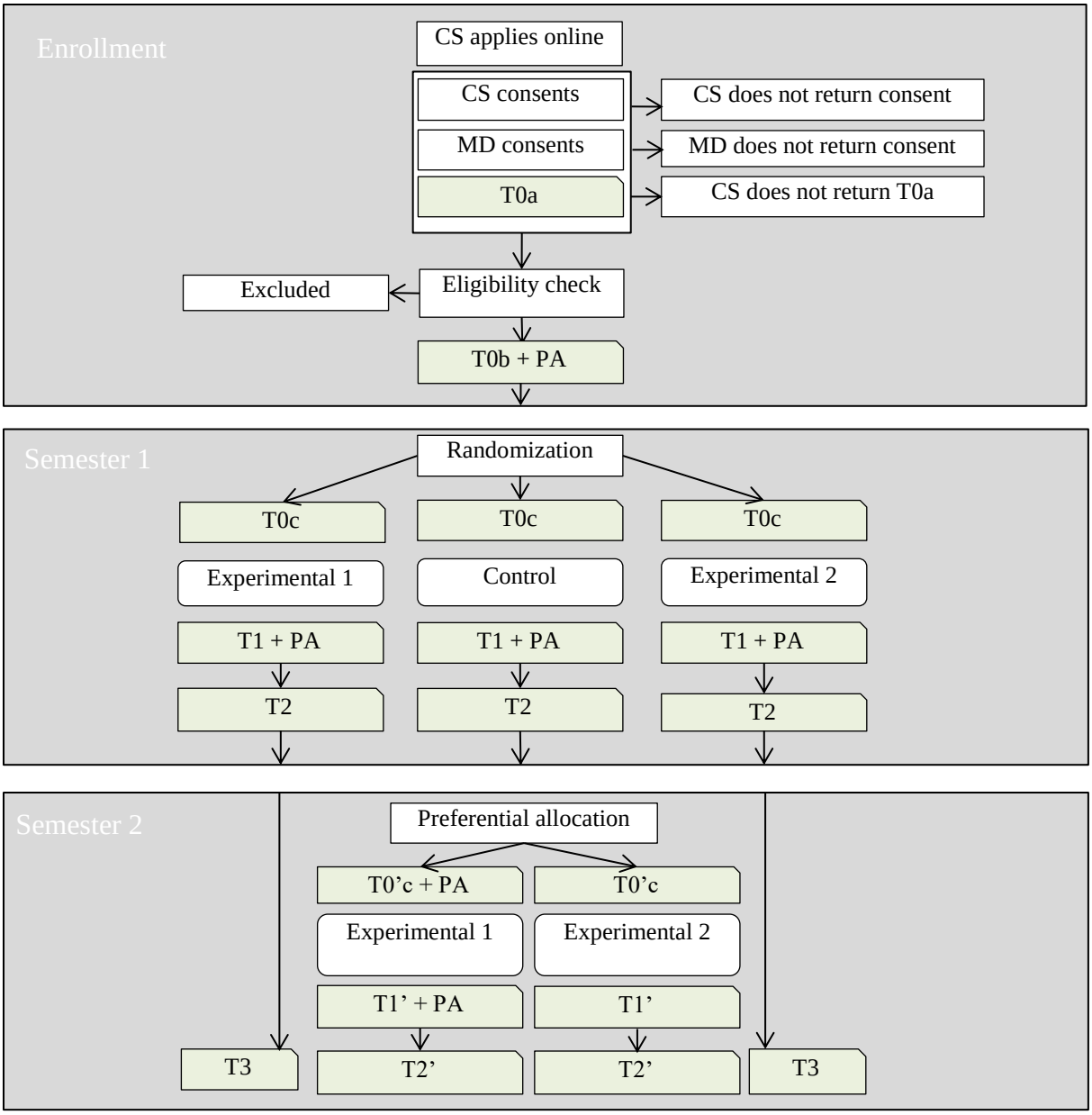


Figure 1. Flow chart of trial design. CS (cancer survivor), MD (medical doctor), PA (physical activity). T0(a-c)-T3 are the main assessments. Mi and Mi´ represent assessments in week i =1,2,3,4,6,9 of the intervention. For addressing the primary research questions on effectiveness, only data from the first semester will be used. *Abbreviations*: Mi = assessments in week 1,2,3,4,6, and 9 of the intervention; PA = physical activity; PANAS = positive and negative affect scale; T0 = baseline assessments; T1 = post-intervention assessment; T2 = follow-up assessment 6 months after randomization; T3 = follow-up assessment 12 months after randomization.

This trial was approved by the Twente Medical Ethical Committee (Enschede, the Netherlands) under number P12-26 and has been registered at The Netherlands National Trial Register under number NTR3483 [42].

Study sample

Recruitment

Participants are recruited in the Netherlands by advertisements in the newsletters of patient associations (both digital and hard-copy), on relevant websites, in regional newspapers, and through social media. Furthermore, participants also are recruited through oral presentations given to cancer patients and in other cancer-related seminars and symposia for patients, care-givers, or both.

Social media and online advertising can be strong tools for reaching a large group of people [43] or even specific patients [44,45]. However, the sample might be younger, more highly educated, and might comprise more females compared to the Dutch CCRF population [46]. However, it will lead to a sample that represents the targeted population for such Internet interventions, and we are likely to include participants who would not have opted for therapy that includes traveling to a health care facility.

Eligibility

The following criteria are used to check eligibility for participation in the trial:

- Completion of a curative-intent treatment for cancer at least three months ago (checked by participant's medical doctor). For this study, surgery, chemotherapy, radiotherapy, immunotherapy, and/or stem cell transplantation are considered treatment. However, the use of anti-inflammatories, and monitoring visits are not considered treatment for this study.
- Patient has been suffering from severe fatigue for at least three months.
- Patients scores 35 or higher on the fatigue severity subscale of the Checklist Individual Strength.
- Aged 19 years old or older.
- At least 18 years old at disease onset.
- Capable of reading and writing in the Dutch language and of using the Internet (implicit eligibility criterion accounted for during registration, but not checked explicitly).

If patients meet one or more of the following criteria, they are excluded from participation:

- Indication of current disease or tumor activity (checked by participant's medical doctor).
- Current or former severe psychiatric morbidity, for example major depression, psychosis, or schizophrenia (checked by the participant's medical doctor).
- Being dependent on a wheelchair for daily activity (self-report).
- Recurrence of cancer during the course of the study (self-report).
- Current substance abuse, except for smoking.
- Previously attended the eMBCT of the Helen Dowling Instituut.

In addition to the mentioned exclusion criteria, please note that:

- Mild depression is not an exclusion criterion. A score of 20 points or higher on the Hospital Anxiety and Depression Scale (HADS) during baseline is considered indicative of depression [47]. Therefore, if the patient scores 20 points or higher, he or she will be contacted by a psychologist from the Helen Dowling Instituut to determine whether the participant has suicidal ideation or suffers from other severe psychiatric morbidity. A participant will only be excluded if, according to the involved psychologist, that is the case.
- Comorbid somatic diseases – such as cardiovascular diseases, cerebrovascular diseases, diabetes, hypertension, and arthritis that are not treatable but are a possible cause of fatigue – are not exclusion criteria but will be registered during the study. Although this choice will probably lead to an underestimated effect size compared to studies that do exclude patients with comorbidities, we expect that such a sample will lead to a better representation of the CCRF population.
- Participants are requested not to take part in any other therapy directed at overcoming fatigue during the study.
- Data of participants who report pregnancy or recurrence of cancer during the course of the study will be excluded from analysis since the fatigue they experience cannot be considered to be of a chronic character according to our definitions. However, if requested, these patients will be allowed to finish the intervention.

Procedures

Participants apply for inclusion in the study at the project website [48,49].

Informed consent

After online registration, participants receive the patient information and informed consent form by direct mail. They are requested to sign and return the informed consent in a prepaid envelope. Also, they receive a registration confirmation by email with login details for the participant's Web portal on the project website. Participants are requested to complete assessment T0a as a check on eligibility. Also, the participant's medical doctor is consulted to check three of the eligibility criteria: finished curative-intent treatment for cancer more than three months ago, no current signs of cancer activity, absence of current or former major psychiatric disease.

Randomization

If the eligibility-criteria are met, the researcher confirms the participant's enrollment. Subsequently, the activity sensor is given to the participant and its setup is explained in a face-to-face meeting in the participant's home or another mutually convenient location. The second baseline assessment starts (T0b), followed by randomization of the participant to 1 of the 3 conditions by a script embedded in the researchers' Web portal and uses the random function of php (rand(1,3)) [50]. The researchers can neither influence nor predict the outcome of the randomization process. Subsequently, the researcher emails the participant about the outcome of randomization, requests the participant to complete the third baseline assessment (T0c), and assigns the participant to a therapist in case the participant has been randomized to an experimental condition. Participants who do not fill out T0c are considered as not being included. The allocation of a therapist is based on current availability of the therapists who are involved in the trial.

Research conditions

Both experimental conditions are described in the Introduction and will be described more extensively in an article on eMBCT by Bruggeman-Everts et al. [34], and a paper on the development of the AAF intervention by Wolvers and Vollenbroek-Hutten [114].

Active control condition

Patients who are assigned to the control condition receive weekly emails containing standard psycho-educational texts about CCRF in order to minimize the dropout rate, following the design of Postel et al. [51]. An example of the information that is offered in this minimal

intervention control condition is given in Appendix D and overlaps completely with the information that is given during both experimental interventions. This condition controls for receiving information on CCRF and for being involved in eHealth research.

Non-adherence and withdrawal

Participants who do not adhere to, or withdraw from, the study or the intervention are contacted by phone and asked for the reason for nonadherence or withdrawal. Participants who want to stop with the intervention are asked to complete a post-intervention assessment at T1 and follow-up assessments at T2 and T3. Participants who withdraw from the study are asked to answer the questions of the fatigue severity subscale of the CIS online or during a telephone conversation.

Assessments

All self-reported questionnaires are Web-assessed via a Web portal on the project website [48,49], developed by Roessingh Research and Development. Participants receive an email when an assessment becomes available and can log in to the Web portal to complete the questionnaires. During the intervention period, each assessment is available for 1 week, but can stay open longer if therapy is postponed due to, for example, illness or holiday. If a participant has not completed it within 6 days, he or she is reminded by email at least once to complete the questionnaire. Within each assessment, the questionnaires are grouped on the basis of importance and subject. Item sequences of the questionnaires for the mediating factors and outcome measures differ between the assessments. Personal data is stored separately from the research data. An overview of all the assessments is shown in Tables 2 and 3.

Physical activity data is collected using the same device as that used for the ambulant activity feedback therapy: a 3D-accelerometer (ProMove 3D) combined with a mobile phone that collects the accelerometer data and sends it to a secured Web server at Roessingh Research and Development [52]. However, the mobile phone does not give feedback on activity, but does state whether the system is working properly and sends an error message if the connection to the sensor fails. Participants are reminded by email to wear the accelerometer on the day before the start of the week in which they will be using it.

Outcome measures

Fatigue

Fatigue severity will be assessed with the CIS, which consists of 20 items that score on a 7-point Likert scale [53,54]. The CIS has 4 subscales (fatigue severity, motivation, concentration, and physical fatigue) of which the fatigue severity subscale will be used as the primary outcome (8 items, range: 8–56 points). The CIS has shown good discriminative validity in a working population [55], is sensitive to changes in the chronic fatigue syndrome population [56], and has previously been used with cancer survivors [7,57]. The CIS strongly resembles the Multidimensional Fatigue Inventory, which is often used in international studies [54]. Fatigue severity will be assessed at T0a, T0b, M3, M6, M9, T1, T2, and T3. However, the other three subscales will only be assessed at T0b, T1, T2, and T3.

Mental health

Mental health will be assessed from the results of two questionnaires: the Positive and Negative Affect Scale (PANAS [113]) and the Hospital Anxiety and Depression Scale (HADS [58]), both of which are included in an item bank for cancer survivors [59]. The PANAS consists of 20 items that score on a 5-point Likert scale and has 2 subscales: positive and negative affect. The HADS consists of 14 items on a 4-point scale, has been validated for a Dutch-speaking population [60], and has previously been used to assess psychological distress in cancer patients [61]. Mental health will be assessed at T0a, T1, T2, and T3.

Perceived ability to work

The work ability score, which is assessed with the first question of the work ability index [62,63], will also be used as an outcome parameter. It asks: “Imagine that your working ability in the best period of your life is rated 10 points. How would you rate your working ability at the present moment?”. It is assessed at T0b, T1, T2, and T3.

Working hours and the level of absenteeism are assessed with questions from the Trimbos and iMTA questionnaire on costs associated with psychiatric illness (TIC-P) [64]). These will be assessed at T0b, T2, and T3.

Table 2. Assessments of outcome measures and potentially mediating factors.

Parameter	**Primary outcome**	T0*	M_i/M_i'	T1/T1'	T2/T2'	T3
Fatigue severity	*Checklist Individual Strength;* subscale fatigue severity: 8 items on a 7-pt. Likert scale.	a, b	3,6,9	x	x	x
	Secondary outcomes					
Other dimensions of fatigue	*Checklist Individual Strength*; physical and cognitive fatigue and motivation subscales: 4 items for each subscale, all on a 7-pt. Likert scale.	b		x	x	x
Affect	*Positive And Negative Affect Scale:* 20 items on a 5-pt. Likert scale.	a		x	x	x
Psychological distress	*Hospital Anxiety and Depression Scale*: 14 items on a 4-pt scale.	a		x	x	x
Self-perceived ability to work	*Work Ability score*: 1 item on a 0-10 numeric rating scale (NRS).	b		x	x	x
Return to work and working hours	Adapted questions of the *Trimbos and iMTA questionnaire on costs associated with psychiatric illness.*	b			x	x
	Primary mediating factors					

Mindfulness	*Freiburg Mindfulness Inventory short form* [65,66]: 14 items on a 4-pt Likert scale.	b	3,6,9	x	x	x
Physical activity	Accelerometry: ProMove 3D [52]. Both summative PA and daily PA decline will be considered.	b	3,6,9**	x		
Sleep quality	*Subjective Sleep Quality Scale* [67]:15 items (yes/no), and one self-conceptualized item (yes/no) that translates into: "Did you use sleep medication?"	b	3,6,9	x	x	x
Sense of control over fatigue	*Self-Efficacy Scale* [56]: 7 items on a 4-pt Likert scale.	b	3,6,9	x	x	x
Credibility and expectancy	*Credibility and Expectancy Questionnaire* [68]: 6 items of which 4 are on a 9-pt. Likert scale, and 2 items on a 0-100 NRS.	c/c'	1,2,4			
Working alliance	*Working Alliance Inventory short form* [69, 70]: 12 items on 5-pt scale, subscales: goal, task, bond.		1,2,4			
	Secondary mediating factors					
Perceived physical activity	Four self-conceptualized questions on perceived activity volume, comparative volume and satisfaction with volume.	b		x	x	x

Self-efficacy on activities	Selected items from the self-efficacy scales of Bandura [71] and Rodgers [72,73]: 13 items on a 0-100 NRS, subscales: planning and coping.	b		x		
Catastrophizing	*Fatigue Catastrophizing Scale* [74,75] 9 selected items on a 5-pt. Likert scale.	b		x		
Fear of cancer recurrence	Two selected items on a 7-pt. Likert scale [100].	b		x		
Causal attributions	One self-conceptualized open answer question that translates into: "What do you consider as the cause of your fatigue?"	b		x		

* Baseline assessment T0 consists of three time-points: T0a: before eligibility check; T0b: after inclusion and T0c: after randomization. T0c' is assessed after preferential allocation.

** All physical activity measurements are blind, except for the experimental activity feedback condition at M_3, M_6, and M_9. In the second semester, M_3', M_6', and M_9' do not include a physical activity measurement in the mindfulness condition. *Abbreviations*: NRS = numeric rating scale; pt = point; PA = physical activity; M_i and M_I' = assessments at week i (1,2,3,4,6,9) of the intervention.

Mediating factors

Several categories of mediators will be considered: intervention-specific mediators for either eMBCT (eg, mindfulness, catastrophizing, and fear of cancer recurrence) or AAF (eg, physical activity, perceived physical activity, and self-efficacy on physical activity), and generic mediators (eg, sleep quality, sense of control over fatigue, credibility, expectancy, working alliance, and causal attributions). Furthermore, a distinction is made between primary and secondary mediating factors: primary factors are assessed at multiple occasions during the intervention in order to study the timely development of those factors; secondary factors are not assessed during the intervention. A complete overview of all assessments on mediating factors is given in Table 2.

Demographics, medical history, and control factors

Several other factors are assessed, including demographics, medical history, and control factors. All are listed in Table 3.

Table 3. Other assessments.

Demographics, medical history, and control factors	**T0***	**T1/T1'**	**T2/T2'**	**T3**
Age, gender, education, family status, nationality, time since diagnosis, time since previous treatment, fatigue duration, psychological counseling in the past, comorbidity.	a			
Cancer type, cancer treatment, perceived life threat of cancer (7-pt. Likert scale), known heredity of cancer (yes/ no/ don't know), former experience with attention focusing exercise (yes/no), religious beliefs, perceived social support (*Multidimensional Scale of Perceived Social Support* [77]: 12 items on a 7-pt. Likert scale).	b			
Medication use, substance use (caffeine, nicotine, alcohol, drugs), quality of life (1 item on a 0 -10 numeric rating scale (NRS)).	a	x	x	x
Pain intensity and limitations by pain (2 items on a 7-pt. Likert scale), body mass index.	b	x	x	x
Life events since previous assessment, professional help received for fatigue outside the scope of the study protocol.		x	x	x
Perceived effectiveness of the intervention (5 items of which 1 item 0-10 NRS and 2 yes/no questions), perceived social support in following the intervention (1-10 NRS).		x		

Social desirability: 6 selected items from the *Balanced Inventory of Desirable Responding* [79] on 5-pt. Likert scale.			x	

Abbreviations: NRS = numeric rating scale; pt = point; PA = physical activity. *Baseline assessment T0 consists of three time-points: T0a: before eligibility check; T0b: after inclusion; and T0c: after randomization.

Analysis plan

Overview

SPSS software will be used for data management and Mplus [80], which is latent variable modeling program, for the subsequent analyses. The exact versions of the software used will be reported in the future papers.

Pre-analysis

Power analyses

The sample size for analyses for data relating to the primary objective has been calculated for a repeated measures analysis of variance: based on an alpha of .05, a minimal detectable effect size of $f^2 = .15$, and a power of .80, a total number of 55 participants [81] is required in each group to answer the primary research question of this study in a statistically valid manner.

We expect to be able to include 330 eligible participants within a period of 2 years, based on a mean of 3.7 intakes per week for the eMBCT of the Helen Dowling Instituut in 2011. An estimated attrition of 30% of the participants during both experimental interventions and 15% during the minimal intervention control condition [51] would leave us with 77 participants in each experimental group and 94 participants in the control group at T2. Again, we expect a dropout rate of 30% during the second semester. Such a dropout would leave a total of 110 participants completing each experimental intervention. Ten percent of the participants may have to be excluded from the analyses because of recurrence or diagnosis of metastasis. That would result in 198 participants that complete the full trial. We expect that this number will be enough for testing the 6 mediating factors or effect predictors: A classical, conservative power calculation (analysis of variance for testing 6 mediators or effect predictors with an intermediate effect size ($f^2 = .08$), corrected according to Bonferroni (alpha = .05/6), and at a power of .80 [81]) would result in approximately 254 participants being needed. We expect

that the actual power when including 198 participants, and not the required 254 participants, will be great enough to detect up to 6 mediators or effect predictors with the use of Bayesian statistics [76]. Bayesian statistics allow analysis on small sample sizes [76,77], as more power can be generated with the use of prior information which is incorporated in the model that is being tested. Various papers describe comparisons between traditional null hypothesis testing and Bayesian estimation [82-85]. For this study, prior knowledge is available for many parameters, such as the effects of mindfulness in cancer survivors [23,25,66,86] and the role of working alliance in online interventions [87]. Examples of these methods can be found in both applied psychology and social science articles [88-92].

Missing data handling

Missing data will be analyzed considering their pattern and randomness following guidelines proposed by Schafer and Graham [93]. Bias due to systematic missing data will be managed according to guidelines proposed by Asendorpf et al. [94].

Descriptives

Quantitative analyses will be conducted on an intention-to-treat basis. A flow diagram following the CONSORT guidelines will be included. Descriptive statistics will be calculated and presented. Independent samples' t-tests and χ^2 tests will be performed to check for baseline differences between the respective experimental conditions and the control condition with respect to demographic variables (eg, family status, age, gender, and level of education), time since end of treatment, and baseline levels of the outcome variables. If we find statistically significant differences in the mean of fatigue severity across baseline descriptives, dummy variables will be added to the model as covariates to control for these differences.

Core analysis

Effectiveness

Overview

Five steps will be taken to evaluate the effectiveness of both interventions, which are explained here in a generic way. The specific hypotheses on the effectiveness of the interventions in our study are shown in Textbox 1.

Box 1. Hypotheses on effectiveness

Primary outcome

In both experimental conditions,

- fatigue severity
  - decreases during the intervention, and
  - remains decreased after 6 months,
- after 6 months, fatigue severity has decreased significantly more compared to the control condition.
- after 6 months, more participants show a clinically relevant reduction of fatigue severity compared to the control condition. A patient is considered clinically improved if he or she has a reliable change index of more than 1.96, according to the reliable change index, and the end score has to be within the normal range, that is a score < 1 standard deviation above the mean of a normative group [95], i.e. a score < 30.4 on CIS fatigue severity [51].

Secondary outcomes

For both interventions we expect that:

- After 6 months, mental health and work ability have improved more than in the control condition.
- After 12 months, fatigue severity, work ability and mental health remain improved in both interventions groups.
- Improvements in mental health and work ability after 6 and 12 months are related to reductions in fatigue severity.

Return to work and reduced absenteeism will be studied as explorative outcomes.

Step 1

Overall effectiveness will be tested in an intention-to-treat analysis by a multiple group latent growth model [79] using data from the first semester. This technique allows individuals to have an individual growth trajectory over time and compensates for missing data in an elegant way.

Since different growth patterns are expected for the pre-intervention period, the intervention period, and the post-intervention period, we will apply piecewise growth modeling so that a slope factor will be estimated for each of the 3 periods (Figure 2). Initial intercepts will be

configured to represent the T0b score. This intercept and the pre-intervention slope factor will be constrained to be equal between all three conditions (and this assumption will be checked), whereas the subsequent slope factors will be estimated separately for the three conditions.

The fit of the piecewise model will be compared with a quadratic model. In the quadratic model, the entire first semester is modeled with one slope factor and one quadratic factor for each of the three conditions and an intercept that represents T0b and is constrained similarly to the piecewise model.

Both models will be run both with and without using time-varying loadings in order to check whether corrections should be made for differences in timings between the questionnaires. Growth factor estimates and model fits for all four models will be reported (Table 4).

Table 4. Growth factor estimates of four different latent growth models.

	Fixed loadings	**Time-varying loadings**
Piecewise, linear	Mean: I, S(pre), S(int), S(post) Variance: I, S(pre), S(int), S(post)	Mean: I, S(pre), S(int), S(post) Variance: I, S(pre), S(int), S(post)
Quadratic	Mean: I, S, Q Variance: I, S, Q	Mean: I, S, Q Variance: I, S, Q

Abbreviations: I = intercept, S = linear slope, Q = quadratic slope.

Neither the participants nor the researchers (FBE and MW) are blinded to allocation. Therefore, an independent statistician (RvdS) who is blind to the allocation will test the primary hypothesis.

The same procedure will be followed for the secondary outcomes, except that the initial intercept of mental health will represent T0a, rather than T0b, because T0b does not include an assessment of mental health.

Results of frequentist analyses will be reported by *p*-values (significant in case < .05) and with 95% confidence intervals. Parameter estimates of models by means of Bayesian estimators will be reported with 95% central credibility intervals.

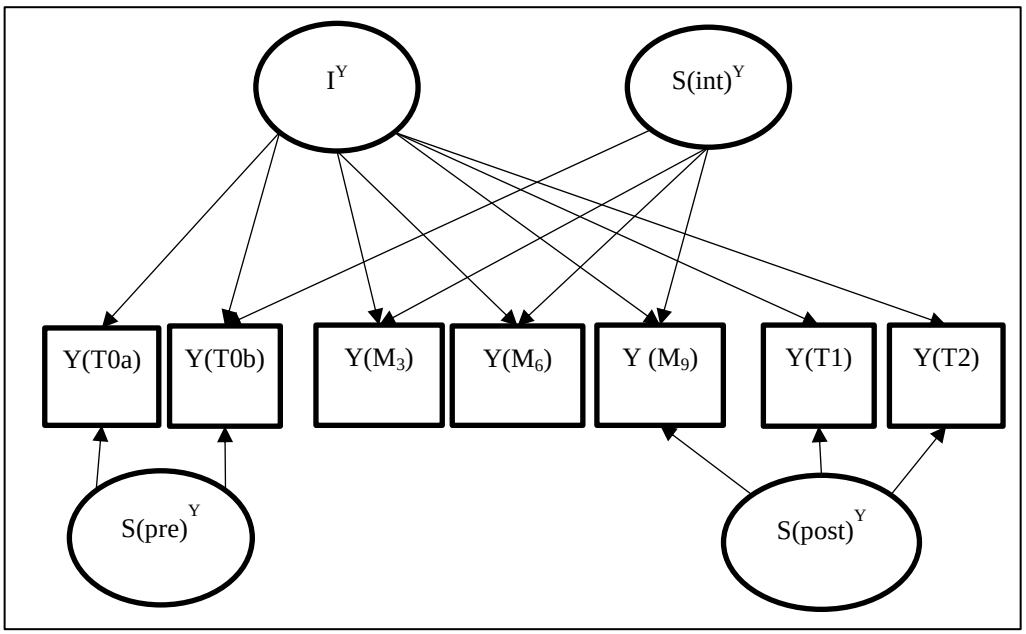


Figure 2. Simplified representation of a piecewise linear latent growth model, with latent intercept factor (I^Y), latent slope factors pre-intervention ($S(pre)^Y$), during the intervention ($S(int)^Y$), and post-intervention ($S(post)^Y$), and seven indicators Y. Error terms, correlation coefficients, and covariances are left out.

Step 2

The effect size of both experimental interventions will be calculated according to recommendations in Feingold (2009) [96] for both primary and secondary outcomes.

Step 3

The proportion of participants who make clinically relevant progress on the primary outcome will be calculated for all three conditions; again, in an intention-to-treat analysis. Percentages and standard deviations of the reliable change index will be presented.

Step 4

A latent growth model will be built of the primary outcome, in which the outcome measures that have been measured at T3 will also be included, as distal outcomes of changes in the primary outcome during the first semester.

Step 5

A growth mixture model (GMM) will be used to further explore differences between individuals, and more specifically to identify subpopulations (latent classes) with homogeneous growth trajectories of the primary outcome within the experimental groups. The Bayesian information criterion will be used for model selection [96].

If convergence considerations allow, this model will be adjusted to allow covariance of the growth factors in order to acknowledge individual variation around the estimated growth trajectories. The trace plots will be inspected to check whether the models have converged to global solutions and a set of diverse starting values will be used. For more information on these analyses, we refer to an introduction to GMM and latent class growth analysis by Jung and Wickrama [97] and examples of similar analyses in the field of Internet interventions [98] and cancer patients [41].

Mediators

Overview

The analysis of the mediators of the experimental conditions can be roughly subdivided into two steps: first analyze the primary factors individually for their longitudinal correlations with the outcome (Step 6), then combine the relevant factors in a multivariate analysis (Step 7). The specific hypothesis on the mediating factors of the interventions in this study are shown in Textbox 2.

Textbox 2. Hypotheses on mediators

We expect that, for AAF, increasing mean cumulative daily PA and reductions of daily PA decline are specific mediators.

We expect that, for eMBCT, developing mindfulness skills is a specific mediator.

We expect that sleep quality, working alliance, sense of control over fatigue, credibility, and expectancy are generic mediators for both e-therapies.

The mediating role of the following factors will be explored: number of sessions completed, changes in causal attributions [99], decreased catastrophizing thoughts about fatigue [8], decreased fear of cancer recurrence [100,101], changes in perceived activity [102], increased self-efficacy on physical activity [103].

Step 6

For analyzing the mediators of the experimental conditions, first we want to see whether there is a correlation between the growth trajectories of our outcome parameter and the potential mediator over time. The hypotheses considering mediators are shown in Textbox 2. The combined data from the participants in the first semester and data from the preferentially assigned participants in the second semester will be used.

The following subhypotheses will be tested for each primary mediator (these are also shown in Figure 3):

- Is the growth of the primary outcome (S^Y) for the entire study population correlated with growth of the potential mediator (S^Z)?
- Is such correlation independent of group?
- Does the potential mediator change over time in the specific group, so is the slope factor (S^Z) substantially unequal to zero?
- Is the slope factor in the specific group substantially greater than the slope factors in the other groups?

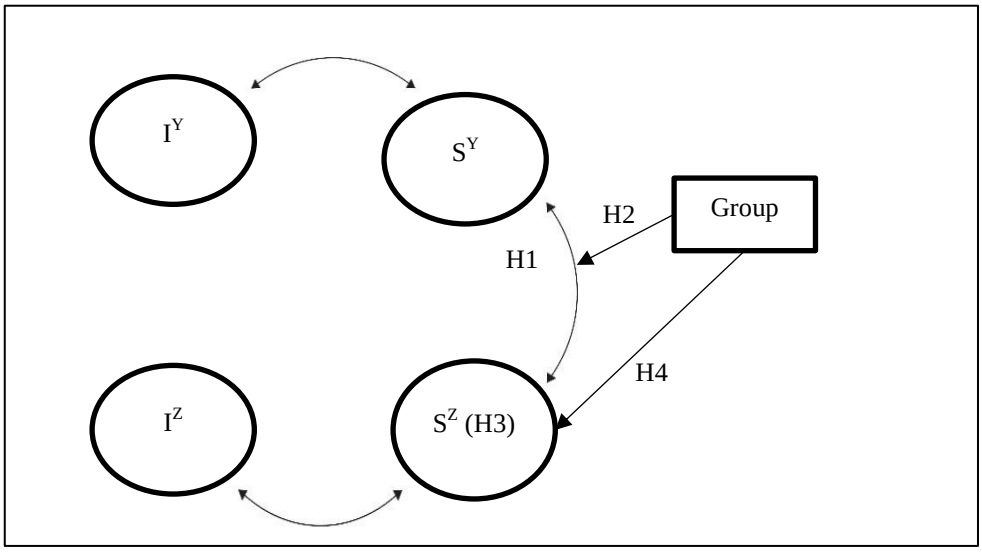


Figure 3. Strongly simplified representation of a correlated growth model in which I^Y and S^Y represent the intercept and slope factors of the latent growth model of the outcome parameter, and I^Z and S^Z represent the latent growth factors of the mediator. H1-4 represent the four sub-hypotheses of Step 6. All indicators have been left out for clarity.

In these 4 subhypotheses, the first is congruent with testing the "conceptual theory" in classical mediation analysis, and subhypothesis 3 with testing the "action theory." If

subhypotheses 1-4 all are true, the factor will be considered a specific mediator for that intervention. If subhypotheses 1, 2, and 3—but not 4—are true, the factor will be considered a general mediator for fatigue severity. If either subhypothesis 1 (conceptual theory) or 3 (action theory) is false, the factor will not be considered a mediator.

Step 7

The next step in studying potential working mechanisms is a single-step, multiple-mediation analysis using structural equation modeling [104-106]. By estimating such a model, we expect to obtain a comprehensive model for all the working mechanisms of the intervention. It should be noted that this model assumes that an intervention works in the same way for all participants in a particular group [107]. Again, data from both semesters will be used.

A separate model will be tested for each intervention. Each model will have the following paths (Figure 4), where X = independent variable (1/0 for specific intervention vs control group), Y = outcome variable (difference score T2-T0b of the primary outcome measure), and Z = mediator:

- *a*: X regressed on Z.
- *b*: Z regressed on Y;
- *c'*: direct effect of X on Y.

For each experimental intervention, the starting model will consist of all the significant primary mediators of Step 6 that have also been assessed in the control group. In other words, the factors that have shown to be mediators in the correlated growth model will be the starting point for this model. The models will then be complemented with the secondary mediating factors described of Textbox 2. Mediating factors for which the indirect effect (a × b) is insignificant will be removed stepwise, after which a final model will be created.

Model fit, standardized path coefficients - including indirect effects -, and the total effect of at least the first and final models will be reported with 95% confidence intervals.

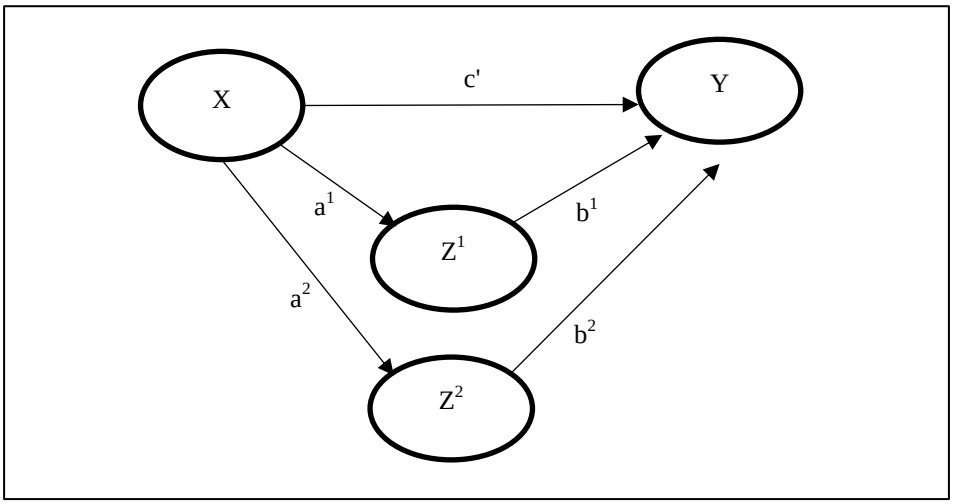


Figure 4. Multiple mediation model with independent variable (X), dependent variable (Y), and two mediators (Z). Direct effect (c'), and indirect effects (a x b) are shown.

Effect predictors

Overview

Two complementing approaches for analyzing the effect predictors are addressed in steps 8 and 9 of this analysis plan. The specific hypotheses on the effect predictors for both interventions in this particular study are shown in Textbox 3.

Textbox 3. Hypotheses on effect predictors

We expect that for AAF, low perceived physical activity predicts reduction of fatigue severity.

We expect that for eMBCT, low perceived concentration, previous experience with mediation exercises, high perceived life threat from cancer, and a high education level predict reduction of fatigue severity.

In general, we expect that low perceived social support, longer time since last treatment, suffering from more comorbidities [108], and having strong somatic attributions [57] predict small effects on fatigue severity in both interventions. We expect that high sense of control and good sleep quality predict large effects in both experimental conditions.

Other factors will be included for explorative research.

Step 8

To find out which participants benefit most from each intervention, the final model of fatigue severity of Step 1 will be extended with potential effect predictors (Textbox 3) that load on the latent growth factors "linear slope" (the "post randomization" linear slope in case of the piecewise model) and, if applicable, "quadratic slope". As the regression coefficients of all potential effect predictors on the development of fatigue severity will be freely estimated across the three intervention groups, this is also called a moderation effect of intervention.

Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

Step 9

To identify common effect predictors of homogeneous subpopulations within the heterogeneous population, rather than identifying effect predictors for individual growth patterns, the final step will consist of regressing predictors on latent classes. Therefore, the final model of Step 5, namely the unconditional GMM, will be extended. Again, several potential effect predictors will be regressed onto this model, but this time on the latent class factor, instead of on the latent growth factors. The three-step procedure proposed by Vermunt [109] will be used for model selection. This step will be carried out separately for each experimental condition.

Factor loadings of all hypothesized effect predictors will be reported. Those with the highest loadings will be compared between the conditions in order to find differential effect predictors.

Results

Recruitment for the trial started in March 2013 and is expected to continue until April 2015. No major changes have been made to the protocol. However, due to an error in the randomization algorithm between January 14, 2014, and July 15, 2014, allocation was dependent on the number of participants who were allocated at once. This in turn was completely random. Consequently, 10 participants were allocated directly to the AAF group; four other participants were divided equally between the 2 experimental interventions; and 15 accounts (of which, one was a dummy account) were equally divided between the three

groups. None of the researchers were aware of this error, as this allocation could very well have simply been the result of the "roll the dice" scenario that should have been applied. How many participants were allocated at once was not the subject of the researchers' decision-making. Therefore, we argue that allocation has still been random and, accordingly, data for all considered participants will be processed as originally planned.

At the time of this writing in January 2015, 269 patients have registered at the project website. Of these, 111 have been officially included in the study, 50 were excluded from participation, and 35 withdrew before their eligibility was checked. The remaining patients are still in the enrollment phase. The main reason for exclusion so far has been a score lower than 35 on the CIS fatigue severity subscale (60%). Furthermore 11% did not meet the psychiatric stability requirement, 8% were younger than 18 at the time of cancer diagnosis, and 8% were still receiving cancer treatment.

Current group sizes as of January 2015 for participants in the first semester are 36 (AAF), 24 (eMBCT), and 32 (control). However, 19 participants have not yet been randomized. Initial responses to the primary research question are expected to be available by the end of 2015.

Discussion

Principle findings

This paper has described the design, hypotheses and analysis plan of a randomized controlled trial in order to study the effectiveness, mediation, and effect predictors of two Internet-based interventions for CCRF. Although recruitment and inclusion have already started, publishing the analysis plan is of great value because it will help to prevent outcome reporting bias [110] and adds validity information to the final studies [111].

By using multiple assessments during the intervention, the proposed trial design is suitable for studying the chronological development of both potential mediators and fatigue. That has two main advantages. Firstly, the data will be suitable for analyses that allow for variation in the individual fatigue trajectories. We do not expect that either of the interventions that have been included in the trial will be beneficial for all participants: our study sample will be highly heterogeneous considering for example tumor and treatment types. Therefore, the analyses on

individual growth trajectories can acknowledge that expectation and test that hypothesis. This will substantiate the interpretation of the results on effectiveness and will be an important first step in identifying what works for whom. Secondly, this study design enables us to use a fully longitudinal mediation analysis, at least for the most important factors, rather than using indirect effects analysis in cross-sectional mediation analysis.

Another important feature of the proposed design is that by comparing two different interventions with an active control group, therapy-specific elements of the interventions can be distillated from the data acquired during this trial. This advantage counts for both the effect predictors and the mediators. Knowledge about such differentiating factors can and should be used to better inform patients with CCRF and to improve allocation of patients with CCRF to suitable interventions. As a result, an increase in the overall effectiveness of relevant interventions can be established.

In this paper, we have presented the trial design, our hypotheses, and a detailed analysis plan. In accordance with good clinical practice, and to avoid outcome reporting bias, this paper was submitted before any of the data was analyzed. All methods are now openly predetermined, therefore any future publication describing this trial can be valued reliably on its quality.

Limitations

A limitation of the current paper is that for most instruments, this paper does not include information on its properties or a thorough rationale for its choice. More extensive information on the actual instruments will be reported in subsequent papers on the results of the various research questions posed in this trial.

Conclusion

Given the growing number of patients suffering from CCRF, the availability of effective Internet interventions potentially strengthens current health care for this population substantially. We have proposed a design to study two Internet interventions in order to gain insight into their effectiveness, mediators, and effect predictors, which fully acknowledges differences between individual patients and differences in the way they respond to each intervention. Results on the effectiveness and mediators will give useful information for improving both the quality and availability of such interventions. Also, identifying effect

predictors for positive intervention effects will improve the referral of patients to relevant interventions. By presenting our hypotheses and analytic strategy before completion of data collection, this paper is a first step in carefully reporting on this comprehensive trial.

Appendices

APPENDIX A – AAF

Picture of the ProMove accelerometer and mobile phone app with feedback.

Image of the accelerometer/activity sensor.

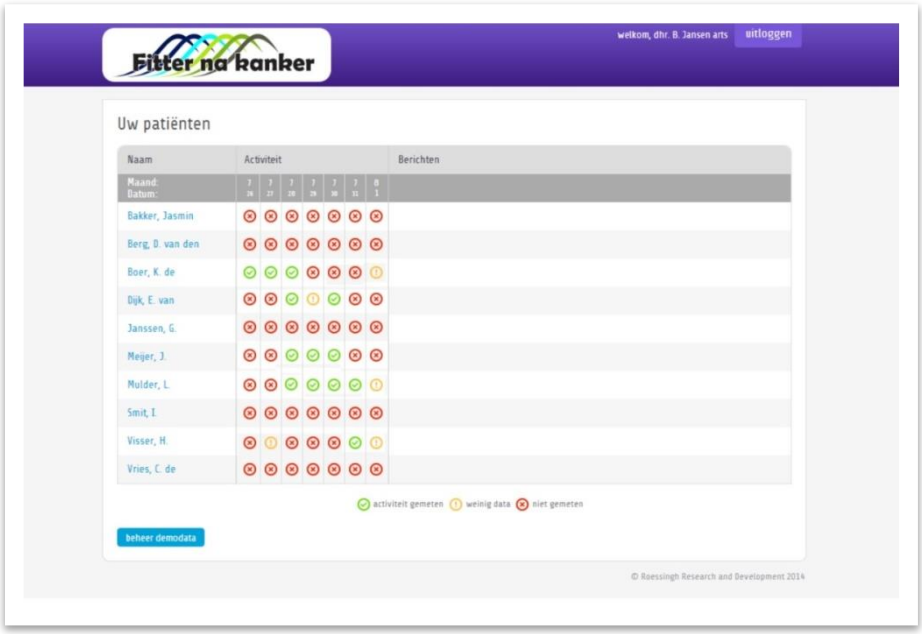
Demonstration how the activity sensor was worn in the AAF intervention.

In week 1, the PDA provided feedback on the patient's physical activity based on a reference line that followed his baseline physical activity level.

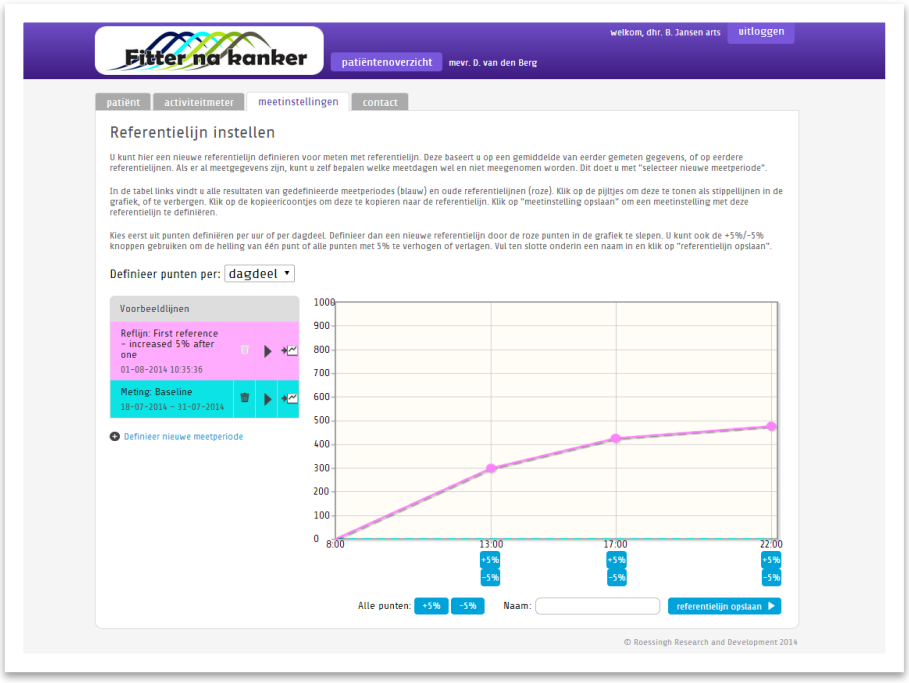
APPENDIX B – AAF Web portal

Additional screenshots of the therapist and participant's web portal for ambulant activity feedback therapy (Dutch, and anonymized).

Therapist's web-portal

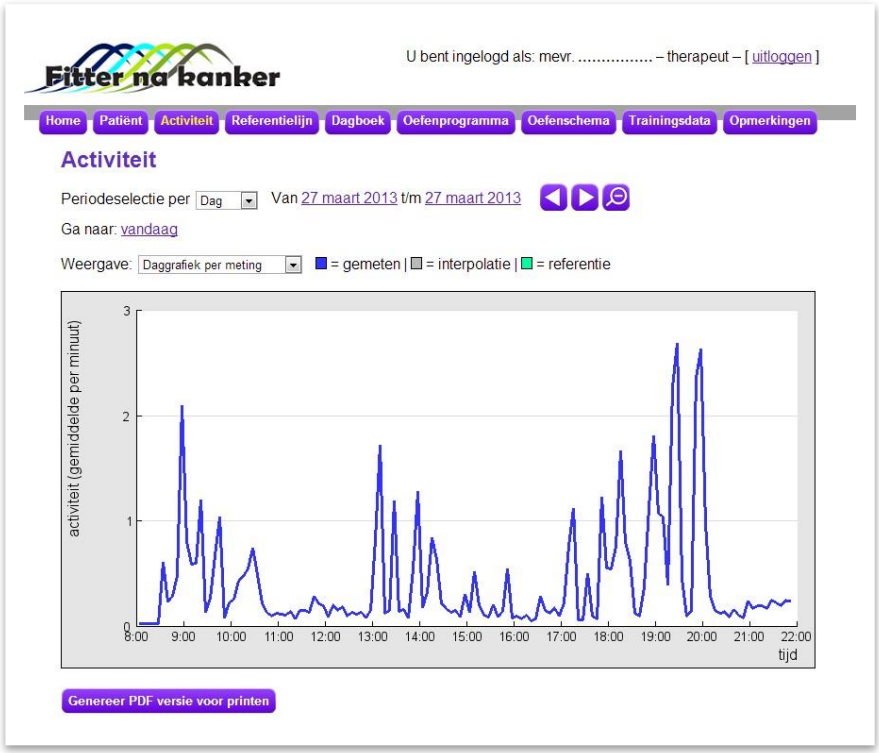


Overview of activity tracking of multiple participants

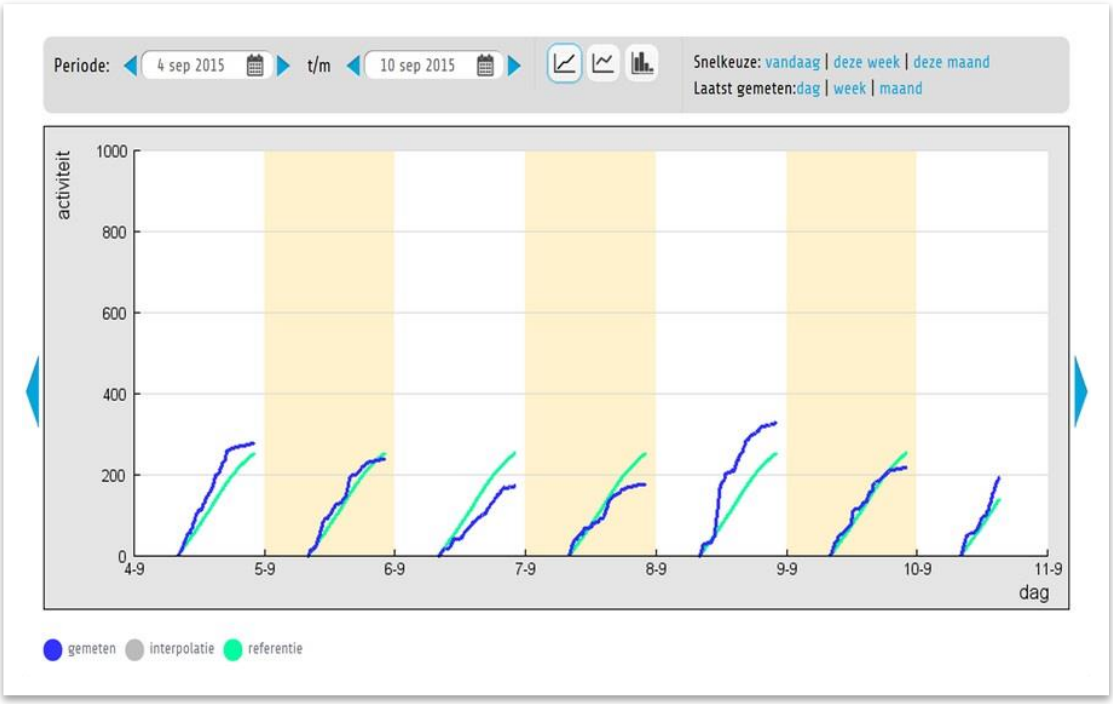


The webpage where the therapist could adapt the reference line

Participant's web-portal:



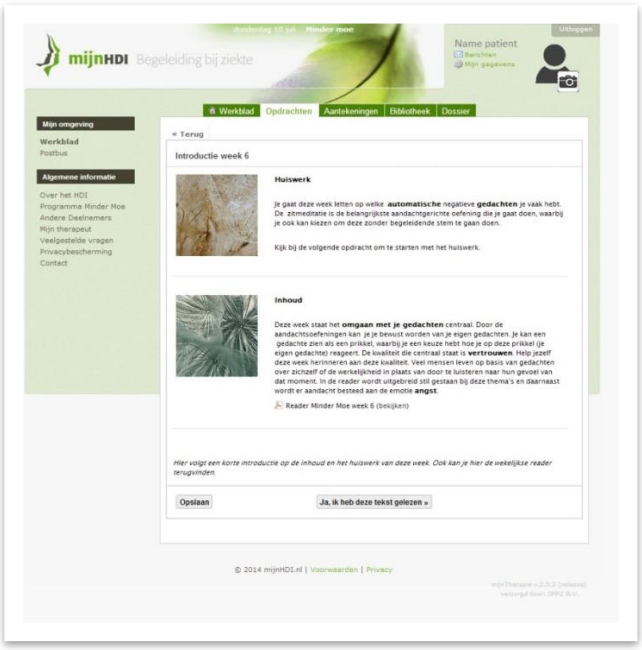
In week 6 patients could login to the portal and see past physical activity pattern.



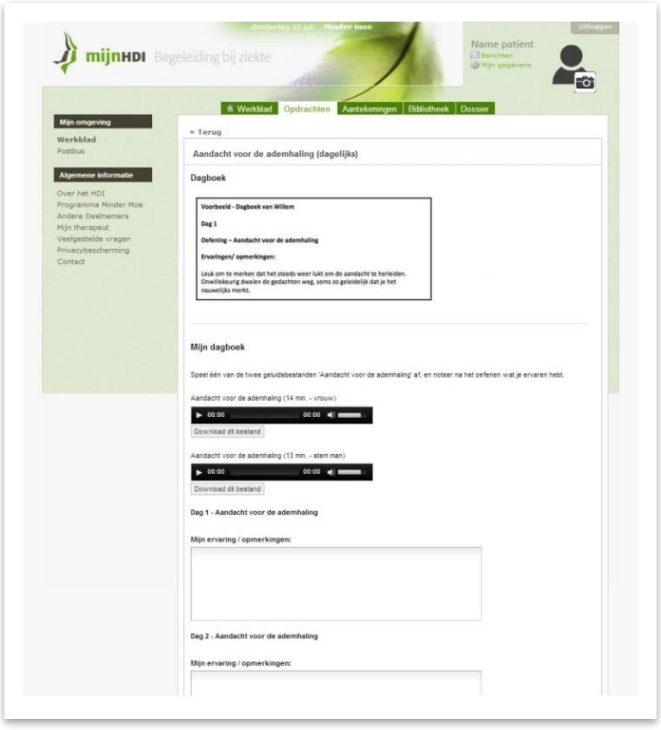
Weekly overview of physical activity pattern (blue line) along the reference line (green line)

APPENDIX C – eMBCT Web portal

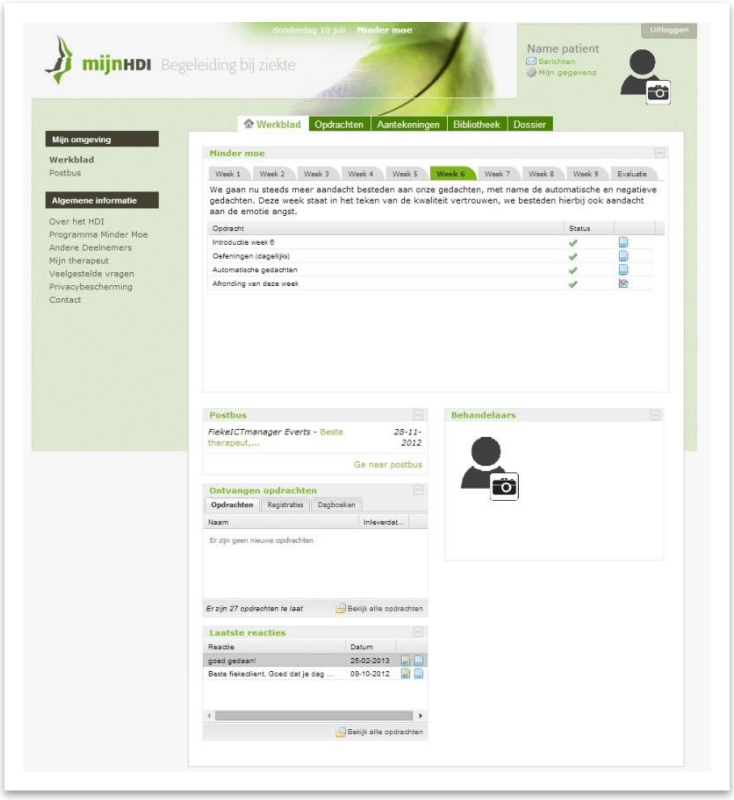
Additional screenshot of the patient Web portal for eMBCT (Dutch).



Every week started with an introduction of the week's and a reader could be downloaded from the portal.



The patient could download the mindfulness exercises on the portal, and wrote down his experiences with doing the exercises in his log file.



When the therapist had sent her feedback to the patient's log file, the patient could read this message on the portal.

APPENDIX D – Psycho-education

Example of an information letter for the minimal intervention control condition (Dutch).

Fitter na kanker

Informatie week 1

Vermoeidheid bij en na kanker

Vermoeidheid bij of na kanker komt veel voor. Bijna iedereen heeft er tijdens de behandeling van kanker last van. Ongeveer één op de drie patiënten blijft ook na de behandeling langdurig erg moe. Dus ook als er geen lichamelijke oorzaken voor vermoeidheid meer aan te wijzen zijn, kan iemand dus moe blijven. Daar zijn verschillende oorzaken voor. Met behulp van begeleiding is het mogelijk om deze oorzaken te ontdekken en te leren er beter mee om te gaan. Hierdoor kan herstel mogelijk worden.

Waarom blijf ik zo moe?

In de volgende e-mails zullen er enkele verklaringen genoemd worden voor chronische vermoeidheid. Een aantal hiervan komen in de e-mails van komende weken uitgebreider aan bod.

Lichamelijke gevolgen van de behandeling

Tijdens de ziekte en de behandelingen krijgt een lichaam het zwaar te verduren. Het gevecht tegen kanker en het herstellen van de behandeling kost energie. Ook kan de behandeling nawerkingen hebben waardoor u nog lange tijd moe blijft. Wij raden aan om uw vermoeidheidsklachten altijd eerst met de (huis)arts te bespreken, zodat een lichamelijke behandelbare oorzaak uitgesloten kan worden.

Angst

Door de kanker kun je angstiger geworden zijn. Angst kan heel moe maken. Wij hebben allemaal onze manieren om met angst om te gaan. Een van de meest voorkomende manieren is dat we hem niet willen voelen en proberen er zo min mogelijk aan te denken. Vaak helpt dat, maar soms kost het wegduwen van angst zoveel energie dat je daar erg moe van wordt. Het helpt om te ontdekken wat jouw manier is om met angst om te gaan. Je kunt vervolgens leren om er anders mee om te gaan, zodat je minder last hebt van vermoeidheid.

APPENDIX E – CONSORT E-HEALTH checklist

CONSORT E-HEALTH checklist V1.6.1 [112].

see link at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4526958/

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Chapter 4

Validation of the Dutch Freiburg Mindfulness Inventory in patients with medical illness

Based on:

Bruggeman-Everts, F.Z., Van der Lee, M.L., Van ‘t Hooft, E.F.M. & Nyklíček, I. Validation of the Dutch Freiburg Mindfulness Inventory in Patients With Medical Illness. *SAGE Open* (2017) 8;7(2). DOI: 10.1177/2158244017705936

Abstract

Objective: Most validation studies of the Freiburg Mindfulness Inventory (FMI) involved healthy subjects. Validation in patients who suffer from a life-threatening medical illness is needed, to investigate the FMI's validity in medical psychology research and practice.

Methods: Psychometric properties of the Dutch FMI were examined in two patient groups of two different studies: (Sample 1) cardiac patients (n = 114, mean age 56 ± 7 years, 18% women), and (Sample 2) severely fatigued cancer survivors (n = 158, mean age 50 ±10 years, 77% women).

Results: Confirmatory factor analysis (studied only in Sample 2) provided good fit for the two-factor solution (*Acceptance* and *Presence*), while the one-factor solution provided suboptimal fit indices. Internal consistency was good for the whole scale in both samples (Sample 1 α = .827 and Sample 2 α = .851). The two-factor model showed acceptable to good internal consistency in Sample 2 (*Presence*: α = .823; *Acceptance* α = .744), but poor to acceptable in Sample 1 (*Presence* subscale: α = .577, *Acceptance* subscale: α = .791). Clinical sensitivity was supported in both samples, and construct validity (studied only in Sample 1) was acceptable.

Conclusion: The Dutch FMI is an acceptable instrument to measure mindfulness in patients who experienced a life-threatening illness in a Dutch speaking population.

Introduction

Mindfulness-based interventions (MBI) have shown to effectively reduce psychological symptoms in patients who suffer from a life-threatening medical illnesses, such as coronary heart disease [1,2], and cancer [3–11]. In these interventions patients learn to focus their attention to the present moment experience, in an accepting, non-judgmental way [12–14]. It is proposed that this attention regulation may lead to symptom reduction through exposure, a change in attitude towards one's thoughts, self-management, relaxation and acceptance [15]. Mindfulness is defined by "a mental state achieved by focusing one's awareness on the present moment, while calmly acknowledging and accepting one's feelings, thoughts, and bodily sensations, used as a therapeutic technique" [16].

To investigate whether, or to what extent, mindfulness skills are a working mechanism in MBIs in these patients, there is a need for reliable and valid tools to measure mindfulness [17]. With a valid tool researchers can investigate whether mindfulness changes during the intervention, whether this is related to treatment outcome (mediator, or working mechanism), and if the level of mindfulness can predict treatment outcome (moderator, or effect predictor). This knowledge can be applied in healthcare to better inform patients about how the intervention may work and to improve allocation of patients to suitable interventions.

A group of Dutch experts in the field of mindfulness research and medical psychology (the second MvdL, fouth author IN, dr. M. Schroevers of Leiden University, dr. B. Garssen and C. Völker of the Helen Dowling Instituut, the Netherlands), came together in 2007 to discuss all available mindfulness questionnaires, and to select or create one Dutch questionnaire suitable for measuring mindfulness as a working mechanism in MBIs in patients who experienced a life-threatening medical illness. They chose the Freiburg Mindfulness Inventory (FMI) [18,19] as it includes two fundamental facets that these experts considered most crucial in medical psychology: (1) focus on the present moment including bodily awareness, (2) non-reactivity to the inner experience, thus an accepting attitude [12,20]. For patients who experienced a life-threatening illness, bodily sensations can often be stress evoking since it may remind them of trauma. Therefore, some patients tend to either avoid sensing bodily symptoms [21], or are preoccupied with them [22]. When practicing mindfulness, patients are invited to investigate present bodily experiences, in an accepting, non-judgmental way [12,13,23], thereby exposing themselves to their fears and bodily symptoms which leads to reduced stress [15]. Furthermore, the FMI is a short questionnaire which makes it feasible to assess mindfulness several times during an intervention which is needed if we want to study mindfulness as a working mechanism.

The German FMI has been demonstrated to possess good psychometric qualities [19,24–26]. A French, Finnish, English and Chinese translation of the FMI have been validated in middle-aged non-clinical samples [27–30]. Only Sauer, Walach, Offenbächer, Lynch, and Kohls [31] investigated the psychometric properties of the FMI in a clinical sample, namely patients with psychosomatic conditions. They found good properties for the two-factor solution (*Acceptance* and *Presence)* and showed the scale to correlate positively with health indicators. Most validation studies of the FMI involved healthy subjects [19,26–29,31,32], but validation in specifically patients who suffer from a life-threatening medical illness is needed [33], to

investigate the FMI's validity in medical psychology research and practice. To our knowledge there are no previous validation studies of the FMI involving patients who experienced a life-threatening illness.

Aim of this study

The aim of the present study was to investigate the psychometric properties of the Dutch translation of the FMI in patients who experienced a life-threatening illness. Following the recommendations of Ziegler [33], the validity will be investigated in the following ways:

- To investigate the structural component, we studied the factorial validity of the Dutch FMI.
- To investigate the internal structure of the item pool, we studied the internal consistency of the (sub)scales.
- To investigate the construct of mindfulness measured with the FMI, its relation with other constructs was investigated, to study the convergence and divergence regarding other constructs (construct validity).
- To investigate whether the Dutch FMI translation had sufficient sensitivity to measure change in mindfulness, we studied the clinical sensitivity – also called *responsiveness* – before, during and after a MBI.

Materials & Methods

Selection and development of Dutch FMI

The following mindfulness questionnaires were available in 2007 and were taken into account by the expert panel to select or create one Dutch questionnaire suitable for measuring mindfulness as a working mechanism in MBIs in patients who experienced a life-threatening medical illness: Mindfulness Attention Awareness Scale (MAAS) [34], Southampton Mindfulness Questionnaire (SMQ) [35], Kentucky Inventory of Mindfulness Scale (KIMS) [36], Cognitive and Affective Mindfulness Scale-Revised (CAMS-R) [22,37], Toronto Mindfulness Scale (TMS) [38], Five Facet Mindfulness Questionnaire (FFMQ) [20], and Freiburg Mindfulness Inventory [18,19]. The SMQ was developed and cited as an unpublished manuscript in 2005 [20,38], but published in 2008 [35], so therefore the SMQ was not included in the expert panel's decision making process.

The expert panel started by selecting which of the five facets of mindfulness presented by Baer [20] (1. non reactivity to inner experience, 2. observing sensations, perceptions, thoughts, feelings, 3. acting with awareness, 4. describing/labeling with words, 5. nonjudging of experience) they considered specifically important in medical psychology. They agreed that non reactivity to inner experience (acceptance), and observing sensations, perceptions, thoughts, feelings (presence or awareness) were the most important aspects of mindfulness in medical psychology.

The panel agreed on choosing the FMI based on several reasons. Firstly, the FMI involves the most important facets of mindfulness for evaluating MBIs in medical psychology. Secondly, it holds only 14 items, so it is short and feasible to assess multiple times during an intervention. And thirdly, the items are both negatively and positively framed. Concerning the other questionnaires, the TMS was judged to be more suitable to study specific elements of mindfulness, rather than the overall change in mindfulness in MBIs. CAMS-r was judged to focus more on concentration, rather than acceptance and presence. The SMQ was judged to mostly measure negative thoughts and not emotions, though MBIs are experiential interventions so emotions need to be addressed in evaluation of these interventions. As FFMQ and KIMS hold 39 items, these were not preferred, though FFMQ also measures acceptance and presence. KIMS does not involve presence [36].

The German FMI as well as the English FMI were translated into Dutch, by respectively a German native speaker and an English native speaker who both spoke Dutch fluently. Both translations were then critically examined by the expert panel mentioned in the introduction, until consensus about the Dutch translation of the items had been reached. See Appendix A for the Dutch translation of the FMI.

Procedure

Data from the Dutch version of FMI were collected in two different samples. The first sample (Sample 1 of the *MindfulHeart* study) involved cardiac patients who recently had a percutaneous coronary intervention (PCI) and who followed a brief Mindfulness-Based Stress Reduction (MBSR) group intervention. For a detailed description about the *MindfulHeart* study, see Nyklíček, Dijksman, Lenders, Fonteijn, and Koolen [1]. In the current paper we

used data from 107 participants who filled in the FMI (mean age 56 ± 7 years; 18% women) who were randomly assigned to either a 4-session MBSR group intervention (n = 55), or a minimal MBSR self-help control group (n = 52). All participants filled in several questionnaires (see Nyklíček et al. [1] and *Measurements*), including the FMI, before and after the intervention.

The second sample (Sample 2 of the *eMBCT* study) involved severely fatigued cancer survivors who followed a therapist guided, web-based, individual 9-week Mindfulness-Based Cognitive Therapy (eMBCT) aimed at reducing cancer-related fatigue (mixed cancer types). The FMI was filled in by 158 patients (mean age 50 ± 10; 77% women). They were asked to fill in the FMI through a link on their personal webpage at the beginning of week 1, 3, 6 and 9 of the intervention. For a detailed description about the *eMBCT study*, see Bruggeman-Everts, Van der Lee and De Jager Meezenbroek [39].

Measurements

The FMI claims to measure *Mindfulness* with its subfacets *Acceptance* and *Presence*. The internal consistency, measured with Cronbach's α in the German FMI was good (α = .86) [19]. Support was found for sensitivity to change and suitability for the use of FMI in subjects without previous meditation experience [19]. The current Dutch translation of the FMI was used in one other study, and internal consistency was acceptable (α = 0.79) [40]. The following questionnaires were assessed to measure construct validity (see Table 3).

The Cognitive and Affective Mindfulness Scale - Revised (CAMS-R) [41] is proposed to measure the willingness and ability to be mindful, rather than how mindful a person is during the day. It demonstrated acceptable internal consistency (two samples of university students: α = .74 and α = .77) and evidence for convergent and discriminant validity [41]. A strong correlation between the CAMS-R and FMI-30 (r = .60 [20] ; r = .66 [41]), and CAMS-R and MAAS (r = .51;) have been found, which indicates good convergent validity[41].

The Balanced Index of Psychological Mindedness (BIPM) [42] is assumed to measure psychological mindedness, which refers to a person's interest and ability to be in touch with and reflect on one's psychological states and processes. The BIPM showed moderate construct validity (r > .40 with related constructs), acceptable to good internal consistency

(*Interest*: α = .85; *Insight*: α = .76), and strong test-retest-reliability (*Interest*: *r* = .63; *Insight*: *r* = .71) [42].

The Perceived Stress Scale (PSS) [43] is a measure for how often a person has perceived stress in the last month. It showed to have acceptable to good internal consistency (α = .75 to .86) and showed sufficient test-retest-reliability and construct validity [43,44]. A Dutch translation has been used before [45].

The Symptoms of Anxiety-Depression index (SAD-4) [46] was developed as a Dutch screening method for mixed and interrelated symptoms of depression and anxiety in post-myocardial infarction patients. Criterion validity has been supported and internal consistency was good (α = .86) [46].

The Dutch Global Mood Scale (GMS) [47] measures *Positive* and *Negative affect* and it showed to have excellent internal consistency (α = .91 and α = .94 respectively). Test-retest reliability (*r* = .55) and convergent and discriminant validity have been demonstrated [47].

De World Health Organization Quality of Life-Bref questionnaire (WHOQOL-Bref) [48] is used to measure generic quality of life in 4 domains: physical health, psychological health, social relationships, and environment. The internal consistency of the four domains was moderate to good (α =.66 for social relationships to α = .82 for physical health). Sufficient test–retest reliability (*r* = .66 to .87) and adequate discriminant validity was found [48].

The Seattle Angina Questionnaire (SAQ) [49] is used to measure physical health in cardiac patients, in 5 domains: physical limitation, angina stability, angina frequency, treatment satisfaction and disease perception. All domains showed moderate to good internal consistency (α = .66 to .89) [50]. Its content, construct and criterion validity have been demonstrated and it showed to be a reliable and valid instrument for patients who had previously undergone PCI [49].

Statistical analyses

Demographics were calculated for both Sample 1 and 2 separately, and differences between groups were tested using independent samples *t*-tests and χ^2-tests. Significance level was set

at $p \leq .05$. We used multiple imputation [51] to impute missing items. To study the factor structure, we used Mplus version 7.31 [52]. All other analyses were performed using SPSS Version 19 for Windows package (SPSS Inc, Chicago, IL).

Factor structure. Confirmatory Factor Analysis (CFA) using maximum likelihood and oblique rotation (Promax) was performed. Model fit was considered adequate if: CMIN/df < 2; CFI > .90; TLI > .90; NFI > .90; RMSEA < .08, and χ^2-test of $p > .05$ [53,54]. We tested for measurement invariance to see if data of Sample 1 and 2 could be combined for the factor analysis (see Appendix B for results), but this showed that the FMI lacked configural, metric, and scalar invariance across our two study samples. This indicated that the FMI was not stable between these two patient groups and combining the datasets would lead to uninterpretable results. We decided to study the factor structure of Sample 2 (n=158) only, as Sample 1 had too small sample size (n=102) that is likely to lead to statistical artefacts [55]. We expected a two-factor structure, as was found in the German [25,26], Chinese [28], and Finnish version [27]. To test whether two competing models were significantly different, χ^2 difference testing was performed.

Internal consistency. Based on previous research [19,28,29,40] we expected the internal consistency of the Dutch FMI to be at least Cronbach's $\alpha > .70$ ('acceptable').

Construct validity. Using Pearson's correlations, we investigated whether the FMI (factor)scores correlated with (subscales of) questionnaires assessed in Sample 1. We considered correlations $r < .3$ as weak, $.3 \leq r < .5$ as moderate, and $r \geq .5$ as strong [56]. We expected that FMI scores correlated strongly with another mindfulness questionnaire (positive: CAMS-R), and moderately with constructs related to psychological wellbeing (positive: BIPM, GMS positive affect, WHOQOL-Bref; negative: PSS, SAD-4, GMS negative affect) (convergent validity). We expected the FMI scores to correlate weakly with a questionnaire assessing physical health (SAQ) (divergent validity).

Clinical sensitivity. To record the FMIs ability to capture and record a patient's change over time (also called *responsiveness*), we calculated the standardized response mean (SRM) (change divided by standard deviation of change) [57]. In Sample 1 (n = 51) the SRM of FMI scores was calculated between pre and post-intervention. In Sample 2, the SRM was calculated at week 3, 6 and 9, compared to week 1, using all available data (n = 95). Based on

previous studies in which it was found that an increase in mindfulness is associated with improvement of clinical outcome [58–60], and that the FMI is able to distinguish between meditators and non-meditators [19], we hypothesized that after MBSR in Sample 1 and during MBCT in Sample 2, mindfulness increased and that this would be measured with FMI.

Results

The group of Sample 1 involved more men, more comorbidities, lower education, and older patients than the group in Sample 2 (see Table 1 on next page).

Factor structure

In Table 2 (next page), the model fit indices for the one-factor and two-factor model for Sample 2 are shown. The two-factor structure provided good fit indices, while the one- factor model provided suboptimal fit indices.

The factor loadings of each model are shown in Table 3 (next page) and Appendix C. Item 14 (*I am able to smile when I notice how I sometimes make life difficult*) was below 0.5 in the one-factor solution.

Table 1. Demographics of participants in the *MindfulHeart* (Sample 1) and *eMBCT study* (Sample 2) and results of independent samples t-tests and chi-square tests to study differences between groups.

		Sample 1 (*n* = 107)		**Sample 2 (*n* = 158)**		**Difference test**	
		n	*%*	*n*	*%*	*test*	*p*
Gender	Male	88	82.2	37	23.4	$\chi^2 = 86.85$	$p < .001$
Marital status	Married/ Living together	71	66.4	104	65.8	$\chi^2 = .029$	n.s.
Education	Low[1]	7	6.5	8	5.1	$\chi^2 = 18.223$	$p < .001$
	Moderate[2]	61	57.0	50	31.6		
	High[3]	39	36.4	94	59.5		
	Missing	-	-	6	3.8		
Comorbidity	Yes (%)	38	35.5	37	23.4	$\chi^2 = 5.111$	$p < .05$
		M	*SD*	*M*	*SD*		
Age		55.84	7.24	49.78	10.29	$t\ (263) = -5.272$	$p < .001$

Note: [1] Lower vocational education; [2] Secondary education, community college; [3] High professional education or college/university; *Abbreviations*: n.s. = non-significant; *M* = mean; *SD* = standard deviation

Table 2. Fit Indices for the one- and two-factor models of the FMI of Sample 2.

Factor Model	**CMIN/df**	**CFI**	**TLI**	**RMSEA**	**AIC**	**BIC**	**χ^2-test**	**χ^2-difference test**
One-factor	1.999	.865	.840	.080	4702.209	4830.838	$\chi^2(77)=153.948$, $p<.001$	p<.001
Two-factor	1.540	.928	.914	.058	4798.991	4798.991	$\chi^2(76)= 117.038(76)$, $p_{=}.002$	

Abbreviations: CMIN/df = Chi square/degree of freedom ratio; CFI = Comparative Fit Index; TLI = Tucker–Lewis index; NFI= Normed Fit Index; RMSEA = Root Mean Square Error of Approximation. Adequate fit: CMIN/df < 2; CFI > .90; TLI: > .90; RMSEA < .08; and chi-square statistic (χ^2) of $p < .05$. The model with the lowest BIC an AIC best fits the data.

Table 3. Factor structure of one- and two factor models of Sample 2. The one-factor model is called *Mindfulness*, and the two-factors are called *Acceptance* and *Presence*. In this table factor loadings of each item are presented.

	Mindfulness		**Acceptance**		**Presence**	
	factor loading	standard error	factor loading	standard error	factor loading	standard error
FMI1	0.774	0.112	-	-	0.825	0.108
FMI2	0.860	0.125	-	-	0.921	0.119
FMI3	0.852	0.114	-	-	0.850	0.110
FMI4	0.642	0.112	0.723	0.131	-	-
FMI5	0.940	0.123	-	-	0.914	0.119
FMI6	0.694	0.119	0.846	0.141	-	-
FMI7	1.000	0.000	-	-	1.000	0.000
FMI8	0.751	0.125	0.938	0.148	-	-
FMI9	0.809	0.117	1.000	0.000	-	-
FMI10	0.746	0.106	-	-	0.674	0.102
FMI11	0.576	0.120	0.727	0.144	-	-
FMI12	0.748	0.129	0.896	0.154	-	-
RFMI13	0.515	0.124	0.566	0.143	-	-
FMI14	0.442	0.114	0.569	0.131	-	-

Internal consistency

Good internal consistency was found for the one-factor FMI scale in both Sample 1 (α = .827) and Sample 2 (α = .851). The internal consistency of the two-factor solution in Sample 1 was poor for the *Presence* subscale (α = .577) and acceptable for the *Acceptance* subscale (α = .791). In Sample 2 the internal consistency was good for the *Presence* subscale (α = .823), and acceptable for *Acceptance* subscale (α = .744).

Construct validity

In Sample 1. we found moderate to strong correlations between the FMI factors and other psychological constructs, and weak to no correlations with questionnaires assessing unrelated constructs (physical health). We found higher correlations with perceived stress (PSS; negative) and psychological health (WHOQOL-Bref-Psychological health; positive), than with a mindfulness questionnaire (CAMS-R; positive) (see Table 4).

Table 4. Pearson's correlations of one-factor and two-factor FMI solution with questionnaires assessed in Sample 1 (n = 107)

Factor model	One-factor	Two-factor		Hypothesized correlation	α
Scales and subscales	Mindfulness	Presence	Acceptance		
Mindfulness					
CAMS-R	.480*	.418**	.486**	$r \geq .5$	.774
Psychological wellbeing					
BIPM					
• Interest	.373**	.354**	.323**	$.3 \leq r < .5$	.746
• Insight	.259**	.273*	.225*	$.3 \leq r < .5$	.757
SAD-4	-.378**	-.252**	-.459**	$-.3 < r < -.5$	.875
GMS					
• Positive affect	.353**	.290**	.374**	$.3 \leq r < .5$	.897
• Negative affect	-.195*	-.038	-.299**	$-.3 \leq r < -.5$	.932
PSS	-.558**	-.406**	-.637**	$-.3 \leq r < -.5$	.848
WHOQOL-Bref					
• Physical health	.297**	.069	.412**	$.3 \leq r < .5$	.797
• Social relationships	.330**	.300**	.343**	$.3 \leq r < .5$	.537
• Environment	.363**	.294**	.372**	$.3 \leq r < .5$	.797

• Psychological health	.516**	.405**	.576**	.3 ≤ *r* < .5	.791
Physical health					
SAQ					
• Physical limitation	.059	-.021	.139	*r* < .3	.877
• Angina stability	-.002	-.042	.062	*r* < .3	N/A.
• Angina frequency	.124	.019	.191	*r* < .3	.256
• Treatment satisfaction	.228*	.145	.281**	*r* < .3	.559
• Disease perception	.143	-.082	.304**	*r* < .3	.703

Abbreviations: α = Internal consistency measured with Cronbach's alpha; n.s.= non-significant; *r* = Pearson's correlation; CAMS-R = Cognitive and Affective Mindfulness Scale Revised [41]; BIPM = Balanced Index of Psychological Mindedness [42]; PSS = Perceived Stress Scale [43]; SAQ = Seattle Angina Questionnaire [49]; SAD-4 = Symptoms of Anxiety-Depression index [46]; GMS = Dutch Global Mood Scale [47]; WHOQOL-Bref = World Health Organization Quality of Life-Bref questionnaire [48]; N/A = not applicable. *Note*: a measure for internal consistency of the SAQ – angina stability subscale was not applicable, as it holds one item. * $p < .05$ (two-tailed). ** $p < .001$ (two-tailed)

Clinical sensitivity

In Sample 1, an SRM of .598 was measured at post-assessment, meaning there was a moderate responsiveness of mindfulness measured with FMI. In Sample 2, SRM changed from 0.4894 in week 3, to 0.9479 at week 6, and to 1.3136 at week 9, meaning the responsiveness of FMI increased from low to high during the intervention.

Discussion

This is the first study that investigated the psychometric properties of the Dutch translation of the FMI in patients who experienced a life-threatening illness. Two different samples were used in this study, namely Sample 1 which consisted of cardiac patients from the *MindfulHeart* study, and Sample 2 that consisted of severely fatigued cancer survivors from the *eMBCT* study. Factor analyses in Sample 2 provided more support for the two-factor solution than the one-factor solution. The internal consistency was good for the one-factor model in both Samples. The two-factor model showed acceptable to good internal consistency in Sample 2, but poor to acceptable internal consistency in Sample 1. We found that FMI was clinically sensitive in both Samples, and that construct validity (studied only in Sample 1) was acceptable. We conclude that the Dutch translation of the FMI is an acceptable instrument to assess mindfulness in patients who experienced a life-threatening illness.

In line with the findings of the Finnish validation study [27], we found a high correlation between the FMI, and perceived stress (PSS) and psychological health (WHOQOL-Bref). This suggests that mindfulness measured with the FMI, is related to these constructs, which are important outcomes in medical psychology. This high correlation may suggest the usefulness of introducing mindfulness to alleviate stress, although it does not learn us anything about causality. Therefore it is important to study working mechanisms, not only with mediation analyses, but also assessing if a rise in mindfulness precedes drops in perceived stress in prospective investigations.

This study is subject to some limitations. First, the *Mindfulheart* study and the *eMBCT* study were not originally designed to investigate the psychometric properties of the FMI, which resulted in a too small sample size to perform factor analysis in Sample 1, and item deletion to improve, as this may lead to statistical artefacts [55]. Also construct validity could only be investigated in Sample 1. Second, to investigate if the FMI is indeed measuring the concept of mindfulness, one needs a 'gold standard' to compare it with (criterion validity). However, despite that mindfulness research has grown in the last decade [61], there is still no consensus about a gold standard. Third, this study lacked a control group, and therefore we could not investigate test-retest validity to control for response shift bias [62,63]. the results of clinical sensitivity were dependent on whether mindfulness indeed increased during MBSR in Sample 1 and MBCT in Sample 2, and thus, one could not test whether poor responsiveness of the measurement would be due to a lack of treatment effect, or a lack of clinical sensitivity. And fourth , though self-assessed questionnaires have the advantage that it is quick and convenient, they are subject to systematic bias such as the Hawthorne effect, the overconfidence effect, social desirability, and cognitive dissonance [63].

As mindfulness is a complex construct, we prefer to focus on certain aspects of mindfulness that are not only key facets of mindfulness definitions, but also are thought to be the key working mechanisms of MBI in patients who have experienced a life-threatening illness: focus on the present moment including bodily awareness, with an accepting attitude. This study showed acceptable psychometric properties of the FMI in these patients, and therefore we conclude that the Dutch FMI is an acceptable instrument to measure mindfulness as a working mechanisms in MBIs for patients who experienced a life-threatening illness.

Appendices

APPENDIX A – Dutch translation of the FMI

In this file the Dutch translation of the FMI is presented. For details about the development of this translation see the Material and Methods section.

Hieronder staat een aantal uitspraken die betrekking hebben over uw ervaring van de ***afgelopen week***. Plaats bij elke uitspraak een ***cirkeltje*** rond het ***cijfer*** dat het best voor U van toepassing is. Er zijn geen goede of slechte antwoorden, probeer eerlijk en spontaan te antwoorden. Uw eigen indruk is het enige dat telt.

1 = zelden 2 = soms 3 = redelijk vaak 4 = bijna altijd

1	Ik sta open voor de ervaring van het moment	**1 2 3 4**
2	Ik ben me bewust van mijn lichaam, of ik nu aan het eten, koken, schoonmaken of praten ben	**1 2 3 4**
3	Als ik merk dat ik er met mijn aandacht niet bij ben, keer ik rustig terug naar de ervaring van het moment	**1 2 3 4**
4	Ik kan mezelf waarderen	**1 2 3 4**
5	Ik heb aandacht voor waarom ik iets doe	**1 2 3 4**
6	Ik zie mijn fouten en moeilijkheden zonder mezelf te veroordelen	**1 2 3 4**
7	Ik sta in contact met mijn ervaring in het hier-en-nu	**1 2 3 4**
8	Ik accepteer onaangename ervaringen	**1 2 3 4**
9	Ik ben vriendelijk naar mezelf wanneer dingen verkeerd lopen	**1 2 3 4**
10	Ik neem mijn gevoelens waar zonder mezelf erin te verliezen	**1 2 3 4**
11	In moeilijke situaties kan ik even stilstaan in plaats van direct te reageren	**1 2 3 4**
12	Ik ervaar momenten van innerlijke rust, zelfs als de omstandigheden pijnlijk of stressvol zijn	**1 2 3 4**

13	Ik ben ongeduldig met mezelf en met anderen	**1 2 3 4**
14	Ik kan glimlachen als ik merk hoe ik het mezelf soms moeilijk maak in het leven	**1 2 3 4**

APPENDIX B – Measurement invariance

In this appendix the results of the Measurement Invariance of Sample 1 and Sample 2 are presented. This was done in Mplus to see if data of both studies could be combined in the factor analysis. The results show that the FMI lacked configural, metric, and scalar invariance across both study samples, indicating that the FMI was not stable in this varied patient group who experienced a life threatening illness.

Mplus input

```
TITLE: CFA FMI Study 1 and 2

DATA:  FILE IS CFA_study1and2.dat;

VARIABLE:    NAMES ARE PPN INSTITUUT GROEP GESLACHT LEEFTIJD BURGELIJ OPLEIDING
PSYHULP COMORB FMI1 FMI2 FMI3 FMI4 FMI5 FMI6 FMI7 FMI8 FMI9 FMI10 FMI11 FMI12
rFMI13 FMI14 FMIT1;
USEVARIABLES= FMI1 FMI2 FMI3 FMI4 FMI5 FMI6 FMI7 FMI8 FMI9 FMI10 FMI11 FMI12 rFMI13
FMI14;
GROUPING IS Groep(1=study1 3=study2);
MISSING= all(-999);

MODEL:

  f   BY  FMI1  FMI2  FMI3  FMI4  FMI5  FMI6  FMI7  FMI8  FMI9  FMI10  FMI11  FMI12  rFMI13
FMI14;

ANALYSIS:
MODEL = CONFIGURAL METRIC SCALAR;

OUTPUT:
sampstat stand ;
```

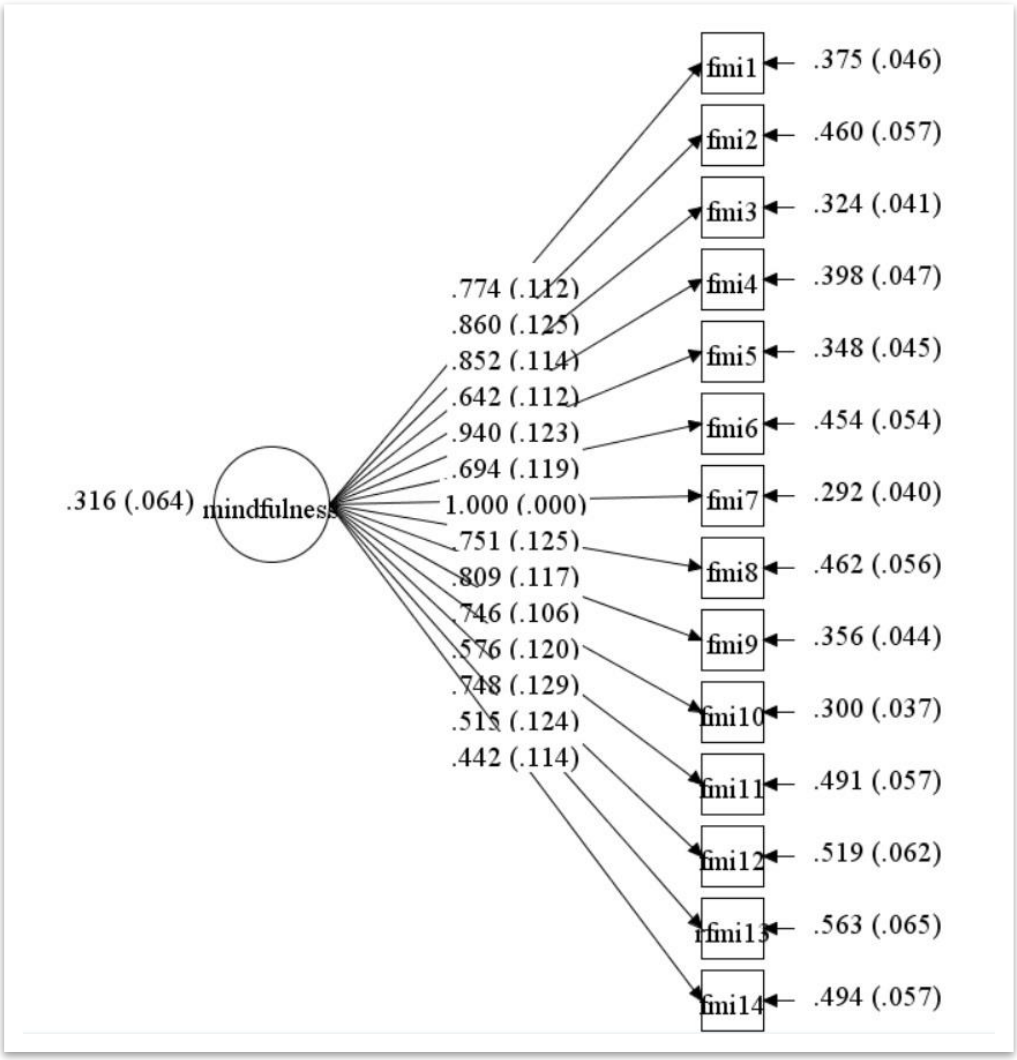
Mplus Output:

```
MODEL FIT INFORMATION

Invariance Testing

                  Number of                    Degrees of
     Model        Parameters      Chi-square    Freedom     P-value

     Configural         84            284.216       154       0.0000
     Metric             71            326.723       167       0.0000
     Scalar             58            384.812       180       0.0000

                                                 Degrees of
     Models Compared              Chi-square     Freedom     P-value
```

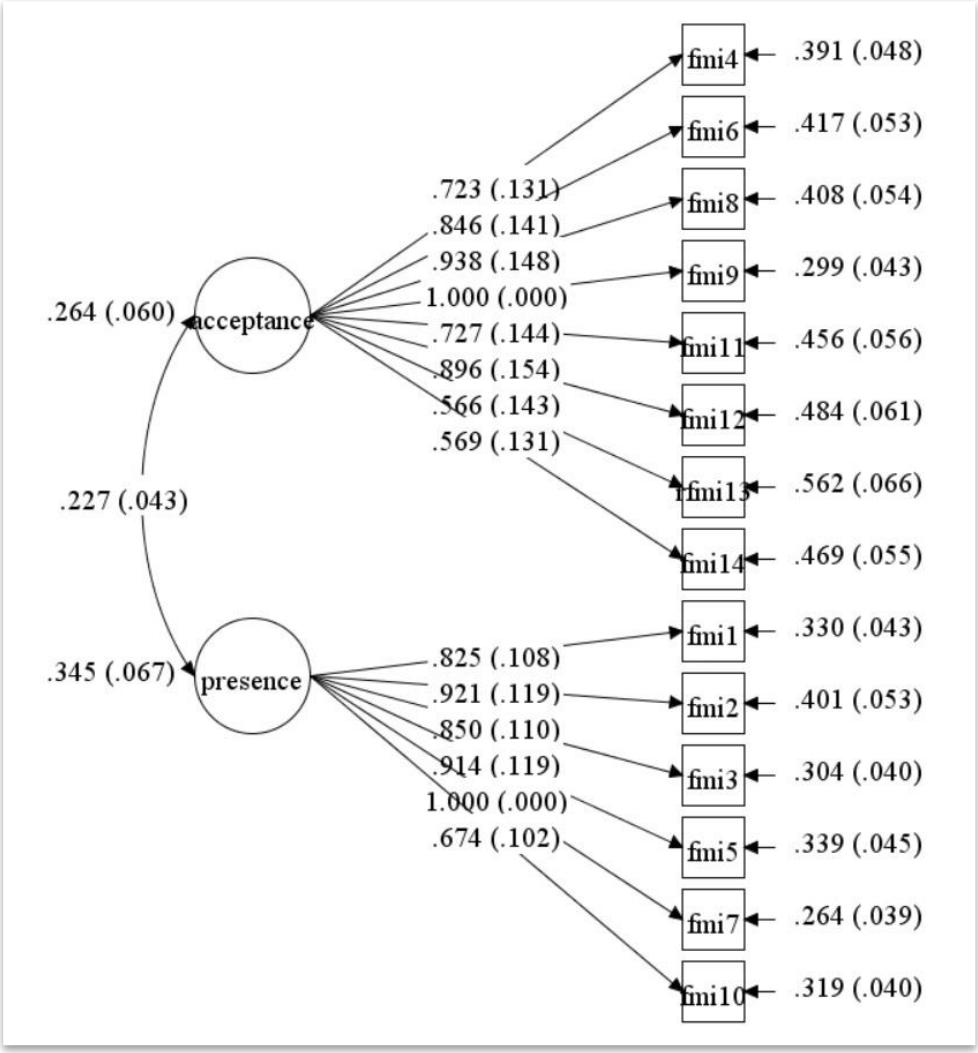
Metric against Configural	42.507	13	0.0001
Scalar against Configural	100.596	26	0.0000
Scalar against Metric	58.089	13	0.0000

APPENDIX C – Factor structure FMI

In the figures below, the factor structure of the one- and two-factor model for the FMI are shown for Sample 2, that consisted of severely fatigued cancer patients (n=158).



Sample 2, one-factor model



Sample 2, two-factor model

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Chapter 5

Effectiveness of two Web-based interventions for Chronic Cancer-Related Fatigue compared to an active control condition: Results of the 'Fitter na kanker' Randomized Controlled Trial.

Based on:

Bruggeman-Everts, F.Z., Wolvers, M.D.J., Van de Schoot, R., Vollenbroek-Hutten, M.M.R. & Van der Lee, M.L. Effectiveness of two internet interventions for Cancer-Related Fatigue: results of a 3-armed Randomized Controlled Trial 'Fitter na kanker'. *Journal of Medical Internet Research* (2017) 19(10): e336, DOI:10.2196/jmir.7180

Abstract

Background: Approximately one third of all patients who have been successfully treated for cancer, suffer from chronic cancer-related Fatigue (CCRF). Effective and easily accessible interventions are needed for these patients.

Objective: The current paper reports on the results of a 3-armed randomized controlled trial investigating the clinical effectiveness of two different guided Web-based interventions for reducing CCRF compared to an active control condition.

Methods: Severely fatigued cancer survivors were recruited via online and offline channels, and self-registered on an open-access website. After eligibility checks, 167 participants were randomized via an embedded automated randomization function into: (1) physiotherapist-guided ambulant activity feedback (AAF) therapy encompassing the use of an accelerometer (n = 62); (2) psychologist guided Web-based mindfulness-based cognitive therapy (eMBCT; n = 55); or (3) an unguided active control condition receiving psycho-educational e-mails (PE; n = 50). All interventions lasted nine weeks. Fatigue severity was self-assessed using the Checklist Individual Strength – Fatigue Severity subscale (primary outcome) six times from baseline (T0b) to six months (T2). Mental health was self-assessed three times using the Hospital Anxiety and Depression scale and Positive and Negative Affect Schedule (secondary outcome). Treatment dropout was investigated.

Results: Multiple group latent growth curve analysis, corrected for individual time between assessments, showed that fatigue severity decreased significantly more in the AAF and eMBCT groups compared to the PE group. The analyses were checked by a researcher who was blind to allocation. Clinically relevant changes in fatigue severity were observed in 66% (41/62) of patients in AAF, 49% (27/55) of patients in eMBCT, and 12% (6/50) of patients in PE. Dropout was 18% (11/62) in AAF, mainly due to technical problems and poor usability of the accelerometer, and 38% (21/55) in eMBCT, mainly due to perceived high intensity of the program.

Conclusion: Both the AAF and eMBCT interventions are effective for managing fatigue severity compared to receiving psycho-educational e-mails. Reducing the intensity of eMBCT and improving usability of the accelerometer in the AAF may reduce dropout rates.

Introduction

Cancer-related fatigue (CRF) is 'a distressing, persistent, subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning' [1]. In approximately 30% of the patients who have been successfully treated for cancer, severe fatigue persists for months or even years [2]. This persistent fatigue, termed chronic CRF (CCRF) is often accompanied by distress and poor mental health [1,3].

Physical activity interventions and psychosocial interventions specifically designed to reduce CCRF have been shown to be effective [4–9]. Readily accessible interventions are needed for patients who do not have the energy or time to travel to a specialized health care institute [10,11], and so we have developed two different Web-based interventions aimed at reducing CCRF: (1) a physiotherapist-guided Ambulant Activity Feedback (AAF) [12], and (2) a psychologist-guided Web-based Mindfulness-Based Cognitive Therapy (eMBCT) [13]. See Wolvers et al. [14] for an elaboration on the theoretical models underlying these interventions.

The overall aim of the project *More fit after cancer* – in Dutch 'Fitter na kanker', hereafter FNK-trial – was to study the effectiveness, effect predictors and mediators of AAF and eMBCT in comparison to a minimal active control condition that consisted of e-mails with psycho-education (PE) about CCRF [14]. The current paper reports on the clinical effectiveness of AAF and eMBCT in reducing fatigue severity and improving mental health in severely fatigued cancer survivors compared to PE. We hypothesized that fatigue severity would be reduced more, and mental health would be increased more in AAF and eMBCT compared to PE, between baseline and six-month follow-up.

Methods

Patients & Setting

In our previous article [14] we provided a detailed description of the methods of the trial. Severely fatigued cancer survivors were recruited via both online and offline channels (via patient organizations, walk-in consultation services, social media, newspapers, and health care professionals, see Appendix A), inviting them to follow a Web-based intervention in a research setting for their fatigue and invited them to register on an open-access website

[15,16]. To recruit a group of participants with open expectations, we did not specify the exact content of the interventions in the advertisements. See Appendix B (advertisement) and see Appendix C (informed consent) for the information given during recruitment.

Participants – all cancer types included – had finished curative-intent cancer treatment (with the exception of hormonal treatment as this often is low intensive and may last up to five years) at least three months previously, and had been suffering from severe fatigue ever since (≥ 35 on the Checklist Individual Strength – fatigue severity subscale (CIS-FS) [7,17]). Participants had no current or former severe psychiatric morbidity such as suicidal ideation, psychosis, or schizophrenia, were >19 years old, and at least 18 years old at disease onset. For external validity purpose, non-treatable comorbid somatic diseases that were possible causes for fatigue (such as rheumatoid arthritis, diabetes, myocardial damage) were no exclusion criteria, but were registered during the study. We chose not to statistically control for these co-morbidities, but to check whether co-morbidities were equally divided between the conditions, see Appendix D. We contacted the participant's medical doctor (general practitioner, oncologist or other medical specialist), after giving consent by the participant, to check for psychiatric morbidity and whether curative intent cancer treatment had finished at least three months previously.

We aimed to include 330 participants so as to be able to study working mechanisms in addition to effectiveness of the interventions. Despite persistent recruitment efforts and an extension of the recruitment period by three months, this number proved infeasible as we had to exclude more patients than anticipated (see Figure 1). However, we continued recruiting until we had enough participants to study the effectiveness with enough power, namely 55 participants per condition [14].

Trial design

Participants were randomized in one of three conditions by a computerized tool [14], which included two experimental conditions: (1) AAF and (2) eMBCT; or (3) an active control condition in which participants received psycho-educational information (PE). The intervention period was nine weeks for all three conditions. The primary outcome was self-perceived fatigue severity measured after the eligibility check (T0b: baseline), three times during the intervention (M3, M6, M9), two weeks after completion of the interventions (T1),

and six months after baseline (T2: primary outcome). Secondary outcome was mental health, measured at recruitment (T0a), T1 and T2. All outcomes were self-reported and Web-assessed. Participants were reminded to complete the measurements twice, and at T2 participants were also reminded by telephone. Dropouts from the treatment groups were interviewed by telephone to inquire about their reasons for dropping out.

Randomization, masking and blinding

We have described the randomization process in detail in our trial article [14]. Randomization was carried out blind via a script embedded in the researchers' Web portal and used the random function of php (rand(1,3)) [18]. The researchers could neither influence nor predict the outcome of the randomization process. Due to an error in the website's randomization algorithm, allocation was temporarily dependent on the number of participants who were allocated at the same time between January 14th 2014 and July 15th 2014 (see Wolvers et al. [14] for more information). This resulted in unequal sample size of the conditions. We argue that the participants were randomly assigned as it was not the researchers' decision making how many participants were allocated at the same time. Neither researchers, participants, nor therapists were blind to treatment, as the medical ethical committee insisted that we announced the minimal intervention as our control group. An independent statistician (RvdS) was blind to allocation while checking all analyses. We did not specify the exact content of the interventions in the advertisements, to limit influencing the expectations before the trial began.

Interventions

See Appendix A-D in Chapter 3 for additional screen shots of all interventions studied. The eMBCT is a Web-based psychologist guided intervention, which follows the MBCT protocol specifically designed for CCRF [19,20]. It aims to change the behavioral and cognitive reactions of the patient to cancer-related stressors including fatigue itself [5,19,21]. Following the original eMBCT protocol, participants who were randomized into eMBCT, were diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, Text Revision (DSM-IV-TR) [22]. The intervention's time-investment involves reading the weekly information, doing mindfulness exercises while listening to the MP3 files, filling out logs with their experiences, reading the weekly feedback of the therapist and replying to this feedback by e-mail weekly. The time investment for participating the eMBCT

is estimated on average four hours per week for nine weeks. Participants could not continue with a next session before they had registered their experience with homework assignment of the previous week. Bruggeman-Everts et al. [13] have published a pilot study on the effectiveness of eMBCT and a detailed description of the eMBCT protocol, setting and development.

The AAF consists of a home-based physiotherapist-guided protocol in which participants use an accelerometer to gain insight in their physical activity pattern, and increase or balance their daily activities in ways that improve their energy levels [5,23]. The time investment for the AAF intervention is estimated to be three hours per week (on average) for nine weeks. The time-investment involves taking notice of the Personal Digital Assistant messages, responding to these messages by changing physical activity, reading the weekly feedback from the physiotherapist, reading the weekly feedback from the physiotherapist, reporting experiences, and replying to the feedback by email. Participants could not continue with the following session before they had registered their experience with homework assignment from the previous week. See Wolvers and Vollenbroek-Hutten [12] for a detailed description of the development of AAF.

Patients in the PE condition received psycho-educational e-mails describing possible causes of fatigue, sleep hygiene, balancing energy during the day, and how to cope with worrying thoughts. We estimated that patients dedicated ten minutes per week to the nine-week minimal control intervention. The intervention involves reading the psycho-educational information in no-reply emails. Whether participants had indeed read the psycho-educational information was not checked, as asking participants was considered unreliable. This psycho-educational information was derived from the eMBCT protocol for CCRF [13,19], and was included in the current eMBCT and AAF protocols, so participants in all three conditions were given the same psycho-education.

Outcomes

The primary outcome fatigue severity was measured using the CIS-FS [7,17], which consists of eight items that are rated on a seven-point Likert scale (range 8-56, Cronbach's α = 0.84). The CIS closely resembles the Multidimensional Fatigue Inventory [24,25]. The secondary outcome was the concept of 'mental health' measured using both negatively and positively

framed questionnaires [26]: The Positive and Negative Affect Schedule (PANAS) [27,28] was used to measure Positive Affect (PA, range 10-50, α = 0.90) and Negative Affect (NA, range 10-50, α=0.89), and the Hospital Anxiety and Depression Scale (HADS) [29–31] (range 0-42, α = .88) was used to measure distress.

Baseline characteristics were assessed including demographics, medical history, and help received in the past. Participants could only continue with the next week's exercises after finishing the previous, adherence was calculated based on the week number participants had reached. The proportion of non-adherence was based on the number of participants who dropped out of the intervention before completing six weeks of the protocol (i.e. intended usage) [14].

Data analyses

First, analyses of variance (ANOVA) and χ^2-tests were performed to: (1) check for differences in baseline characteristics between all conditions; and (2) check whether baseline variables correlated with missing data patterns to check if data was randomly missing. The significance level was set at $P< .01$ to correct for multiple testing. This resulted in no auxiliary variables or covariates being included in the model. Outcome measures were checked for normality and outliers and resulted in no modifications being made. These analyses were performed in SPSS Version 23 for Windows package (SPSS Inc, Chicago, IL).

Second, Latent Growth Modeling (LGM) was performed to test which model best fit the longitudinal data of the outcome measures (CIS-FS, HADS, PA and NA) using Mplus version 7.31 [32]: (1) a linear versus linear and quadratic slope, (2): one slope versus a piece-wise model with two slopes (piece-wise only for CIS-FS); and (3) with versus without individual timescores (the exact time points when a participant filled in the assessment). See Appendix E for the procedure of selecting the best fitting model for CIS-FS. Next, we studied the effectiveness of AAF and eMBCT compared to PE by testing whether the trajectories of the best fitting model significantly differed between the three conditions by applying Wald testing (for linear slopes) or χ^2 difference testing (for linear and quadratic slopes). This was done on an intention-to-treat (ITT) basis (thus including adherent and non-adherent participants) and we checked whether the results for CIS-FS changed when only including participants who were adherent to treatment

Third, to measure the clinical importance in addition to statistical significance, the proportion of participants who were clinically relevantly changed on CIS-FS was calculated for each condition, using the reliable change index (RCI) [33,34]. See Appendix F for the calculations of the proportion of clinically relevantly changed participants. We used a clinical cut-off score of a normative group (CIS-FS < 28.0 [35]) which consisted of non-fatigued breast cancer survivors [35]. In our trial design paper [14], we suggested to use a normative group of women without a history of breast cancer [35], however we think it is better to use a normative group that indeed had a history of cancer, as it is such a disruptive illness, and comparing the group to healthy subjects would be less informative. The proportions of participants who had *recovered* (passed both the cut-off score of the normative group and the RCI criteria), *improved* (passed the RCI criteria in the direction of fatigue reduction), and *unchanged* (did not pass the RCI criteria), or *deteriorated* (passed the RCI in the direction of fatigue increase) were all calculated.

Finally, notes of and quotations from the telephone interviews with non-adherent participants were analyzed by close reading, followed by clustering of emerging themes concerning reasons for dropping out. ANOVA and χ^2-tests were performed to identify differences between adherent and non-adherent participants. The proportion of non-adherent participants was calculated.

Results

Patients

Between March 2013 and June 2015, 360 persons applied on the website to participate (see Figure 1 for flowchart). See Appendix A for details about the recruitment over the course of time. Applicants for the FNK-trial had heard about the project via family or friends (16.1%, *n* = 58/360), via patient societies (12.5%, *n* = 45/360), through a search on the Internet (11.7%, *n* = 42/360), via health professionals (5.8%, *n* = 21/360), or otherwise (unknown) (53.8%, *n* = 194/360).

We excluded 23.8% (*n* = 86/360) of the applicants (mean age = 56.3 years; standard deviation (SD) = 13.3; 59.3%, *n* = 51/86 women) for the reasons given in Figure 1, and another 26.4% (*n* = 95/360) declined to participate (mean age = 58.0 years; SD = 12.7, 67.4% (*n* = 64/95)

women) before the eligibility criteria were checked. Eventually, 179 participants were included (see Appendix D for baseline characteristics); of these, four participants dropped out before filling in T0b (mean age = 60.5 years; SD = 7.7; 75.0%, *n* = 3/4 women), and eight participants were excluded from analyses due to cancer recurrence during the study (mean age = 59.8 years; SD = 6.5; 50.0%, *n* = 4/8 women), leaving 167 participants for analyses.

Participants were randomized in one of the three conditions: (1) AAF (*n* = 62); (2) eMBCT (*n* = 55); or (3) PE (*n* = 50). All participants in the eMBCT group met the DSM-IV-TR criteria for undifferentiated somatoform disorder, of whom four out of 55 (7.3%) were additionally diagnosed with a sleeping disorder, seven (12.7%) experienced work-related psychosocial problems, and six (10.9%) suffered from problems in their peer-support group.

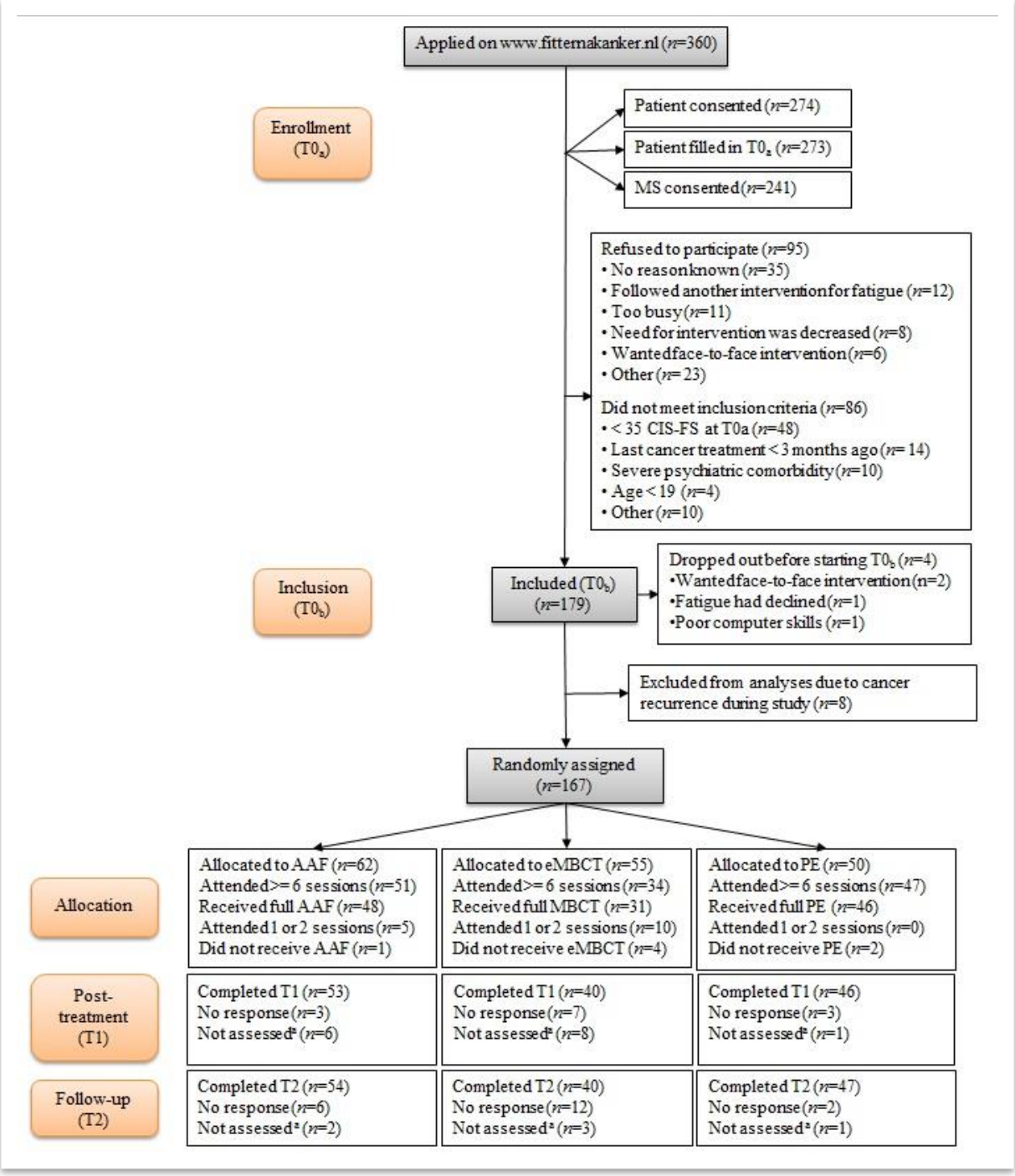


Figure 1. Flowchart FNK-trial. [a] The last five participants were not included in the analysis, as they were still in the trial at time of analysis.

Effectiveness

Model selection for CIS-FS showed that a model with both linear and quadratic slopes, with individual timescores, freely estimated mean and slope variances, and with residual variances

fixed to be equal between conditions, best fitted the data. Figure 2 shows the sample means of CIS-FS between T0b and T2 per condition.

Chi-Square difference testing (see Table 1), with linear and quadratic slopes fixed to be equal between conditions, showed that the CIS-FS trajectories differed between all three conditions (χ^2 (4) = 27.63, p < .001). More specifically, the trajectories of AAF and PE differed (χ^2 (2) = 28.28, p < .001), and eMBCT and PE differed (χ^2 (2) = 10.89, p = .004), while the trajectories of AAF and eMBCT were equal (χ^2 (2) = 2.19, p = .34). When only including adherent participants (n = 132), the results were similar: the slopes of AAF and eMBCT were equal (χ^2 (2) = 0.991, p = .61), while the slopes of PE and AAF differed (χ^2 (2) = 28.109, p < .001), and PE and eMBCT differed (χ^2 (2) = 9.735, p = .008). The slope estimates indicated that CIS-FS decreased significantly more in the AAF and eMBCT conditions compared to the PE condition.

The model fits for HADS, PA and NA were best for linear models with individual timescores and slope variances fixed at 0. As shown in Table 2, the slopes in all three conditions were significantly different from zero, HADS and NA decreased, and PA increased. Table 3 presents the results of Wald testing, and shows that there were no significant differences in slopes between the HADS, PA and NA between conditions.

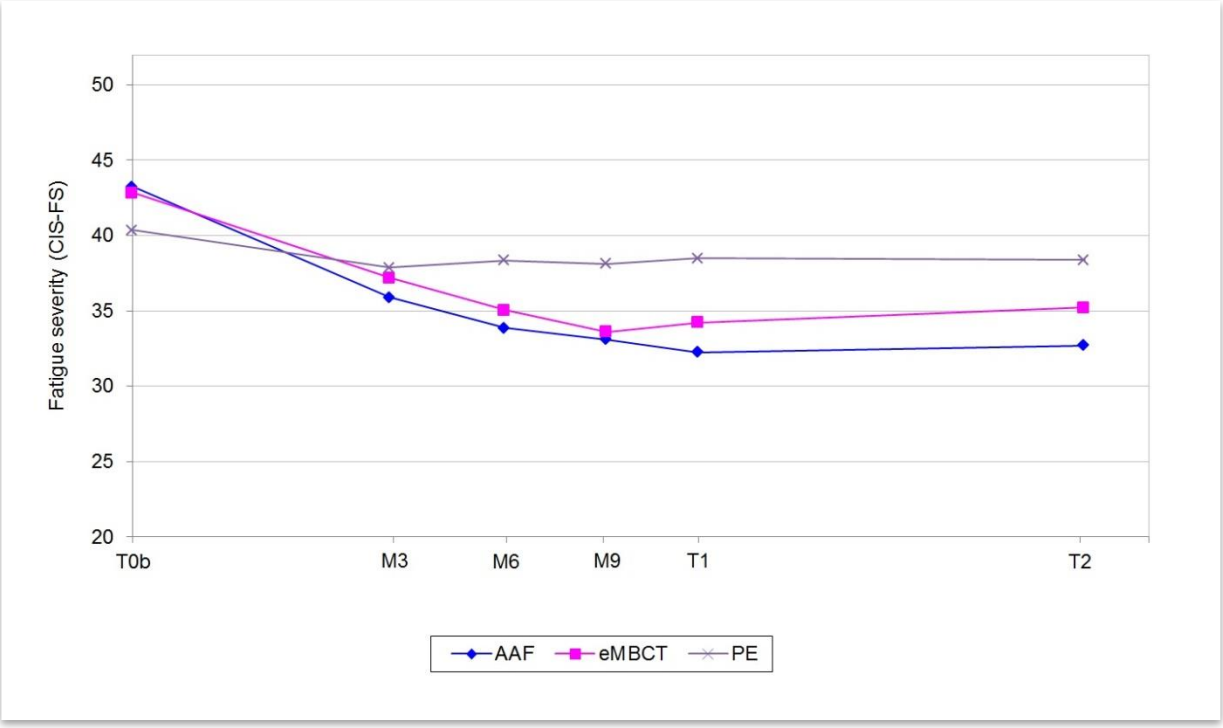


Figure 2. Sample means of fatigue severity (CIS-FS) for all three conditions (n=167). On the x-axis, the mean of timescores between T0b and M3, M6, M9, T1 and T2 are shown. Please note that the model included individual time scores. The average timescores (denoted in weeks, with standard deviations between brackets) between T0b and M3, M6, M9, T1, and T2 were 7.6 (2.4), 11.0 (2.8), 14.0 (2.6), 16.7 (3.2), and 28.1 (1.9), respectively. See Appendix E for the average distribution of individual timescores between T0b and T2.

Table 1. Results of the Chi-square testing of fatigue severity change (CIS-FS) between groups

Hypothesis test	**Results Chi-square test**
AAF = eMBCT = PE	χ^2 (4) = 27.63, p < .001
AAF = PE	χ^2 (2) = 28.28, p < .001
eMBCT = PE	χ^2 (2) = 10.89, p = 0.004
AAF = eMBCT	χ^2 (2) = 2.19, p = .34

Table 2. Model results of all outcome measurements. The mean intercepts and mean slope factors of all outcome measures with standard errors (in brackets) are presented.

Outcome	Condition	Intercept at T0 (I)	Linear slope factor (S)	Two-tailed *p*-value of linear slope *(p)*	Quadratic slope factor (Q)	Two-tailed *p*-value of quadratic slope *(p)*
CIS-FS	AAF	42.838 (0.873)	-1.072 (0.162)	$p < .001$	0.026 (0.005)	$p < .001$
	eMBCT	42.752 (1.020)	-0.876 (0.178)	$p < .001$	0.022 (0.006)	$p < .001$
	PE	39.893 (1.243)	-0.208 (0.170)	$p = .22$	0.006 (0.006)	$p = .31$
HADS	AAF	13.237 (0.921)	-0.076 (0.017)	$p < .001$	N/A	N/A
	eMBCT	13.903 (0.771)	-0.110 (0.022)	$p < .001$	N/A	N/A
	PE	14.579 (1.012)	-0.083 (0.024)	$p < .001$	N/A	N/A
PA	AAF	31.762 (0.939)	0.101(0.022)	$p < .001$	N/A	N/A
	eMBCT	28.995 (0.932)	0.156(0.026)	$p < .001$	N/A	N/A
	PE	29.422 (1.091)	0.128(0.027)	$p < .001$	N/A	N/A
NA	AAF	20.330 (0.931)	-0.068 (0.023)	$p = .003$	N/A	N/A
	eMBCT	20.718 (0.914)	-0.071 (0.032)	$p = .03$	N/A	N/A
	PE	20.805 (1.215)	-0.082 (0.029)	$p = .004$	N/A	N/A

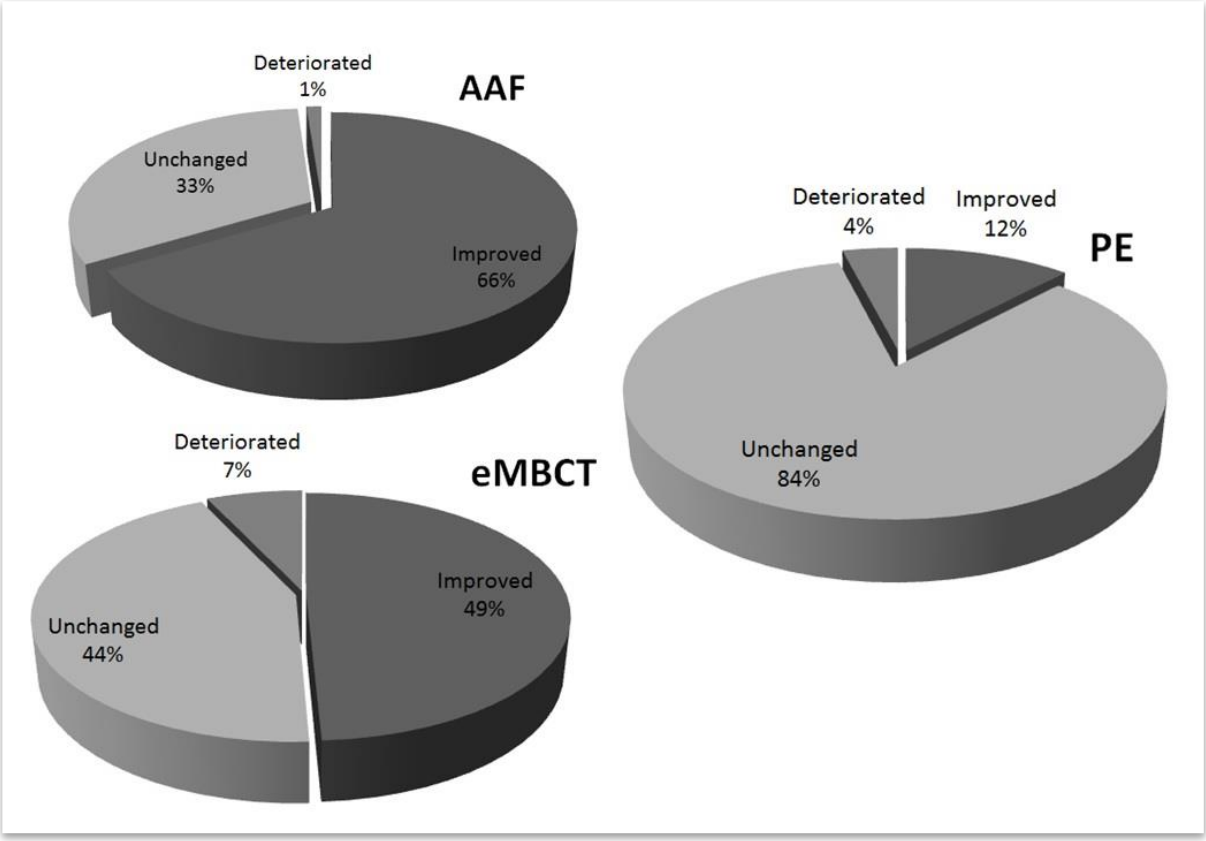
Table 3. Results of Wald testing for differences between conditions (HADS, PA and NA). All Wald tests were nonsignificant, indicating that there was no significant difference between the slopes of the conditions.

	Wald test	**Result**
HADS	AAF = PE	0.067(1), p = .80
	eMBCT = PE	0.665(1), p = .41
	AAF = eMBCT	1.491(1), p = .22
PA	AAF = PE	0.599(1), p = .44
	eMBCT = PE	0.573(1), p = .45
	AAF = eMBCT	2.640(1), p = .10
NA	AAF = PE	0.148(1), p = .70
	eMBCT = PE	0.065(1), p = .80
	AAF = eMBCT	0.006(1), p = .94

Clinically relevant change

The proportion of *recovered* participants for AAF was 21% (13/62), for eMBCT 9% (5/55), and for PE 2% (1/50). Of the adherent participants 26% (13/51) recovered in the AAF condition, 6% (2/34) in the eMBCT condition, and 2% (1/47) in the PE condition. Figure 3 shows the proportion of *improved*, *unchanged*, and *deteriorated* participants per condition. In the AAF condition 66% (41/62) improved, in the eMBCT condition 49% (27/55) improved, and in the psycho-education condition 12% (6/50) improved.

Figure 3. Proportions of clinically relevant changes (improved, unchanged, deteriorated) for each condition (intention-to-treat).



Treatment dropout

Nonadherence, the proportion of participants who dropped out the intervention before completing 6 weeks of the protocol, was 18% (11/62) in the AAF condition, 38% (21/55) in the eMBCT condition, and 6% (3/50) in the psycho-education condition. No differences in baseline characteristics were found between adherent and nonadherent participants. Reasons for dropping out of AAF were mainly technical problems and poor usability of the accelerometer. Nonadherence of eMBCT was mainly due to the high intensity of the program, the exercises were considered too woolly, poor usability of the eMBCT portal, and difficulty in communicating in writing with the therapist. In both interventions, nonadherent participants said they stopped using the intervention due to a lack of confidence that the intervention would help them reduce fatigue. Other reasons were that fatigue had reduced considerably and treatment was no longer desired, or that participants preferred face-to-face contact instead.

Discussion

Main Results

This is the first study to report on effectiveness of two guided Web-based interventions for CCRF. Using latent growth curve modeling, we found that AAF and eMBCT were significantly more effective in reducing fatigue severity than psycho-education. The proportions of participants that showed clinically relevant improvement were 66% (41/62) in the AAF condition, 49% (27/55) in the eMBCT condition, and 12% (6/50) in the psycho-education condition. Mental health improved in all three conditions. Treatment dropout was 18% (11/62) in the AAF condition and 38% (21/55) in the eMBCT condition.

Reasons for dropping out of AAF were technical problems with the accelerometer, and eMBCT was considered to be too intensive. The AAF dropout rate is comparable to other online interventions [36], and in a previous pilot study in clinical practice we also found a dropout rate of 38% in eMBCT [13]. Taking these dropout rates into account, we can conclude that both AAF and eMBCT are effective interventions for reducing fatigue severity.

Strengths & Limitations

Our study design has several strengths. First, in contrast to ANOVA, LGM allows the study of individual longitudinal development instead of average group effects. Furthermore, LGM does not require complete data as it deals with missing data elegantly [37–39], and individual times between assessments can be included in the analysis.

Second, we used an active control condition that consisted of psycho-education. As psycho-education has been found to be effective for cancer-related fatigue [40], comparing AAF and eMBCT to PE is a strict way of evaluating these interventions. Interestingly, fatigue severity did not significantly reduce in the psycho-education condition. We speculate that this lack of effect may be due to the presentation of psycho-education, namely that it was the minimal control intervention. Participants were perhaps disappointed not being randomized to one of the guided interventions. However, mental health did significantly increase in psycho-education.

Third, as we wanted to study the intervention effect alone, we chose T0b (after the eligibility check) as our baseline measurement instead of T0b (at recruitment). As fatigue significantly reduced between T0a and T0b (n = 174, t = 6.293, df = 173, p < .001, r = .548), which was before any experimental intervention took place, choosing T0b as baseline assessment prevented overestimation of the intervention effect. Fourth, to make these results relevant for health care practice, we 1) chose not to exclude patients suffering from comorbidities that may also explain fatigue, 2) we included all cancer types and 3) included patients who were using hormone therapy or antidepressants during the study. We did not control for these contributing factors, except from the check that they were equally divided between the three conditions. In this way, the sample better represents the population for which these interventions were developed, and the results of effectiveness are better representative for health care practice. Although cancer type has not been found to be related to the persistence of fatigue [2], comorbidities (e.g. thyroid dysfunction, cardiovascular diseases, rheumatism) and the use of hormone therapy or antidepressants are presumably influencing the level of fatigue [41,42]. Therefore the effectiveness we found would probably be higher if we had chosen to study a population without comorbidities. In contrast, other researchers may choose exclusion criteria to limit confounding factors with the intervention effect to study the proof of concept. Although this decision is valid for research purposes, it consequently extends the gap between research findings and healthcare practice [43]. Therefore, we and others (e.g. Treweek and Zwarenstein [44]) encourage researchers to study interventions that are intended to be applied in health care practice using a pragmatic randomized controlled trial (RCT) study design, thus with no strict exclusion criteria that extend the gap between research and healthcare practice.

In previous research it was found that female breast cancer patients with high education are well represented in the population that seeks support in mental health institutes specialized in psycho-oncology [45]. We therefore think the current sample, that has a large proportion of female breast cancer patient and a high level of education, is representative for this population, but less representative for the cancer population in general.

In line with the arguments above, clinicians and researchers should be cautious when comparing the effectivity results reported by different intervention studies (e.g. for comparison Gielissen et

al. [8] and Abrahams et al. [44]), because assessment points, normative groups, data analyses methods, and inclusion and exclusion criteria vary. A limitation of this study was the unequal sample size of the conditions. As was previously reported in our trial design paper [14], the unequal sample size was partially caused by an error in the website's randomization algorithm.

We noted several disadvantages of the RCT study design when evaluating these Web-based interventions. One limitation is that in an RCT design, the intervention is "frozen" in time, while technical applications evolve rapidly, resulting in the intervention being outdated when the effectiveness has been investigated. For example, the eMBCT webpage (developed in 2010) functioned poorly on a tablet, which led to treatment dropout of participants who used a tablet instead of a computer. Smaller and more elegant accelerometers have also come to the market, which affected the credibility of the devices that were used in this study. Another limitation of our study design is that we had to exclude participants based on scoring too low on CIS-FS at recruitment, despite the fact that they said they indeed suffered from extreme fatigue. Another limitation was that the norm group that was used to calculate the percentage of clinically relevant improved participants was younger than our sample (norm group: mean age = 45.9 years; *SD* = 6.3 [35] versus our sample: mean age = 55.1; *SD* = 10.1) and only consisted of breast cancer patients. Ideally we would have used a non-severely fatigued group of cancer survivors, of around the same age as our sample, but this was not available in existing literature. In conclusion, both the AAF and eMBCT are effective for managing fatigue severity compared to receiving psycho-educational emails. This is the first study that reported on the effectiveness of Web-based interventions for CCRF compared to an active control condition. The analytical methods of this study were new, and thereby added to the scientific knowledge on evaluating the clinical effectiveness of Web-based interventions. We are currently working on the analyses of a one-year follow-up [46]. To improve the interventions we are also studying working mechanisms [47,48], and which baseline characteristics predict treatment outcome. Additionally, in order to better attune interventions to the patients' needs and reduce dropout, we performed qualitative analysis of semi-structured interviews with participants about their experiences with the interventions [49].

Appendices

APPENDIX A - Recruitment over the course of time

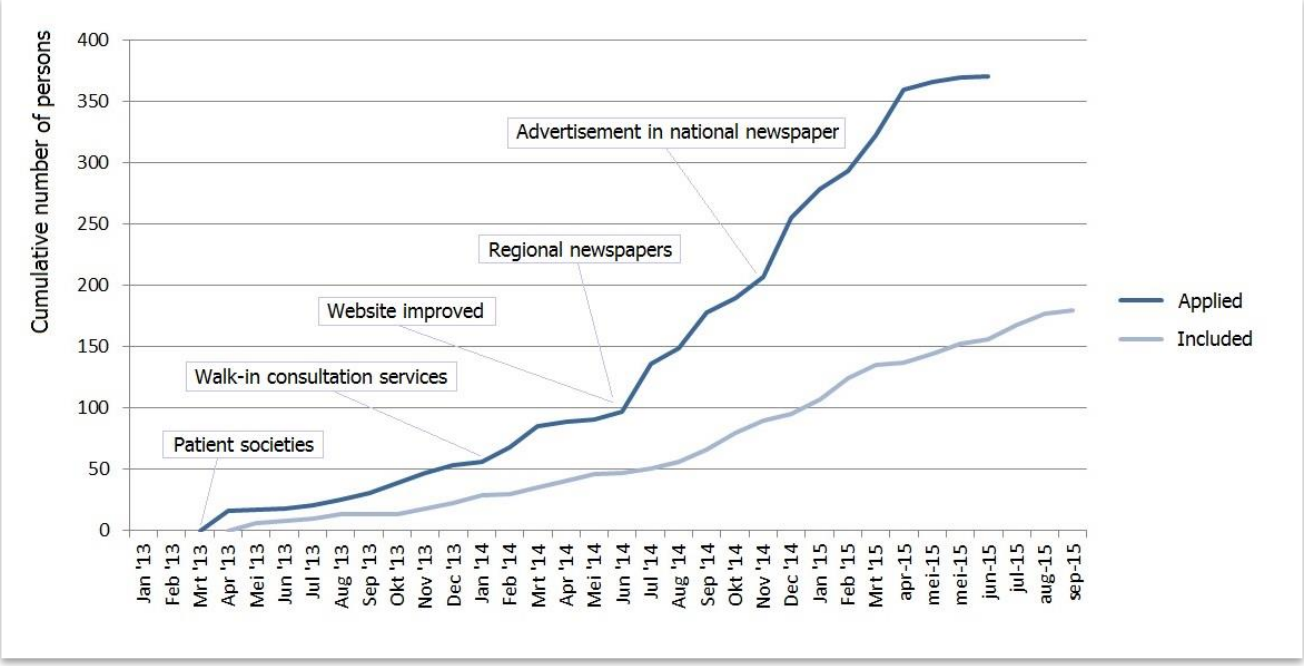


Figure Appendix A. Recruitment over the course of time. The cumulative number of persons who applied to participate in the study and the number of included participants are shown over the course of recruitment time. The figure also shows when major recruitment actions were performed, such as when the improved Web page was launched.

APPENDIX B - Recruitment material (translated from Dutch)

Are you suffering from fatigue after cancer? Have you had cancer in the past, but are you still suffering from fatigue? Then please apply for the study *Fitter na kanker*. In this study we will investigate two different internet interventions. Participants are offered an internet intervention that is guided by a psychologist or physiotherapist. For more information and application, go to www.fitternakanker.nl. *Fitter na kanker* is a collaboration between the Helen Dowling Instituut and Roessingh Research and Development, and is subsidized by the Alpe d'HuZes/KWF-fund.

APPENDIX C - Informed consent (translated from Dutch)

Informed consent for the study *Fitter na kanker* – Research on the effectiveness and working mechanisms of two different e-therapies for chronic fatigue after cancer

- I consent to participate in the above mentioned research.
- I have read the information letter for the study, and I have understood the purpose of the study and how much time-investment it will cost me.
- I have had plenty of time to think about my participation and have had the opportunity to ask questions. These questions have been answered satisfactorily.
- It is clear to me that I can withdraw from the study at any time, and that it has no consequences for me.
- I consent that the authorized persons of the Helen Dowling Instituut and Roessingh Research and Development, members of the medical ethics committee, and competent authorities may have access to my research data. They are required to keep these research data secret.
- My research data are processed in scientific reports, but I understand that I cannot be recognized therein as a person. I know whom I can turn to with questions about the study.
- I know that if I were to decide to discontinue my participation in the study, my research data gathered prior to this decision may still be processed together with other data collected as part of this study.
- I give permission to the researchers of FNK-trial to contact me for any future research. I know I am free to participate in future research or not.

APPENDIX D - Baseline characteristics of included participants (n=167)

Baseline characteristics	**M (SD)/%**
Demographics	
Age (years)	55.1 (10.1)
Women	72.6 (*n*=130)
Dutch nationality	98.9 (*n*=177)
Living with partner and/or children	86.6 (*n*=155)
Religious beliefs	
No	61.5 (*n*=110)
Christian	25.7 (*n*=46)
Other	12.8 (*n*=23)
Education	
Low	3.4 (*n*=6)
Middle	32.4 (*n*=58)
High	64.2 (*n*=115)
Employment	
Paid job	41.9 (*n*=75)
Absent from work	24.6 (*n*=44)
Work ability (0-10)	2.17 (1.69)
Medical history	
Cancer diagnosis	
Breast	*n*= 81
Blood, bone marrow, Hodgkin's	*n*= 27
Reproductive organs	*n*= 27
Digestive system	*n*= 18
Head and neck	*n*= 11
Urinary tract	*n*=9
Leukemia	*n*=8
Other	*n*= 24
Time since first cancer diagnosis	
<1 yr	2.3 (*n*=4)
1-2 yr	21.4 (*n*=37)
2-5 yr	35.3 (*n*=61)
> 5 yr	41.0 (*n*=71)
Time since final cancer treatment	
< 6 months	1.7 (*n*=3)
6 months - 1 year	14.5 (*n*=25)

1-2 year	25.6 (*n*=44)
2-5 year	33.1 (*n*=57)
> 5 year	25.0 (*n*=43)
Cancer recurrence in the past	8.9 (*n*=16)
Hereditary form of cancer	3.4 (*n*=6)
Lymph nodes affected	40.8 (*n*=73)
Metastases	13.9 (*n*=24)
Good prognosis	76.5 (*n*=137)
Type of cancer treatment [a]	
Surgery	76.5 (*n*=137)
Chemotherapy	68.7 (*n*=123)
Radiotherapy	58.1 (*n*=104)
Hormonal therapy	29.6 (*n*=53)
Immunotherapy	7.3 (*n*=13)
Stem cell or bone marrow transplantation	6.1 (*n*=11)
Other	1.7 (*n*=3)
Operation only	8.9 (*n*=16)
Operation, radiotherapy and chemo	34.1 (*n*=61)
Comorbidity	
No comorbidity	49.2 (*n*=88)
One comorbidity	33.5 (*n*=60)
More than one comorbidity	17.3 (*n*=31)
Medication use between T0b and T2	
Hormone therapy	21.8 (*n*=38)
Changed hormone therapy use	*n*=5
Antidepressants	4.5 (*n*=7)
Changed antidepressants use	*n*=1
Duration of fatigue	
0- 1 year	21.3 (*n*=38)
1-5 years	46.6 (*n*=83)
> 5 years	31.0 (*n*=57)
Help received	
Psychological counseling in the past	49.2 (*n*=88)
Has received help to cope with cancer in the past	68.2 (*n*=122)
No experience with attention-focused exercises, such as meditation or yoga	44.1 (*n*=79)
Followed any other form of psychological care for fatigue at baseline	8.4 (*n*=15)

Fatigue	
CIS-FS T0a	45.5 (5.4)
CIS-FS T0b	42.0 (7.9)
Mental Health	
PANAS total	50.9 (7.0)
Negative affect	21.1 (7.9)
Positive affect	29.8 (7.3)
HADS total	14.3 (7.0)
≥20 at baseline	22.3 (*n*= 40)

[a] Numbers do not sum to n = 167, as some participants had undergone multiple cancer treatments. *Abbreviations*: CIS-FS = Checklist Individual Strength-fatigue severity subscale; HADS = Hospital Anxiety and Depression Scale; PANAS = Positive and Negative Affect Schedule; M = Mean; SD = standard deviation

APPENDIX E - Selection procedure and results of best model fit for fatigue severity

Figure E.1 below shows the various tested models for fatigue severity trajectory (CIS-FS). We tested if a linear or linear and quadratic slope would best fit the data. As the timing of assessments varied between participants (see lower part of figure E.1 for the variation per assessment), we also ran a model with individually varying times of assessments, known as timescores [50], instead of the fixed factor loadings reflecting our study design [0,1,2,3,4,8]. In that way, we were able to include in the model the exact time points when a participant completed the assessment. Also, for the CIS-FS data, we tested whether a piece-wise model would better fit the data than a non-piece wise model, thus a separate slope during the intervention (slope 1: T0b–M3–M6–M9) and a separate slope after the intervention (slope 2: M9–T1–T2) in favor of one slope (T0b–M3–M6–M9–T1–T2). The model selection procedures for HADS and PANAS were similar, except that no piece-wise model was estimated because the secondary outcome measures were assessed three times (T0b–T1–T2). Therefore, only the procedure for CIS-FS is shown in this appendix.

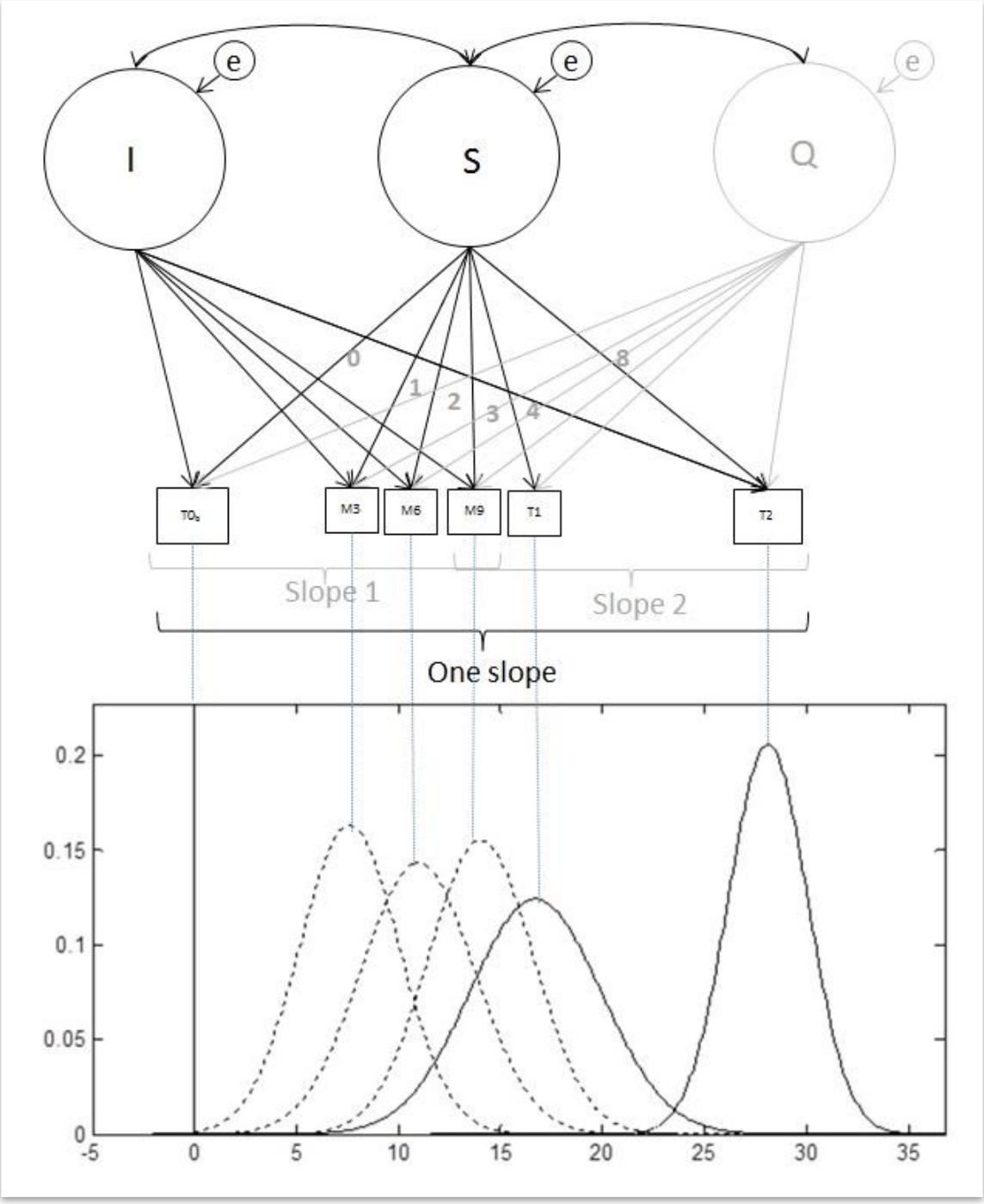


Figure E.1. Illustration of the piece-wise latent growth curve model of CIS-FS with timescores. We compared models with: (1) linear or quadratic growth terms; (2) with or without individual time between assessments (timescores), and (3) one slope or two piece-wise model (slope 1 and 2). The factor loadings in this figure make up the metric of time reflecting our study design [0,1,2,3,4,8]. The lower part of the figure shows the estimated density plots of the timing (weeks) of assessments (timescores) on the x-axis, and probability on the y-axis. *Abbreviations*: I = intercept, S = linear slope, Q = quadratic slope, e = residual variance.

Table E.1 The average time between assessments in weeks are shown.

Timeframe	Mean	Standard deviation	range
T0b-M3	7.60	2.443	3-18
T0b-M6	10.96	2.785	7-23
T0b-M9	14.04	2.567	10-24
T0b-T1	16.71	3.215	12-29
T0b-T2	28.10	1.936	23-37

In Table E.2 below, the AIC and BIC model results are shown for each model tested. These models differed in terms of:

- slope: linear (is) or linear and quadratic (isq)
- model: piece-wise (PW) or one trend line (*LGM*)
- time modeling: with or without timescores (*TSC*).

In the second step, model fit was improved by imposing constraints (see abbreviations below table). The model with the lowest fit indices (AIC and BIC sumscore), and secondly the most parsimonious model, resulting in model selection of *B2.LGM_CIS_isq_TSC.inp* for the effectiveness analysis. When the variances or residual variances of the means and slopes were not significantly different from zero in all three conditions, these were constrained to be equal between conditions to see if this would improve model fit. When error messages for the residual variances were present, these were constrained to be equal between conditions.

Table E.2. STEP 1. Run all models without constraints

name input Mplus	constraint	AIC and BIC	AIC+BIC	warnings/errors
A1.LGM_CIS_is.inp	none	(AIC) 5.698.798 (BIC) 5.801.692	11.500.490	none
B1.LGM_CIS_isq.inp	none	(AIC) 5.597.179 (BIC) 5.737.488	11.334.667	WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP eMBCT AND PE IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES.CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE T2CISZ. WARNING: THE LATENT VARIABLE COVARIANCE MATRIX (PSI) IN GROUP EMBCT IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR A LATENT VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO LATENT VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO LATENT VARIABLES. CHECK THE TECH4 OUTPUT FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE S.
A2.LGM_CIS_is_TSC.inp	none	(AIC) 5.667.421 (BIC) 5.770.315	11.437.736	none
B2.LGM_CIS_isq_TSC.inp	none	(AIC) error (BIC) error	0	THE MODEL ESTIMATION DID NOT TERMINATE NORMALLY DUE TO AN ILL-CONDITIONED FISHER INFORMATION MATRIX. CHANGE YOUR MODEL AND/OR STARTING VALUES. THE MODEL ESTIMATION DID NOT TERMINATE NORMALLY DUE TO A NON-POSITIVE DEFINITE FISHER INFORMATION MATRIX. THIS MAY BE DUE TO THE STARTING VALUES BUT MAY ALSO BE AN INDICATION OF MODEL NONIDENTIFICATION. THE CONDITION NUMBER IS 0.479D-10. THE STANDARD ERRORS OF THE MODEL PARAMETER ESTIMATES COULD NOT BE COMPUTED. THIS IS OFTEN DUE TO THE STARTING VALUES BUT MAY ALSO BE AN INDICATION OF MODEL NONIDENTIFICATION. CHANGE YOUR MODEL AND/OR STARTING VALUES. PROBLEM INVOLVING THE FOLLOWING PARAMETER: Parameter 36, Group PE: T2CISZ

name input Mplus	constraint	AIC and BIC	AIC+BIC	warnings/errors
C1.PW_CIS_is_is.inp	none	(AIC) 5.600.617 (BIC) 5.740.927	11.341.544	WARNING: THE LATENT VARIABLE COVARIANCE MATRIX (PSI) IN GROUP EMBCT IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/ RESIDUAL VARIANCE FOR A LATENT VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO LATENT VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO LATENT VARIABLES. CHECK THE TECH4 OUTPUT FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE S1. WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP PE IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE T2CISZ.
D1.PW_CIS_isq_is.inp	none	(AIC) 5.579.688 (BIC) 5.766.767	11.346.455	WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP AAF IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE TBCISZ. WARNING: THE LATENT VARIABLE COVARIANCE MATRIX (PSI) IN GROUP EMBCT IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/ RESIDUAL VARIANCE FOR A LATENT VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO LATENT VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO LATENT VARIABLES. CHECK THE TECH4 OUTPUT FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE I. WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP PE IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE TBCISZ.

C2.PW_CIS_is_is_TSC.inp	none	(AIC) 5.670.371 (BIC) 5.810.681	11.481.052	none
D2.PW_CIS_isq_is_TSC.inp	none	(AIC) 5.684.750 (BIC) 5.871.830	11.556.580	WARNING: THE MODEL ESTIMATION HAS REACHED A SADDLE POINT OR A POINT WHERE THE OBSERVED AND THE EXPECTED INFORMATION MATRICES DO NOT MATCH. AN ADJUSTMENT TO THE ESTIMATION OF THE INFORMATION MATRIX HAS BEEN MADE. THE CONDITION NUMBER IS -0.325D-02. THE PROBLEM MAY ALSO BE RESOLVED BY DECREASING THE VALUE OF THE MCONVERGENCE OR LOGCRITERION OPTIONS OR BY CHANGING THE STARTING VALUES OR BY USING THE MLF ESTIMATOR.

Table E.3. STEP 2. Improve fit with adding constraints based on output in step1: a) When variances were non-significant in all groups they were constraint to 0; b) When residual variances were non-significant, they were constraint to be equal between groups; c) When residual variances were non-significant, they were constraint to be equal between groups

name input Mplus	constraint	AIC and BIC	AIC+BIC	warnings/errors
A1.LGM_CIS_is.inp	s@0	(AIC) 5.697.432 (BIC) 5.781.617	11.479.049	none
A2.LGM_CIS_is_TSC.inp	s@0	(AIC) 5.672.659 (BIC) 5.756.844	11.429.503	none
B1.LGM_CIS_isq.inp	res var (1)	(AIC) 5.586.788	11.260.880	none

		(BIC) 5.674.092		
B2.LGM_CIS_isq_TSC.inp	q@0	(AIC) 5.657.207 (BIC) 5.769.455	11.426.662	WARNING: THE MODEL ESTIMATION HAS REACHED A SADDLE POINT OR A POINT WHERE THE OBSERVED AND THE EXPECTED INFORMATION MATRICES DO NOT MATCH. AN ADJUSTMENT TO THE ESTIMATION OF THE INFORMATION MATRIX HAS BEEN MADE. THE CONDITION NUMBER IS -0.102D-06. THE PROBLEM MAY ALSO BE RESOLVED BY DECREASING THE VALUE OF THE MCONVERGENCE OR LOGCRITERION OPTIONS OR BY CHANGING THE STARTING VALUES OR BY USING THE MLF ESTIMATOR.
B2.LGM_CIS_isq_TSC.inp	s@0	(AIC) error (BIC) error	0	THE STANDARD ERRORS OF THE MODEL PARAMETER ESTIMATES COULD NOT BE COMPUTED. THIS IS OFTEN DUE TO THE STARTING VALUES BUT MAY ALSO BE AN INDICATION OF MODEL NONIDENTIFICATION. CHANGE YOUR MODEL AND/OR STARTING VALUES.
B2.LGM_CIS_isq_TSC.inp	res var (1)	(AIC) 5.581.389 (BIC) 5.668.693	11.250.082	none
B2.LGM_CIS_isq_TSC.inp	q@0 en s@0	(AIC) 5.668.360 (BIC) 5.761.900	11.430.260	none
C1.PW_CIS_is_is.inp	[s2](1)	(AIC) 5.597.636	11.329.346	WARNING: THE LATENT VARIABLE COVARIANCE MATRIX (PSI) IN GROUP EMBCT IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/ RESIDUAL VARIANCE FOR A LATENT

		(BIC) 5.731.710		VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO LATENT VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO LATENT VARIABLES. CHECK THE TECH4 OUTPUT FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE S1. WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP PE IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE T2CISZ.
C1.PW_CIS_is_is.inp	[s2](1) en res var (1)	(AIC) 6.266.864 (BIC) 6.344.814	12.611.678	none
C1.PW_CIS_is_is.inp	res var (1)	(AIC) 5.589.511 (BIC) 5.676.814	11.266.325	none
C2.PW_CIS_is_is_TSC.inp	s2@0	(AIC) 5.675.016 (BIC) 5.787.264	11.462.280	none
C2.PW_CIS_is_is_TSC.inp	s1@0 and s2@0	(AIC) 5.666.057 (BIC) 5.759.597	11.425.654	none
D1.PW_CIS_isq_is.inp	[s2](1)	(AIC) 5.576.497	11.333.838	WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP AAF IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN

		(BIC) 5.757.341		OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE TBCISZ. WARNING: THE LATENT VARIABLE COVARIANCE MATRIX (PSI) IN GROUP EMBCT IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/ RESIDUAL VARIANCE FOR A LATENT VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO LATENT VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO LATENT VARIABLES. CHECK THE TECH4 OUTPUT FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE I. WARNING: THE RESIDUAL COVARIANCE MATRIX (THETA) IN GROUP PE IS NOT POSITIVE DEFINITE. THIS COULD INDICATE A NEGATIVE VARIANCE/RESIDUAL VARIANCE FOR AN OBSERVED VARIABLE, A CORRELATION GREATER OR EQUAL TO ONE BETWEEN TWO OBSERVED VARIABLES, OR A LINEAR DEPENDENCY AMONG MORE THAN TWO OBSERVED VARIABLES. CHECK THE RESULTS SECTION FOR MORE INFORMATION. PROBLEM INVOLVING VARIABLE TBCISZ.
D1.PW_CIS_isq_is.inp	res var (1) en [s2](1)	(AIC) 6.155.517 (BIC) 6.280.236	12.435.753	none
D1.PW_CIS_isq_is.inp	res var (1) en q1@0	(AIC) 5.564.601 (BIC) 5.661.259	11.225.860	none
D1.PW_CIS_isq_is.inp	res var (1)	(AIC) 5.573.097 (BIC) 5.707.171	11.280.268	none

D2.PW_CIS_isq_is_TSC.inp	s1@0	(AIC) error (BIC) error	0	THE STANDARD ERRORS OF THE MODEL PARAMETER ESTIMATES COULD NOT BE COMPUTED. THIS IS OFTEN DUE TO THE STARTING VALUES BUT MAY ALSO BE AN INDICATION OF MODEL NONIDENTIFICATION. CHANGE YOUR MODEL AND/OR STARTING VALUES.
D2.PW_CIS_isq_is_TSC.inp	s2@0	(AIC) 5.685.188 (BIC) 5.834.852	11.520.040	WARNING: THE MODEL ESTIMATION HAS REACHED A SADDLE POINT OR A POINT WHERE THE OBSERVED AND THE EXPECTED INFORMATION MATRICES DO NOT MATCH. AN ADJUSTMENT TO THE ESTIMATION OF THE INFORMATION MATRIX HAS BEEN MADE. THE CONDITION NUMBER IS -0.197D-01. THE PROBLEM MAY ALSO BE RESOLVED BY DECREASING THE VALUE OF THE MCONVERGENCE OR LOGCRITERION OPTIONS OR BY CHANGING THE STARTING VALUES OR BY USING THE MLF ESTIMATOR.
D2.PW_CIS_isq_is_TSC.inp	s1@0 and s2@0	(AIC) error (BIC) error	0	THE ESTIMATED COVARIANCE MATRIX FOR AAF IS NOT POSITIVE DEFINITE AS IT SHOULD BE. COMPUTATION COULD NOT BE COMPLETED. PROBLEM INVOLVING VARIABLE Q1. THE CORRELATION BETWEEN Q1 AND I IS -1.071 THE RESIDUAL CORRELATION BETWEEN Q1 AND I IS -1.071 THE PROBLEM MAY BE RESOLVED BY SETTING ALGORITHM=EM AND MCONVERGENCE TO A LARGE VALUE. THE MODEL ESTIMATION DID NOT TERMINATE NORMALLY DUE TO AN ERROR IN THE COMPUTATION. CHANGE YOUR MODEL AND/OR STARTING VALUES

Abbreviations: LGM = latent growth model, thus one trend line; PW = Piece-wise latent growth model; is = slope is linear; isq = slope is both linear and quadratic; TSC = with individual timescores; no TSC = model-based timescores [0,1,2,3,4,8]; res var (1) = residual variances constrained to be equal between groups; s@0 = linear slope variance is constrained to 0 in all groups; q@0 = quadratic slope variance is constrained to 0 between groups; [s](1) = slope mean is constrained to be equal between groups; BIC = Bayesian Information Criterion; AIC = Akaike Information Criterion

APPENDIX F - Calculations of proportion reliably changed participants

The proportion of participants who were clinically relevantly changed on fatigue severity (CIS-FS) was calculated using the reliable change index (RCI) [33,34]. The Reliable change index (RCI) was calculated according to the method proposed by Jacobson & Truax [33] (see also Maassen [34]).

The RCI per individual was calculated by applying the following formula:

(3) $$RCI = \frac{X_2 - X_1}{S_{diff}}$$

where $X_2 - X_1$ is the individual change score of CIS-FS between T0b and T2. To be able to calculate the RCI for all participants – so also for participants who had missing data at T2 – we used the estimated intercepts of CIS-FS at T2 of the best fitting model (see Appendix 3 for model selection). These intercepts were obtained using the FSCORE function in the SAVE command of Mplus.

S_{diff} was calculated by applying the following formula:

(4) $$S_{diff} = \sqrt{2(SE)^2}$$

where *SE* is denoted by:

(5) $$SE = SD_1\sqrt{1 - r_{xx}}$$

where SD_1 is the standard deviation of the norm group and r_{xx} is the test-retest reliability of the CIS-fatigue severity subscale.

The norm group consisted of non-fatigued cancer survivor (n=93) [35] (Mean CIS-FS = 19.6, *SD* = 8.4). The cut-off norm group was *M* +1 *SD* = 28.0. The test-retest reliability was r_{xx} = 0.88 based on Vercoulen et al. [51].

Then, the proportion of clinically relevant improved participants was calculated based on the following definitions:

Improved: passed RCI in direction of fatigue reduction, thus RCI < - 1.96

Unchanged: did not pass the RCI, thus - 1.96 < RCI < 1.96.

Deteriorated: passed RCI in direction of fatigue increase, thus RCI > 1.96

Recovered: passed RCI in direction of fatigue reduction, thus RCI < - 1.96 and CIS-FS T2 was below the cut-off point of the norm group, so below 28.

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Chapter 6

Understanding change in online Mindfulness-Based Cognitive Therapy for Chronic Cancer-Related Fatigue

Based on:

Bruggeman-Everts, F.Z., Van der Lee, M.L., Wolvers, M.D.J., Van de Schoot, R & Vollenbroek-Hutten, M.M.R. (submitted). Understanding change in Web-based Cognitive Therapy for chronic cancer-related fatigue.

Abstract

Background: Online Mindfulness-Based Cognitive Therapy (eMBCT) showed to be effective in reducing chronic cancer-related fatigue in cancer survivors (CCRF). In order to gain insight in how and for whom reduction in fatigue severity may be established during eMBCT, the current paper reports on a comprehensive model of predictors and working mechanisms for fatigue severity change.

Design: A three-armed randomized controlled trial called 'Fitter na kanker' was performed (n=167), in which participants were randomized to (1) eMBCT (*n* = 55), (2) a physiotherapist-guided ambulant activity feedback (AAF) therapy encompassing an accelerometer (*n* = 62), or an active control condition consisting of weekly e-mails with psycho-education (PE) concerning CCRF (*n* = 50). This study design allowed to study specific and generic predictors and working mechanisms for eMBCT. Fatigue severity was assessed at baseline (T0b), three times during the intervention (week 3, 6, and 9), and two weeks after intervention completion (T1). Constructs of interest were: *mindfulness* (*acceptance* and *presence*), *sleep quality*, *working alliance*, *sense of control over fatigue*, *credibility* and *expectancy* of the intervention, *fear of cancer recurrence* and *fatigue catastrophizing*. The latter two constructs were assessed before and after the intervention and all other constructs were additionally assessed three times during the intervention.

Methods: Using latent growth curve analyses slope factors (linear change) of each construct were estimated. The predictive value of (1) the baseline values (predictors) and (2) the slope factors (working mechanisms) for fatigue severity change were investigated in two separate multiple group regression analyses.

Results: High *sense of control* at baseline (β = -0.451, SE = 0.116, $p < .001$) appeared to be a specific predictor in eMBCT, and high *credibility* in PE (β = -0.436, SE = 0.148, $p = .003$). The predictors explained 33% of the variance in eMBCT, 12% in AAF, and 19% in PE. An increase in *sense of control* was a significant working mechanism in eMBCT (β = -0.598, SE = 0.093, $p < .001$), as well as in AAF (β = -0.651, SE = 0.083, $p < .001$). A decrease in *fatigue catastrophizing* was a specific working mechanism in PE (β = 0.391 , SE = 0.146, $p < .001$). The working mechanisms explained 55% of the variance of fatigue change in eMBCT, 48% in AAF, and 52% in PE.

Conclusions: We conclude that (1) patients with high *sense of control* at baseline benefit from eMBCT, (2) patients with high *credibility* of psycho-education about CCRF benefit from PE, (3) an increase in *sense of control* is a generic working mechanism for fatigue severity reduction in both eMBCT and AAF, and not in PE, and (4) a decrease in *fatigue catastrophizing* is a specific working mechanisms in PE. While baseline and change in *expectancy, mindfulness (acceptance and presence), sleep quality, fear of cancer recurrence,* and *fatigue severity* was not related to outcome. This information contributes to indication and augment effects of these treatments in clinical practice.

Introduction

Fatigue is known as the most distressing long term symptom after cancer and cancer treatment [1]. About one third of cancer survivors (patients with complete remission or no evidence of disease, and not currently receiving cancer treatment) suffer from severe persisting fatigue [2,3], a condition we call chronic cancer-related fatigue (CCRF).

Mindfulness-Based Cognitive Therapy (MBCT), specifically designed to reduce CCRF, has shown to be effective in a 2-armed randomized controlled trial (RCT) [4]. At the Helen Dowling Instituut (a health care institute, specialized in psycho-oncology, situated in Bilthoven, the Netherlands) an online version of this MBCT protocol [4] has been developed, called eMBCT [5,6]. On a password-secured website [7], patients can download information about CCRF and mindfulness exercises. They are asked to do the exercises for 45 minutes daily and write down their experiences with doing these exercises in a log file. Their personal psychologist responds to this log file and thereby guides the patient through the 9-week protocol. For more information about the eMBCT protocol, see Bruggeman-Everts et al. [8] and Wolvers et al. [5].

In a recent 3-armed RCT *More fit after cancer* – in Dutch 'Fitter na kanker', hereafter FNK-trial – it was shown that eMBCT and a physiotherapist-guided Ambulant Activity Feedback (AAF) were effective in reducing fatigue severity in severely fatigued cancer survivors, compared to patients in an active control condition who received weekly e-mails with psycho-education concerning CCRF (PE) [6]. Identifying which baseline patient characteristics predict which intervention works best for whom will help to refer patients to the treatment that is most likely to help them.

In order to optimize efficacy of treatments it is also useful to identify working mechanisms that are involved in fatigue severity change [9]. By identifying working mechanisms, we gain information on how an intervention works and which constructs are important for improving the intervention. In the current paper we focus on eMBCT and use the results of the other two conditions to see if the predictors were specific for eMBCT or generic. In another study, working mechanisms for AAF were investigated, including change in objective and subjective physical activity behavior [10]. Below, we will underpin our hypothesized constructs that are of interest for explaining change in fatigue in eMBCT. In Table 1 an overview of our constructs is shown.

Theory of eMBCT and hypothesized constructs

The theory behind MBCT suggests that by learning to raise awareness to the present experience non-judgmentally and openly, the patient can become aware of potentially inefficient coping strategies [11,12]. Based on the model of Baer [13], and as reported in a previous study [8], MBCT can help severely fatigued cancer survivors through (1) exposure to fatigue sensations non-judgmentally, thereby reducing distress associated with fatigue through desensitization, (2) cognitively detaching from distressing thoughts and thereby not being overwhelmed by fear of cancer recurrence, (3) raising awareness to the present moment and thereby becoming aware of potentially maladaptive coping strategies and choose to act differently, (4) finding ways to relax through meditation exercises and thereby improving quality of sleep and rest, (5) accepting the present energy level and thereby reducing energy loss that would otherwise be spilled on trying to change, escape, or avoid fatigue. Based on the model of Baer and the previously mentioned research findings, we hypothesized that an increase in mindfulness skills (presence and acceptance) [14–16] is a working mechanism specific for eMBCT, and not for AAF and PE.

Furthermore, an increase in sense of control showed to mediate reduction in fatigue during Cognitive Behavior Therapy (CBT) for chronic fatigue syndrome [17]. Poor sleep quality was associated with high levels of CCRF [2,18–20]. Persistent fatigue in cancer survivors was predicted by fear of disease recurrence in previous studies [21–24], however fatigue can also be a trigger for fear of disease recurrence. Therefore, we also hypothesized that the following constructs related to CCRF [25] were of general predictive value for treatment outcome such

as sleep quality [26–30], fear of cancer recurrence [25], catastrophizing about fatigue [18,31], and sense of control over fatigue [23,32,33].

In addition, more general constructs may play a role in the success of the outcome, such as patient's credibility and expectations of an intervention [34–36], and the working alliance [37]. Credibility has been defined as 'how believable, convincing, and logical the treatment is' and expectancy as 'improvements that clients believe will be achieved' [38]. These constructs have not been studied before quantitatively in (online) mindfulness-based interventions for cancer patients [39]. Nor have change in these constructs, thus patients being positively surprised about the effect of the intervention or being disappointed about the effect during the intervention, been studied before.

The quality of the working alliance has been defined as the extent to which a patient and a therapist work collaboratively and purposefully and connect emotionally [40]. In previous studies it was found that the quality of the alliance early in treatment predicted outcome at the end of psychotherapy [41–43] and online CBT [44], and is not merely an artefact of improvement [45]. However, in other studies investigating the role of the working alliance in online psychotherapy, such an association was not found [46,47]. It is not clear how important client-therapist relationship or working alliance is for home-based interventions with online contact.

Aim of the study

In the current paper, we report on a multiple regression analysis of hypothesized specific and/or generic predictors and working mechanisms of eMBCT for CCRF, to provide a comprehensive model that helps to understand change in fatigue severity in eMBCT, and thereby aids to improve eMBCT and whether or not referring to eMBCT.

We hypothesized that baseline values and/or linear change of the following constructs were associated with fatigue reduction during the course of eMBCT: *mindfulness*, *sense of control* over fatigue symptoms, *sleep quality*, *fear of cancer recurrence*, *fatigue catastrophizing*, *working alliance* rated by the participant, and *expectancy* and *credibility* of the intervention according to the participants.

Methods

Setting and participants

A 3-armed randomized controlled trial was performed (*n* = 167), in which 55 participants were randomized into eMBCT, 62 participants into AAF, and 50 participants into PE. Patients were recruited with the information that they could receive an intervention guided by a psychologist aimed at the psychological aspects of fatigue or a physiotherapist aimed at changing physical activity. In that way, we aimed to recruit a group of participants with high and low expectancy of the interventions, so these participants were not specifically motivated to follow a mindfulness-based intervention. See Wolvers et al. [5] for an extensive description of the methods of the FNK-trial [1]. Participants were on average 55 years old, 73% (*n* = 130) was female, 87% (*n* = 155) lived together with others, 64% (*n* = 115) was highly educated, and 42% (*n* = 75) had a paid job. Breast cancer was most prevalent in the sample (*n* = 81), followed by blood/ bone marrow cancer or Hodgkin's (*n* = 27), and cancer in the reproductive organs (*n* = 27). One-third had been suffering from fatigue longer than 5 years (31%; *n* = 57) and 22% (*n* = 38) was following hormonal therapy at the time of baseline assessment. See Bruggeman-Everts et al. [6] for all baseline characteristics, and the results of the effectiveness of eMBCT and AAF compared to PE. Questionnaires were assessed online via a password-secured webpage [48,49], at recruitment (T0a), at baseline yet before randomization (T0b), directly after randomization (T0c), multiple times during the intervention (M1, 2, 3, 4, 6, and 9, following the subsequent week of the intervention), and/or one week after the intervention (T1). See Table 1 for an overview when each construct was assessed. Participants who stopped before completing the intervention (eMBCT *n* = 24, AAF *n* = 14, PE *n* = 4) were sent the questionnaire at T1, but to limit their burden they were not sent the M-questionnaires during the intervention.

[1] In our original study design – which has been pre-registered [5] – we proposed to study working mechanisms with data from both the first semester and data of participants in the PE condition, who followed AAF or eMBCT in the second semester. However, in the current paper we used the data of only the first semester, as in the second semester about half of these participants did not fill in the M questionnaires (AAF 5 out of 12; eMBCT 11 out of 17), and using this few data twice of the same participants (first and second semester) would incorporate bias.

Interventions

See Wolvers et al. [5] for a detailed description of the interventions, protocol and setting of the FNK-trial.

The eMBCT encompasses a password-secured website where participants could download readers with psycho-education about CCRF, and download audio mindfulness exercises. For nine weeks, participants were asked to read the weekly readers, practice the weekly exercises for at least 45 minutes daily, and write down their experiences with doing these interventions in their personal log file. Their personal psychologist responds to this log file and thereby guides the patient through the 9-week protocol.

The AAF is a physiotherapist-guided ambulant activity feedback therapy encompassing a personal digital assistant (PDA) and an accelerometer, that attempts to balance physical activity level and thereby reducing fatigue. Together with the physiotherapist the participant set goals on the level and intensity of physical activity per day part. These goals were then visualized on the PDA by a reference line, and automated hourly feedback messages were sent to either slow down, activate, or reward the participant according to the physical activity level. The therapist and participant had weekly supportive e-mail contact that also contained psycho-education about CCRF.

In the PE condition, participants received weekly e-mails with psycho-education about CCRF. The same psycho-education was also present in eMBCT and AAF. The interventions of all three conditions lasted 9 weeks.

Measurements

Table 1 presents an overview of the questionnaires that were used to assess each construct, the internal consistency of each questionnaire as measured with Cronbach's alpha, and when it was assessed. Below in the text, we have elucidated each chosen questionnaire.

Table 1. Constructs, questionnaires, internal consistency and time of assessment.

Construct	Questionnaire	Cronbach's α at first assessment	Assessed at
Fatigue severity	CIS-FS	.841	T0b–M3–M6–M9–T1
Credibility of intervention	CEQC	.851	T0c–M1–M2–M4
Expectancy of intervention	CEQE	.920	T0c–M1–M2–M4
Fatigue catastrophizing	FCS	.795	T0b–T1[b]
Mindfulness			
Acceptance	FMI-A	.820	T0b–M3–M6–M9–T1
Presence	FMI-P	.768	T0b–M3–M6–M9–T1
Fear of cancer recurrence	FOCR	N/A[c]	T0b–T1[b]
Sense of control over fatigue	SOC	.818	T0b–M3–M6–M9–T1
Sleep quality	SQ	.860	T0b–M3–M6–M9–T1
Working alliance			
Bond	WAI-SR_B	.886 [a]	M1–M2–M4
Goal	WAI-SR_G	.884 [a]	M1–M2–M4
Task	WAI-SR_T	.887 [a]	M1–M2–M4

Note: [a] = Cronbach's alpha was calculated at M4; [b] = To limit the burden of assessment, FCS and FOCR were only assessed at T0b and T1. [c] As FOCR only consists of one item, the Cronbach's alpha is not applicable (N/A).

Fatigue severity (CIS-FS)

The primary outcome in the current study was change in fatigue severity measured with the Checklist Individual Strength (CIS) - Fatigue Severity subscale (CIS-FS) [18,50,51]. It showed good internal consistency, and has previously been validated in the Dutch cancer population [4,8,50]. The CIS closely resembles the Multidimensional Fatigue Inventory (MFI) [52,53].

Credibility (CEQC) and expectancy of the intervention (CEQE)

The credibility/expectancy questionnaire (CEQ) [54] was used to assess how believable, convincing, and logical the treatment is according to the patient, and how much improvement they believe will be achieved. The questionnaire demonstrated high internal consistency for both factors (*credibility* and *expectancy*) and good test-retest reliability [54], and the Dutch translation has been used previously [55] and showed good psychometric properties. In the current study design, one can only use the CEQ scores to check for correlation between constructs within a group, and not compare the CEQ scores between conditions, as the credibility and expectancy of the particular assigned intervention was assessed, and not the relative *credibility* or *expectancy*.

Fatigue catastrophizing (FCS)

Fatigue catastrophizing was assessed with the Fatigue Catastrophizing Scale (FCS) [56]. It has previously been used to assess *fatigue catastrophizing* in cancer survivors and showed high internal consistency [18].

Mindfulness (FMI)

Mindfulness was assessed with the Freiburg Mindfulness Inventory - short form (FMI-14), which is a 14-item self-report measure of mindfulness, with good reliability and construct validity [57]. Items relate to attentive awareness of the present moment, with an accepting attitude [11]. The FMI has shown to be sensitive to change in level of mindfulness in a MBCT study among cancer patients [58]. A Dutch translation has been validated [59] and it was shown that a two factor structure with the subscale *acceptance* and *presence* best fitted the data. The translation has been used in previous studies and showed sufficient psychometric properties [60,61]. We chose the FMI because it involves the most important facets of mindfulness (i.e. *acceptance* and *presence*) for evaluating MBIs in medical psychology and is relatively short as it only holds 14 items.

Fear of cancer recurrence (FOCR)

We assessed fear of cancer recurrence with one self-developed question: 'How often do you worry about cancer recurrence', and was rated with a 7-point Likert Scale between '1 never' and '7 constantly'. Reliability and validity of this 1-item question was not tested. We wanted to include the construct without burdening the participants too much with potentially disturbing questions about fear of cancer recurrence.

Sense of control over fatigue (SOC)

Sense of control in relation to fatigue complaints – so to what extent the patient feels capable of changing fatigue – was measured with the self-efficacy scale (SE28) [18]. It was adapted from the SE24 used in patients with chronic fatigue syndrome in a previous study [62]. All 7 items were scored on a 4-point Likert scale, range 7-28, with a higher score reflecting more sense of control. It was assessed at M3, 6, and 9.

Sleep quality (SQ)

Sleep quality was assessed with the Dutch version of the Subjective Sleep Quality Scale (SQ) [63], also called the Groningen Sleep Quality Scale [64,65]. The SQ is a self-report questionnaire which comprises 14 statements concerning the quality of sleep of the previous

night. It has been previously used in Dutch populations to determine sleep disturbance and sleep quality [4,66].

Client-therapist working alliance (WAI-SR)

The Working Alliance Inventory – short form revised (WAI-SR) was used to assess working alliance between patient and healthcare professional in eMBCT and AAF. The Dutch translation has good psychometric and predictive quality [67–69]. The WAI-SR uses blanks in the questionnaire to fill in the name of the therapist, but for readability we filled in 'my therapist' at the blanks. It is a 12-item self-report questionnaire with three subscales: (1) agreement between client and therapist on the *goals* of the therapy, (2) the client's agreement with the therapist that the *tasks* of the therapy will address the problems the client brings to treatment, and (3) the quality of the interpersonal *bond* between the client and the therapist. Total scores of the subscales range from 4-20.

During data collection we received feedback from a substantial proportion of participants (n = 19) who said it was too early for them to judge their relationship with their therapist based on one or two online contact moments. Many were actually annoyed by the questions, as they had confidence that the working alliance would develop, but simply could not answer the questions so early in treatment. So, we considered the WAI-SR measured at M1 and M2 as not reliable. At M4, we received feedback that it was easier to answer the questions and therefore we consider the M4 measurement as reliable.

We decided to exclude *therapeutic alliance* from the multiple regression analysis (see section Data analysis) as relatively few participants had filled in WAI-SR at M4 in eMBCT (n = 32) and AAF (n = 51). Including WAI-SR assessed at M4 with missing data, would result in not knowing whether the results of the regression model would be due to including WAI-SR in the model, or analyzing only half of the dataset. Also, slope factors were not estimated for WAI-SR as only the assessment at M4 was considered reliable. We did investigate the correlation between WAI-SR at M4 and linear change of fatigue severity.

Data analyses

First, using Latent Growth Curve modeling (LGM) [70] in Mplus version 7.31 [71], slope factors were estimated of each construct. In our previous study [6] CIS-FS between T0b and six months later was best modeled with both a linear and quadratic slope factor, while including individual time between assessments (time scores) [72]. Consequently, in the

current study we included time scores for estimating the slope factors of all constructs. However, we chose to estimate only linear slope factors (the intercept was specified at T0b), as the scope of the current study was to assess change over time, which would typically be computed by a pre-to-post change score. Since we also collected assessments during the intervention (M1-M9), estimating a linear slope is more precise (i.e., it contains more information) than only using two time points of data.

Second, to investigate associations between all parameters and fatigue change, correlations were calculated per treatment condition between all parameters and fatigue severity change. Scatter plots were created to better understand the interactions between the parameters and fatigue severity change.

Third, regression analysis between all parameters and the fatigue severity slope factor were performed to indicate specific and generic predictors for fatigue severity change for eMBCT. As the parameters often correlated, these could not be combined in one regression model: multicollinearity occurred between baseline and slopes of *fatigue catastrophizing*, *fear of cancer recurrence*, *sleep quality*, *credibility*, and *expectancy* of the intervention. We therefore chose to run two multiple regression analysis for the predictors and working mechanisms separately: (1) a three-group multiple regression analysis with the baseline values, (2) a three-group multiple regression analysis with the slope factors. Furthermore in the PE condition, the baseline values of *expectancy* (CEQE) and *credibility* (CEQC) were highly correlated (r = .824, p < .001). As CEQE showed to have a floor effect [2] at baseline (16%, n = 8) and at M4 (16%, n = 7) in the PE condition, we decided to only report on a multivariate model with the baseline values of *credibility*. For the model including the baseline values of *expectancy* see Appendix D.

Significance was set at p < .01 to control for multiple testing. Standardized regression coefficients and the total explained variance of the model was reported.

[2] When > 15% of the participants reported the lowest possible score [77], which indicates that differences in low expectancy of PE could not be distinguished well by the CEQE questionnaire.

Missing data

In Figure 1 the number of participants who filled in each assessment is shown. Three participants had missing values on all three assessments of CEQ, and thus the regression analyses were performed on 164 participants (eMBCT $n = 55$, AAF $n = 61$, PE $n = 48$).

We performed analyses of variance (ANOVA) and χ^2-tests to check whether baseline variables correlated with missing data patterns. We concluded that data was missing randomly, which resulted in no auxiliary variables or covariates being included in the model.

Mplus uses full information maximum likelihood estimation (FIML) to deal with missing data when estimating the growth parameters [73]. It is a statistical estimation method that calculates the most likely parameter values for a set of observed data. In that way for each individual, a slope factor could be calculated with its variance and residual variance for each parameter.

To be able to estimate a slope factor when data is missing at assessments, a time score of the time of assessment is needed. For missing questionnaires, we have imputed missing time scores with the average time between the corresponding assessments per group, so Mplus could estimate a growth parameter for every participant of each time point.

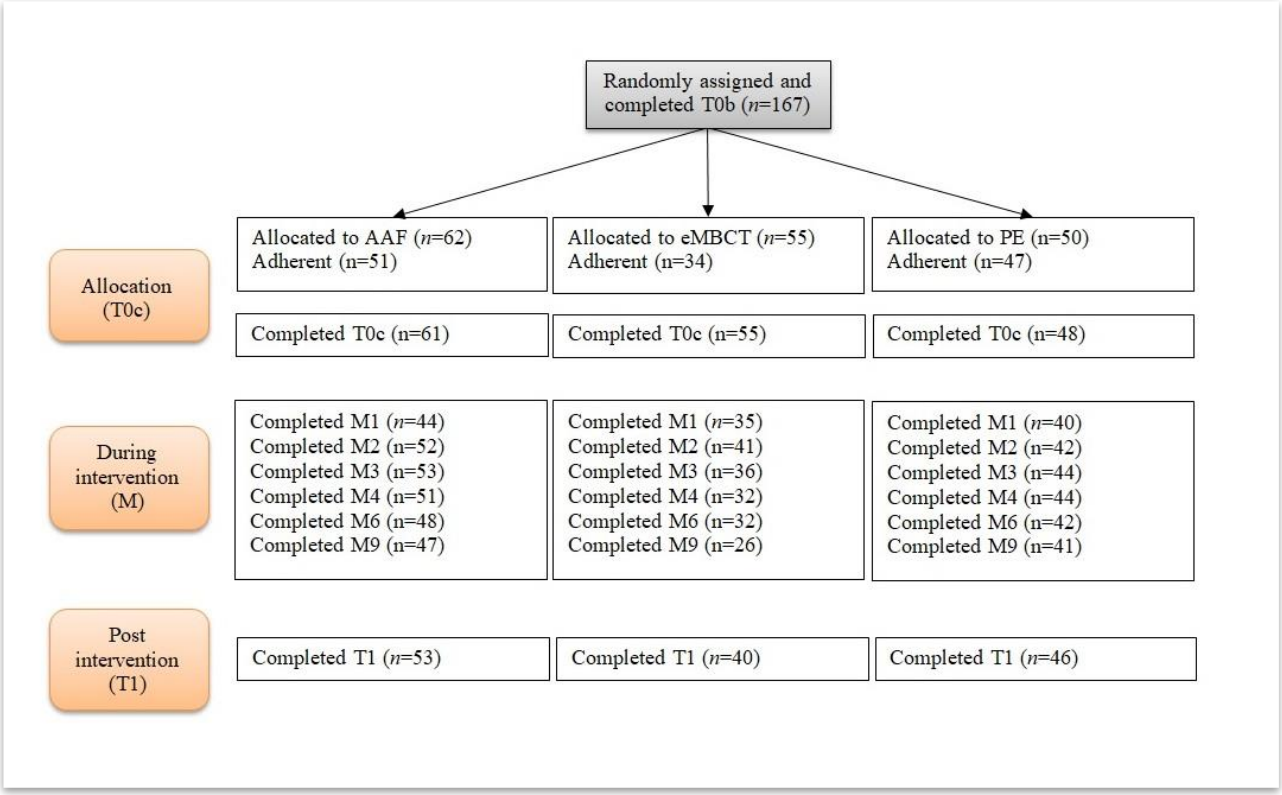


Figure 1. Flowchart of the quantity of participants who filled in the assessments. See Bruggeman-Everts et al. [6] for flowchart of the FNK-trial including enrollment and inclusion.

Results

Modeling of parameters

In Appendix A all the average baseline (indicated with '_I') and slope factors (indicated with '_S') are presented per construct per condition. Interestingly, both mindfulness subscales *acceptance* and *presence* significantly increased in AAF but not in eMBCT and PE. *Sense of control* significantly increased and *fatigue catastrophizing* significantly decreased in both eMBCT and AAF, but not in PE.

Correlations between predictors and fatigue severity

In Table 2 (next page) the results of the correlations between all baseline parameters and fatigue severity change per condition are presented. See Appendix B for scatterplots illustrating the direction of the associations between the constructs and fatigue severity change, and see Appendix C for correlation matrix of all parameters. In eMBCT, we found

that high *sense of control* at baseline (SOC_I) was related to a higher reduction in fatigue severity.

It is shown that in all three groups the slope factor of *sense of control* (SOC_S) was negatively correlated with fatigue severity change, meaning an increase in *sense of control* was related to a reduction in fatigue during the interventions. Change in the *presence* subscale of the mindfulness questionnaire (FMIP_S) was negatively correlated with fatigue severity change in AAF specifically, meaning an increase in *presence* was associated with a reduction in fatigue. An increase in *expectancy* (CEQE_S) was associated with fatigue reduction in eMBCT specifically. And lastly, a decrease in *fatigue catastrophizing* (FCS_S) was related to a decrease in fatigue severity in PE, but not in the other conditions. Credibility, acceptance, sleep quality, and fear of cancer recurrence were not related to fatigue severity change.

Three-group multiple regression analysis for predictors

In Table 3 (next page) the results of the multiple regression analysis of the baseline values on fatigue severity change is shown. High *Sense of control* (SOC_I) was a significant predictor for fatigue reduction specifically in eMBCT (β = -0.451, SE = 0.116, p < .001). High *credibility* (CEQC_I) of the intervention has predictive value for a reduction in fatigue severity in PE (β = -0.436, SE = 0.148, p = .003), though *expectancy* did not have predictive value. No predictors were found to be significant in AAF. The explained variance of the model for eMBCT was 33%, and 12% for AAF, and 19% for PE.

Three-group multiple regression analysis for working mechanisms

In Table 4 (next page), the results for the multiple regression analysis with the slope factors are shown. In both eMBCT (β = -0.598, SE = 0.093, p < .001), and AAF (β = -0.651, SE = 0.083, p < .001) the slope factor of *sense of control* (SOC_S) had a significant predictive value on fatigue severity change. The slope factor of *fatigue catastrophizing* (FCS_S) had predictive value for change in fatigue severity reduction in PE specifically (β = 0.391, SE = 0.146, p < .001). The explained variance was in eMBCT 48%, AAF 55%, and in PE 52%. These results indicate that an increase in *sense of control* is a working mechanism for fatigue severity reduction in both eMBCT and AAF, and *fatigue catastrophizing* in PE.

Table 2. Correlations. In the current table correlation coefficients and significance between predictors and fatigue severity change are shown.

	eMBCT (*n* = 55)		**AAF** (*n* = 62)		**PE** (*n* = 50)	
Parameter	Correlation	*p*	Correlation	*p*	Correlation	*p*
CISFS_I	.289	0.032	-0.138	0.285	0.161	0.265
CEQC_I	-0.063 [s]	0.646	-.284 [s]	0.027	-0.262	0.072
CEQE_I	-0.085	0.537	-0.160	0.218	-0.222 [s]	0.130
FCS_I	0.076	0.583	0.003	0.982	0.087	0.549
FMIA_I	-0.134	0.328	-0.003	0.979	0.023	0.874
FMIP_I	0.016	0.909	-0.048	0.713	0.067	0.645
FOCR_I	0.015 [s]	0.916	0.054 [s]	0.678	0.034	0.816
SOC_I	-.443	0.001	0.088	0.495	-0.135	0.348
SQ_I	-0.264 [s]	0.051	0.092 [s]	0.475	0.060	0.678
CEQC_S	-0.254	0.061	-0.005	0.969	-.292	0.044
CEQE_S	-.390	0.003	-0.143	0.271	-0.192	0.191
FCS_S	-0.021	0.878	0.074	0.567	.622	0.000
FMIA_S	-0.114	0.407	-0.269	0.035	-0.157	0.275
FMIP_S	-0.173	0.206	-.330	0.009	-.280	0.049
FOCR_S	-0.019	0.890	-0.050	0.699	0.173	0.228
SOC_S	-.651	0.000	-.691	0.000	-.632	0.000
SQ_S	0.035	0.799	-0.223	0.081	0.062	0.671
WAI-SR-B	-.113	.539	-.261 [s]	.065	N/A [b]	N/A [b]
WAI-SR-G	-.269	.136	-.325	.020	N/A [b]	N/A [b]
WAI-SR-T	-.351	.049	-.321	.021	N/A [b]	N/A [b]

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; CIS-FS = fatigue severity subscale of the checklist individual strength; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQE = expectancy subscale of the credibility and expectancy scale; CEQC = credibility subscale of the credibility and expectancy scale; WAI-SR-B = working alliance inventory short form revised bond subscale; WAI-SR-G = working alliance inventory short form revised goal subscale; WAI-SR-T = working alliance inventory short form revised task subscale; I = baseline value; S = slope factor; *p* = two-tailed *p*-value; N/A.=not applicable; *n* = number of participants. *Note:* [b] =WAI-SR was only assessed in eMBCT and

AAF; [s] = Correlations were calculated with Spearman's *rho* when the distributions were considered non-normal. Other correlations were calculated with Pearson's

Table 3. Three-group multiple regression analysis with baseline values on fatigue severity change (*n* = 164).

	eMBCT (*n* = 55)		**AAF** (*n* = 61)		**PE** (*n* = 48)	
Parameter	*β* (SE)	*p*	*β* (SE)	*p*	*β* (SE)	*p*
CIS-FS_I	0.222 (0.122)	0.067	-0.053 (0.144)	0.712	0.094 (0.146)	0.519
CEQC_I	-0.112 (0.123)	0.363	-0.316 (0.127)	0.013	-0.436 (0.148)	0.003
FCS_I	-0.238 (0.145)	0.102	0.019 (0.150)	0.898	-0.122 (0.188)	0.517
FMIA_I	-0.198 (0.175)	0.257	0.155 (0.160)	0.335	0.198 (0.214)	0.355
FMIP_I	0.174 (0.174)	0.318	-0.092 (0.150)	0.538	0.027 (0.190)	0.886
FOCR_I	0.059 (0.127)	0.643	0.116 (0.142)	0.415	0.136 (0.159)	0.392
SOC_I	-0.451 (0.116)	0.000	0.146 (0.158)	0.355	-0.387 (0.178)	0.030
SQ_I	-0.252 (0.130)	0.053	0.015 (0.129)	0.910	0.134 (0.138)	0.332
R^2	0.331		0.115		0.193	

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; CIS-FS = fatigue severity subscale of the checklist individual strength; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQC = credibility subscale of the credibility and expectancy scale; I = baseline value; *p* = two-tailed *p*-value; N/A. = not applicable; *n* = number of participants; β = regression coefficient; SE = standard error; R^2 = explained variance.

Table 4. Three-group multiple regression analysis with slopes factors on fatigue severity change (*n* = 164).

	eMBCT (*n* = 55)		**AAF** (*n* = 61)		**PE** (*n* = 48)	
Parameter	*β* (SE)	*p*	*β* (SE)	*p*	*β* (SE)	*p*
CEQC_S	-0.016 (0.130)	.901	0.178 (0.102)	.082	-0.127 (0.120)	.289
CEQE_S	-0.157 (0.132)	.233	-0.177 (0.094)	.058	0.064 (0.125)	.606
FCS_S	0.030 (0.111)	.786	-0.092 (0.095)	.332	0.391 (0.146)	.007
FMIA_S	0.106 (0.133)	.424	-0.192 (0.114)	.092	-0.195 (0.125)	.117
FMIP_S	-0.210 (0.135)	.121	-0.003 (0.116)	.977	0.004 (0.132)	.975
FOCR_S	0.102 (0.112)	.359	-0.063 (0.094)	.501	0.016 (0.114)	.890
SOC_S	-0.598 (0.093)	< .001	-0.651 (0.083)	< .001	-0.350 (0.153)	.022
SQ_S	0.072 (0.109)	.507	-0.104 (0.092)	.261	-0.102 (0.109)	.347
R^2	0.479		0.547		0.518	

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQC = credibility subscale of the credibility and expectancy scale; CEQE = expectancy subscale of the credibility and expectancy scale; S = slope factor; *p* = two-tailed *p*-value; N/A. = not applicable; *n* = number of participants; β = regression coefficient; SE = standard error; R^2 = explained variance

Discussion

These results indicate that for eMBCT, *sense of control* is an important mechanism involved in fatigue severity reduction. Patients with a higher *sense of control* over fatigue may be better capable or better motivated to do the exercises of the eMBCT and profit from the intervention than those with low sense of control. Our finding that *sense of control* is a generic working mechanism in eMBCT and AAF is in line with previous studies in which sense of control over fatigue was found to be a working mechanism in CBT for chronic fatigue syndrome [17,74]. Future data analysis on temporal precedence may teach us how *sense of control* and *fatigue severity* are related. If fatigue change precedes sense of control change in time, this would suggest a directional, and potentially causal role of *sense of control*. Modeling change of these constructs in time goes beyond the scope of the current paper.

Concerning PE, patients with high *credibility* of psycho-education, are probably more likely to closely read the information and benefit from it. Interestingly, the found working mechanism *fatigue catastrophizing* did not significantly change in PE *on average*, but in fact it did reduce in eMBCT and AAF. As all three conditions received similar psycho-education, we speculate that being guided by a therapist removes the association between fatigue and catastrophizing, leading to a reduction in fatigue in eMBCT and AAF, but not in PE.

Our findings concerning the mindfulness constructs contrasts the results of other studies in which mindfulness skills were predicting the outcome of mindfulness-based interventions [14,15]. What may explain the difference with those studies is that the current study involved a mindfulness-based cognitive behavioral treatment delivered via the internet and not face-to-face. Also, to be able to include a group with both high and low expectations in the current study, the exact content of the interventions was not specified during recruitment, but only after randomization. It may be possible that *presence* and *acceptance* are working mechanisms in a subgroup of the participants, for example only in patients with high expectations.

Strengths

The current study has methodological strengths, as change of the constructs during the interventions were estimated with slope factors using LGM instead of an analysis of variance of the average pre-post assessments. The slope factor served as a proxy for a change score while taking into account the longitudinal measurements, the role of time between assessment, the variance between individual slopes, and missing data [75].

The use of data of the FNK-trial allowed us to investigate which parameters were specifically associated with fatigue severity reduction in eMBCT, and which were generic for both experimental interventions (eMBCT and AAF), or generic for all three conditions (eMBCT, AAF, and PE).

Furthermore, compared to other studies, in the current study a more comprehensive model for eMBCT could be investigated as multiple constructs were studied in one model. Many other studies reporting on mediators and working mechanisms in interventions studied one construct, ignoring the relative importance of that construct in an intervention.

Limitations

In the current study we had missing data, especially in eMBCT due to non-adherence. Missing data could have influenced the estimation of the factor slopes, in a way that the estimated slope is mostly based on participants who followed the intervention. However, no baseline characteristics were found that correlated with missing data patterns, and thus we concluded we dealt with randomly missing data. Also, we collected a considerable number of T1 measurements (73% of eMBCT and 85% of AAF), so we expect this bias is limited.

Unfortunately, the development of the therapeutic relationship early in treatment could not be investigated as the questionnaire appeared unsuitable for assessment in week 1 and 2 of the online interventions. We are currently qualitatively studying the role of the therapist in eMBCT and AAF, and how this helped to attune to the patient's needs [76].

Another limitation of the current study was that the fear of cancer recurrence was measured with a self-created 1-item question and of which the psychometrics of this question have not been investigated. Though, we decided to include this 1-item question to be able to include fear of cancer recurrence in our analyses but also not burden the patients too much. The negative finding of FOCR is therefore no evidence that fear of cancer recurrence plays no role in fatigue change in eMBCT.

Notably, the results if this study do not explain the actual process of how change came about, as actual causality is difficult to confirm in intervention studies [9]. For example, change in *sense of control* could very well be a result of fatigue severity reduction, as feeling less fatigued can give you the confidence you can control your symptoms.

Conclusion

This study has given information on how change may be established in eMBCT. Patients with high s*ense of control* over fatigue at baseline benefit well from eMBCT. Therefore, focusing on increasing sense of control at the beginning of eMBCT, may help improve the effectiveness of eMBCT.

The current study indicates that *sense of control* is a working mechanism for fatigue severity change in both eMBCT and AAF, although eMBCT and AAF are two theoretically different

web-based interventions. This finding indicates that eMBCT and AAF help reducing fatigue through general constructs rather than intervention specific constructs. This is in line with previous research, that conclude evidence is still missing for that specific ingredients are needed to resolve particular disorders [37] (p.28). Future data analysis may focus on predictors and working mechanisms of subgroups within eMBCT, testing whether mindfulness may be a working mechanisms for a subgroup of participant. But we can conclude from this study that improving *sense of control* is important for fatigue severity reduction in eMBCT, rather than treatment specific factors such as mindfulness.

Appendices

APPENDIX A – Modeling of parameters

In this appendix, the results of modeling of the parameters are presented. In Table A.1 the average baseline values (indicated by '_I'), and in Table A.2 the average slope factors (indicated by '_S') of each parameter are shown per condition. The sample sizes were, eMBCT *n* = 55, AAF *n* = 62, and PE *n* = 50, except for CEQC_I and CEQE_I where the sample sizes were eMBCT *n* = 55, AAF *n* = 61, and PE *n* = 48.

As can been seen in Table A.2, fatigue severity (CISFS_S) decreased in eMBCT and AAF, and not in PE. Also, sense of control (SOC_S) increased and fatigue catastrophizing (FCS_S) significantly decreased in both eMBCT and AAF, but not in PE. Both mindfulness subscales acceptance (FMIA_S) and presence (FMIP_S) significantly increased in AAF but not in eMBCT and PE. Sleep quality (SQ_S) increased, and credibility (CEQC_S) decreased in AAF, but not in eMBCT or PE.

Table A.1. The average baseline value of each construct per condition.

	eMBCT (*n*=55)	**AAF** (*n*=62)	**PE** (*n*=50)
Parameter	*M* (SD)	*M* (SD)	*M* (SD)
CISFS_I	42.84 (7.95)	43.24 (6.75)	40.34 (8.99)
CEQC_I	18.56 (5.44)	20.59 (4.38)	15.65 (5.88)
CEQE_I	15.32 (5.88)	17.11 (5.04)	12.70 (6.25)
FCS_I	21.7 (5.35)	21.97 (5.92)	21.69 (5.75)
FMIA_I	20.8 (3.79)	21.63 (4.53)	22.2 (5.04)
FMIP_I	17.22 (3.3)	17.42 (3.08)	18.14 (3.73)
FOCR_I	3.22 (1.78)	3.21 (1.73)	3.22 (1.46)
SOC_I	17.75 (2.34)	18.19 (2.13)	17.92 (2.75)
SQ_I	8.98 (3.55)	8.29 (3.81)	7.48 (3.69)

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; CIS-FS = fatigue severity subscale of the checklist individual strength; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQE = expectancy subscale of the credibility and expectancy scale; CEQC =

credibility subscale of the credibility and expectancy scale; I = baseline value; *n* = number of participants; *M* = mean; *SD* = standard deviation

Table A.2. The estimated average slope factors of each construct per condition.

	eMBCT (*n* = 55)		**AAF** (*n* = 62)		**PE** (*n* = 50)	
Parameter	*M* (SD)	*p*	*M* (SD)	*p*	*M* (SD)	*p*
CISFS_S	-0.487 (0.283)	<.001	-0.656 (0.422)	<.001	-0.097 (0.241)	.313
CEQC_S	-0.134 (0.165)	.104	-0.192 (0.366)	.008	-0.215 (0.306)	.060
CEQE_S	-0.034 (0.151)	.674	-0.165 (0.343)	.027	-0.192 (0.322)	.096
FCS_S	-0.178 (0.06)	<.001	-0.173 (0.133)	<.001	-0.045 (0.197)	.490
FMIA_S	0.04 (0.07)	.119	0.082 (0.038)	<.001	0.016 (0.051)	.613
FMIP_S	0.043 (0.05)	.067	0.045 (0.036)	.010	-0.021 (0.036)	.435
FOCR_S	0.01 (0.017)	.526	0.006 (0.042)	.570	0.027 (0.028)	.016
SOC_S	0.101 (0.061)	<.001	0.167 (0.131)	<.001	0.061 (0.103)	.032
SQ_S	0.035 (0.128)	.337	0.088 (0.095)	.002	0.100 (0.039)	.015

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; CIS-FS = fatigue severity subscale of the checklist individual strength; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQE = expectancy subscale of the credibility and expectancy scale; CEQC = credibility subscale of the credibility and expectancy scale; S = slope factor; *p* = two-tailed *p*-value; *n* = number of participants; *M* = mean; *SD* = standard deviation

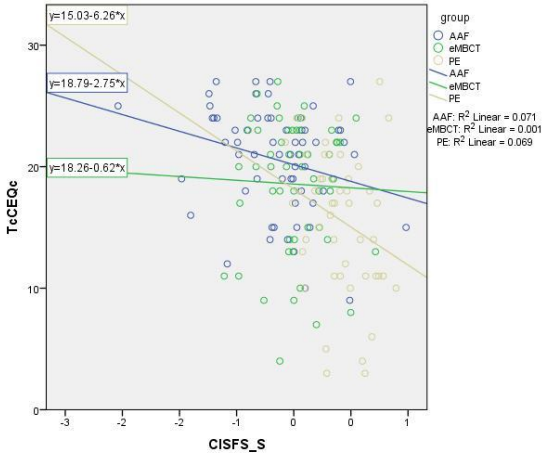
In Table A.3 the average scores at M4 for working alliance (WAI-SR) subscales are shown. Only the assessment at M4 was considered reliable, no slope factor could be estimated.

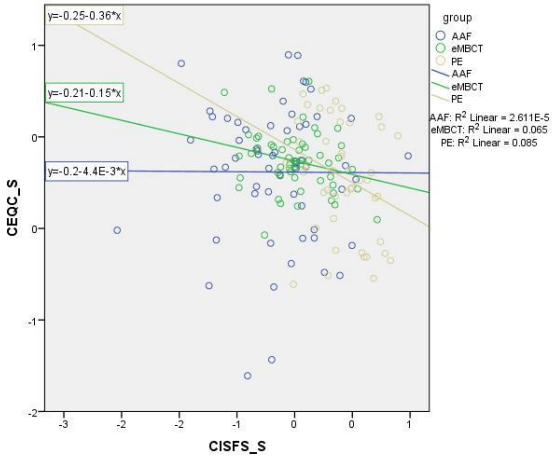
Table A.3. Average score at M4 of working alliance.

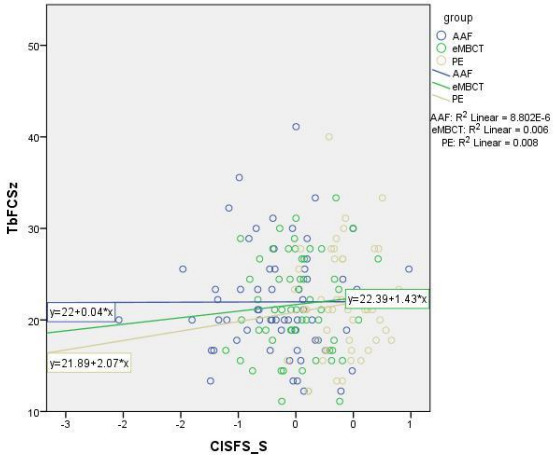
	eMBCT (*n* = 32)	**AAF** (*n* = 51)
Parameter	*M* (SD)	*M* (SD)
WAI-SR-B	15.78 (3.23)	15.9 (3.71)
WAI-SR-G	13.25 (3.48)	14.35 (3.09)
WAI-SR-T	12.38 (3.11)	13.84 (3.26)

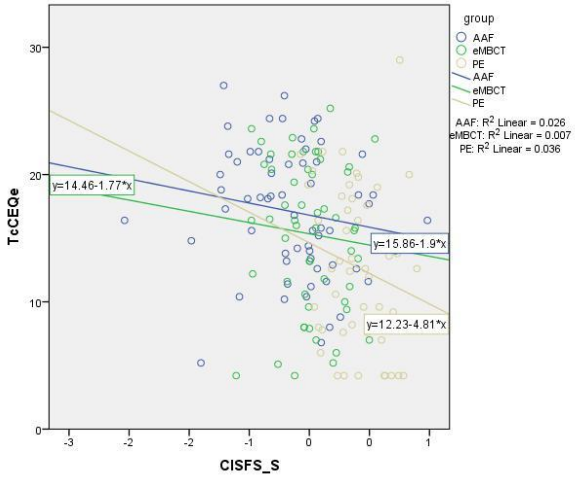
Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; WAI-SR-B = working alliance inventory short form revised bond subscale; WAI-SR-G = working alliance inventory short form revised goal subscale; WAI-SR-T = working alliance inventory short form revised task subscale; *M* = mean; *SD* = standard deviation

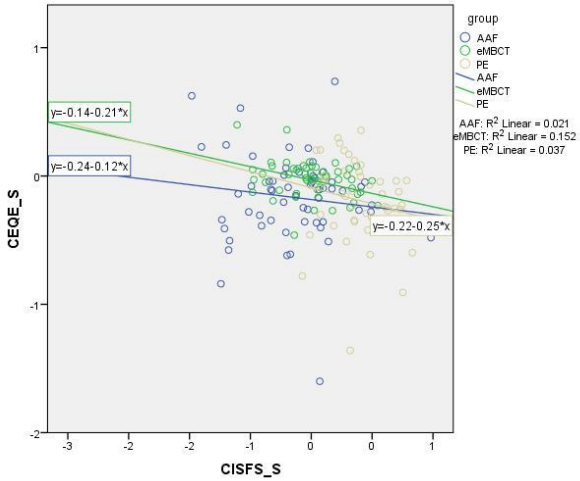
APPENDIX B – Scatterplots of correlations between all parameters and fatigue severity change

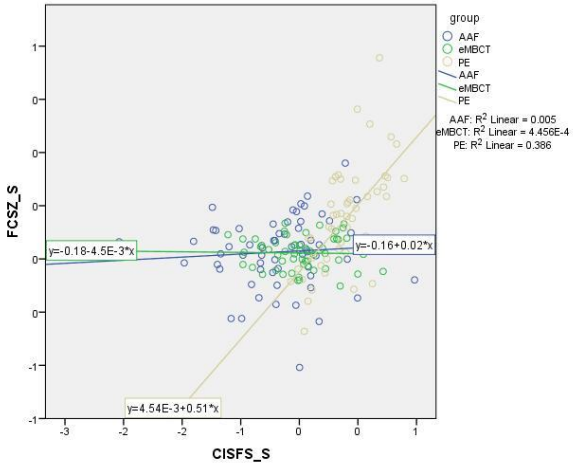


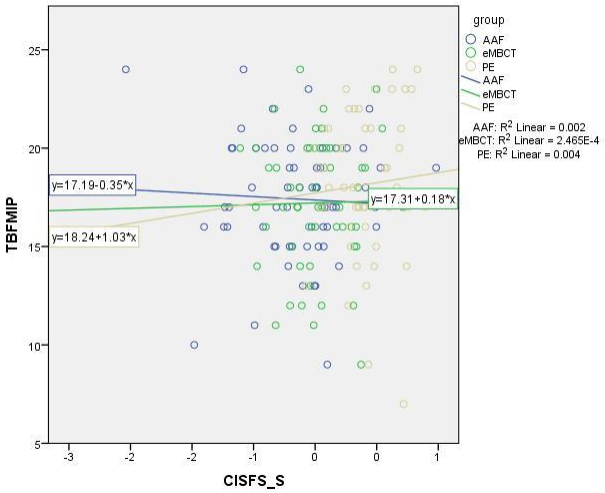








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CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
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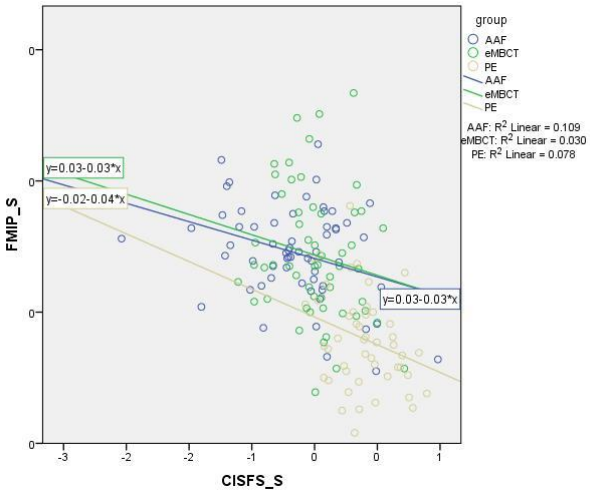
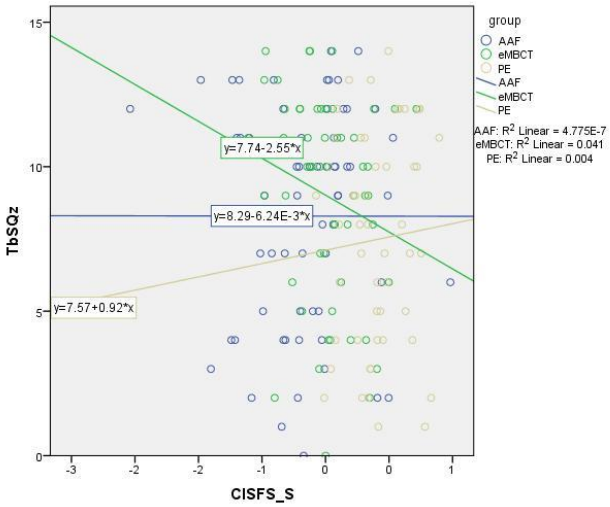
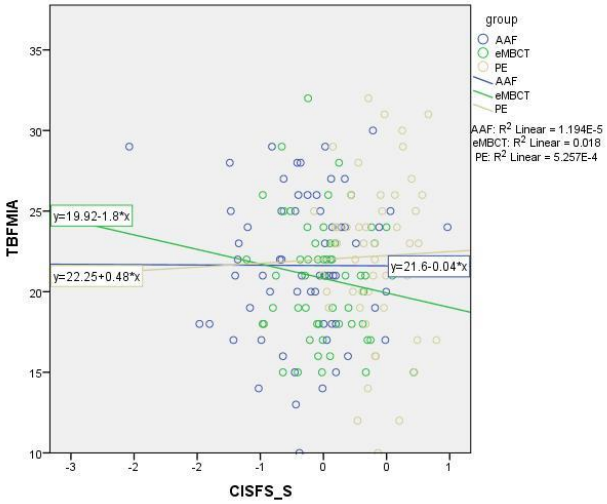
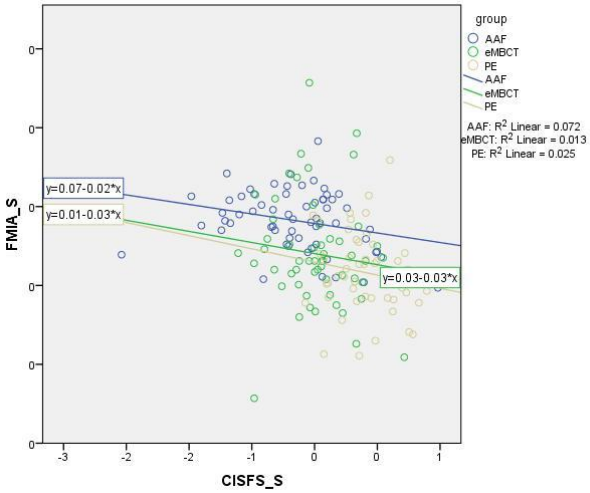
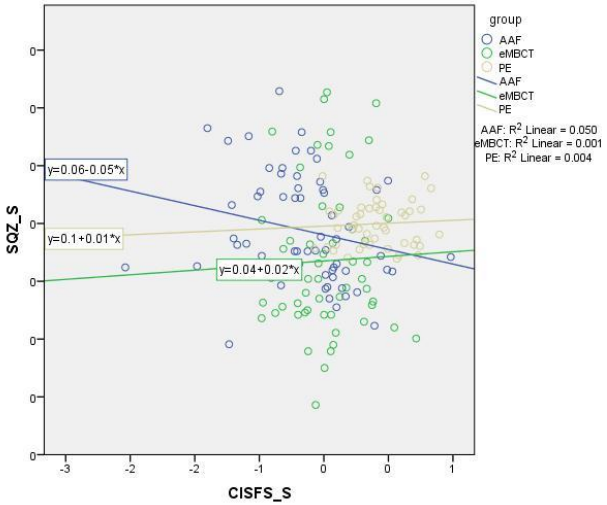
eMBCT: R2 Linear = 2.465E-4
PE: R2 Linear = 0.004
y=17.19-0.35*x
y=17.31+0.18*x
y=18.24+1.03*x

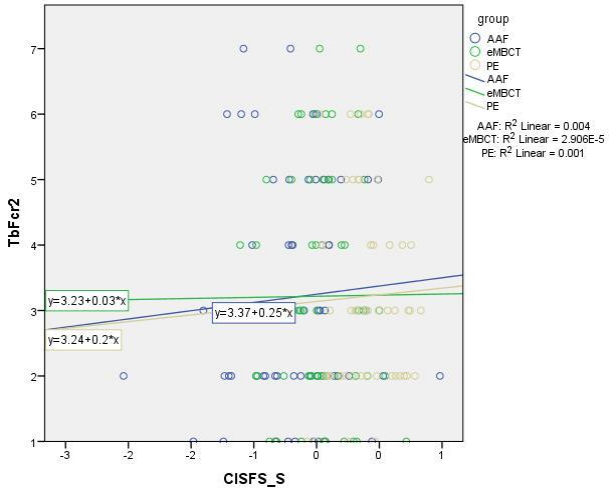

FMIP_S
CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.109
eMBCT: R2 Linear = 0.030
PE: R2 Linear = 0.078
y=0.03-0.03*x
y=-0.02-0.04*x
y=0.03-0.03*x

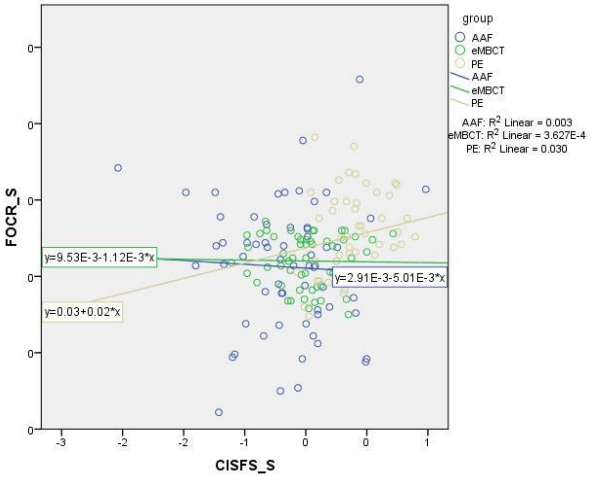

TbSQz
CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 4.775E-7
eMBCT: R2 Linear = 0.041
PE: R2 Linear = 0.004
y=7.74-2.55*x
y=8.29-6.24E-3*x
y=7.57+0.92*x

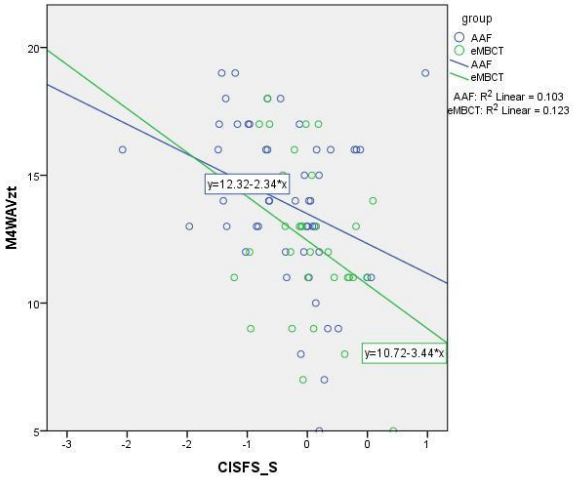

TBFMIA
CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 1.194E-5
eMBCT: R2 Linear = 0.018
PE: R2 Linear = 5.257E-4
y=19.92-1.8*x
y=21.6-0.04*x
y=22.25+0.48*x

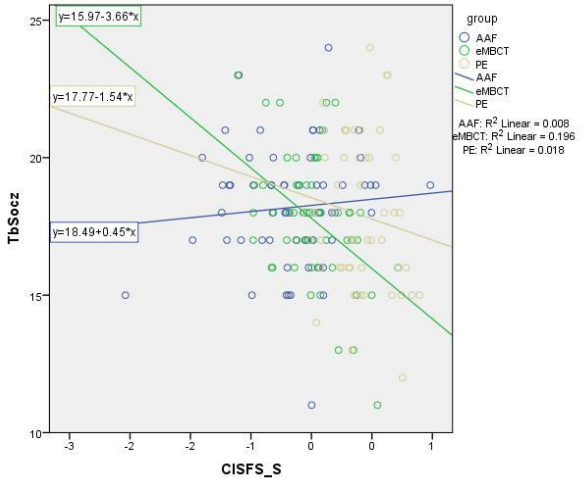

FMIA_S
CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.072
eMBCT: R2 Linear = 0.013
PE: R2 Linear = 0.025
y=0.07-0.02*x
y=0.01-0.03*x
y=0.03-0.03*x

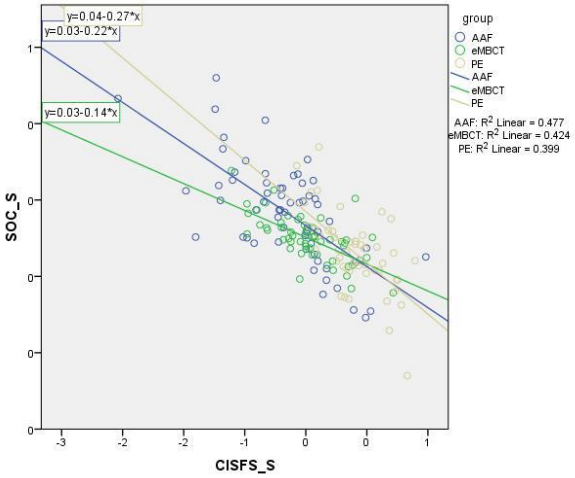

SQZ_S
CISFS_S
group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.050
eMBCT: R2 Linear = 0.001
PE: R2 Linear = 0.004
y=0.06-0.05*x
y=0.1+0.01*x
y=0.04+0.02*x

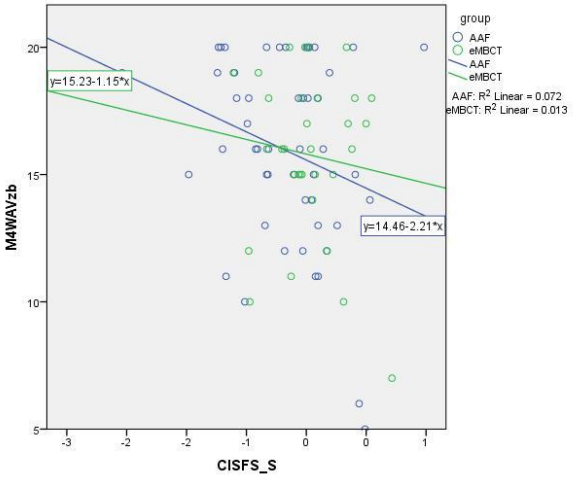

group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.004
eMBCT: R2 Linear = 2.906E-5
PE: R2 Linear = 0.001
y=3.23+0.03*x
y=3.37+0.25*x
y=3.24+0.2*x
TbFcr2
CISFS_S

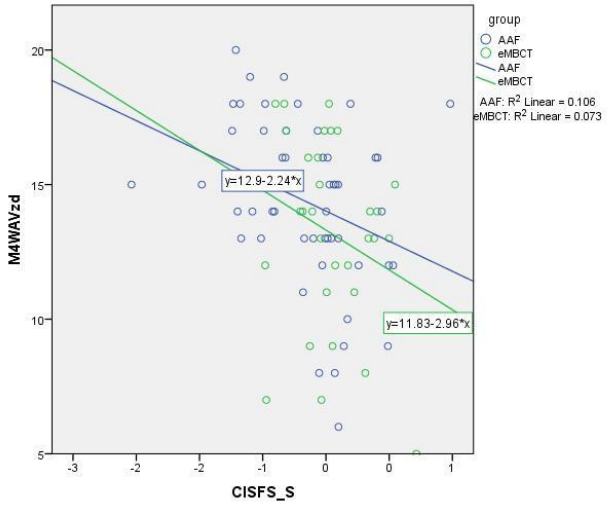

group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.003
eMBCT: R2 Linear = 3.627E-4
PE: R2 Linear = 0.030
y=9.53E-3-1.12E-3*x
y=2.91E-3-5.01E-3*x
y=0.03+0.02*x
FOCR_S
CISFS_S


group
AAF
eMBCT
AAF
eMBCT
AAF: R2 Linear = 0.103
eMBCT: R2 Linear = 0.123
y=12.32-2.34*x
y=10.72-3.44*x
M4WAVzt
CISFS_S


group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.008
eMBCT: R2 Linear = 0.196
PE: R2 Linear = 0.018
y=15.97-3.66*x
y=17.77-1.54*x
y=18.49+0.45*x
TbSocz
CISFS_S


group
AAF
eMBCT
PE
AAF
eMBCT
PE
AAF: R2 Linear = 0.477
eMBCT: R2 Linear = 0.424
PE: R2 Linear = 0.399
y=0.04-0.27*x
y=0.03-0.22*x
y=0.03-0.14*x
SOC_S
CISFS_S


group
AAF
eMBCT
AAF
eMBCT
AAF: R2 Linear = 0.072
eMBCT: R2 Linear = 0.013
y=15.23-1.15*x
y=14.46-2.21*x
M4WAVzb
CISFS_S



In this appendix scatterplots of al significant correlations between a parameter and the slope factor of change in fatigue severity (CISFS_S) are shown.

APPENDIX C – Correlation matrix of all parameters per group

In this appendix, the correlations between all parameters are presented. Spearman's ρ was calculated for non-normally distributed parameters: Baseline sleep quality (SQ_I), fear of cancer recurrence (FOCR_I) and credibility of the intervention (CEQC_I) in eMBCT and AAF, and expectancy (CEQE_I) in PE. Multicollinearity was found in eMBCT, between the baseline values and slope factors of FCS (r = -.939, p < .001), FOCR (r = -.971, p<.001), and SQ (r = -.806, p<.001). In AAF the baseline values and slope factors of FCS (Pearson's r = -.963, p<.001), FOCR (Spearman's ρ = -.904, p < .001), and SQ (r = -.894, p < .001). In PE, the baseline value and slope factor of SQ correlated highly (r = -.929, p < .001). Also, the baseline values of CEQE and CEQC were highly correlated (r = .824, p < .001).

eMBCT Correlations

		CIS-FS_I	CEQC_I	CEQE_I	FCS_I	FMIA_I	FMIP_I	FOCR_I	SOC_I	SQ_I	CIS-FS_S	CEQC_S	CEQE_S	FCS_S	FMIA_S	FMIP_S	FOCR_S	SOC_S	SQ_S
CIS-FS_I	Pearson Correlation	1,000	.289*	0,107	0,121	0,094	0,122	0,046	-0,120	-.319*	.289*	0,047	-0,061	-0,119	0,208	0,138	0,013	0,002	0,109
	Sig. (2-tailed)		0,033	0,436	0,377	0,494	0,376	0,740	0,383	0,018	0,032	0,733	0,660	0,388	0,128	0,314	0,925	0,991	0,428
CEQC_I	Pearson Correlation		1,000	.755**	0,116	-0,122	-0,132	0,204	0,068	-0,100	-0,063	0,143	0,007	-0,124	0,240	.284*	-0,222	0,026	0,066
	Sig. (2-tailed)			0,000	0,400	0,374	0,337	0,134	0,619	0,468	0,646	0,297	0,962	0,367	0,078	0,036	0,103	0,848	0,632
CEQE_I	Pearson Correlation			1,000	0,175	-0,055	-0,102	0,198	-0,085	-0,100	-0,085	0,098	-0,263	-0,155	-0,067	0,080	-0,265	-0,094	0,059
	Sig. (2-tailed)				0,202	0,692	0,459	0,148	0,535	0,468	0,537	0,479	0,052	0,259	0,629	0,559	0,050	0,493	0,670
FCS_I	Pearson Correlation				1,000	-0,227	0,050	.415**	-.284*	-.398**	0,076	-0,016	-0,036	-.939**	0,049	-0,001	-.421**	-0,193	.331*
	Sig. (2-tailed)					0,095	0,718	0,002	0,036	0,003	0,583	0,909	0,792	0,000	0,720	0,993	0,001	0,157	0,014

FMIA_I	Pearson Correlation					1,000	.705**	-0,173	.268*	0,072	-0,134	0,164	0,057	0,214	-.388**	-0,236	0,214	0,234	-0,062
	Sig. (2-tailed)						0,000	0,207	0,048	0,600	0,328	0,230	0,680	0,118	0,003	0,083	0,117	0,086	0,654
FMIP_I	Pearson Correlation						1,000	-0,170	0,039	0,188	0,016	0,130	0,003	-0,129	-.303*	-.524**	0,176	0,159	-0,129
	Sig. (2-tailed)							0,213	0,780	0,170	0,909	0,343	0,984	0,348	0,025	0,000	0,200	0,245	0,346
FOCR_I	Pearson Correlation							1,000	0,066	-.298*	0,015	0,058	0,025	-.383**	0,074	-0,087	-.971**	-0,100	.295*
	Sig. (2-tailed)								0,632	0,027	0,916	0,674	0,856	0,004	0,593	0,529	0,000	0,468	0,029
SOC_I	Pearson Correlation								1,000	-0,025	-.443**	.291*	.342*	0,198	0,057	0,092	-0,030	.470**	0,099
	Sig. (2-tailed)									0,854	0,001	0,031	0,011	0,147	0,680	0,506	0,828	0,000	0,473
SQ_I	Pearson Correlation									1,000	-0,264	-0,063	0,004	.345**	-0,230	-0,179	0,261	0,158	-.806**
	Sig. (2-tailed)										0,051	0,645	0,975	0,010	0,092	0,191	0,054	0,250	0,000
CIS-FS_S	Pearson Correlation										1,000	-0,254	-.390**	-0,021	-0,114	-0,173	-0,019	-.651**	0,035
	Sig. (2-tailed)											0,061	0,003	0,878	0,407	0,206	0,890	0,000	0,799
CEQC_S	Pearson Correlation											1,000	.636**	0,075	0,037	-0,135	-0,085	.266*	-0,064
	Sig. (2-tailed)												0,000	0,586	0,788	0,326	0,539	0,050	0,644
CEQE_S	Pearson Correlation												1,000	0,075	0,110	0,018	-0,031	.378**	-0,049
	Sig. (2-tailed)													0,587	0,422	0,896	0,823	0,004	0,721

FCS_S	Pearson Correlation													1,000	-0,115	-0,009	.394**	0,074	-.338*
	Sig. (2-tailed)														0,404	0,947	0,003	0,593	0,012
FMIA_S	Pearson Correlation														1,000	.655**	-0,008	0,122	0,180
	Sig. (2-tailed)															0,000	0,953	0,375	0,189
FMIP_S	Pearson Correlation															1,000	0,074	0,092	0,219
	Sig. (2-tailed)																0,591	0,505	0,108
FOCR_S	Pearson Correlation																1,000	0,170	-.297*
	Sig. (2-tailed)																	0,214	0,028
SOC_S	Pearson Correlation																	1,000	-0,036
	Sig. (2-tailed)																		0,793
SQ_S	Pearson Correlation																		1,000
	Sig. (2-tailed)																		

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

AAF Correlations

		CIS-FS_I	CEQC_I	CEQE_I	FCS_I	FMIA_I	FMIP_I	FOCR_I	SOC_I	SQ_I	CIS-FS_S	CEQC_S	CEQE_S	FCS_S	FMIA_S	FMIP_S	FOCR_S	SOC_S	SQ_S
CIS-FS_I	Pearson Correlation	1,000	0,142	0,061	0,241	-0,105	0,033	0,181	-.448**	-0,218	-0,138	-0,236	0,064	-0,192	-0,101	-0,128	-0,166	-0,012	0,193
	Sig. (2-tailed)		0,274	0,643	0,059	0,419	0,800	0,159	0,000	0,088	0,285	0,067	0,625	0,136	0,435	0,323	0,198	0,926	0,132
CEQC_I	Pearson Correlation		1,000	.600**	-0,115	0,249	0,080	-0,012	0,158	0,105	-.284*	-.452**	-.257*	0,001	-0,086	0,141	-0,060	.312*	-0,085
	Sig. (2-tailed)			0,000	0,376	0,053	0,541	0,925	0,223	0,422	0,027	0,000	0,046	0,993	0,508	0,280	0,648	0,014	0,517
CEQE_I	Pearson Correlation			1,000	-0,149	0,019	0,053	0,040	0,151	-0,031	-0,160	-0,036	-.468**	0,077	0,068	0,115	-0,118	.313*	0,047
	Sig. (2-tailed)				0,253	0,883	0,683	0,757	0,247	0,812	0,218	0,785	0,000	0,556	0,600	0,378	0,363	0,014	0,721
FCS_I	Pearson Correlation				1,000	-0,182	-0,096	.284*	-.497**	-0,159	0,003	-0,106	0,205	-.963**	0,056	-0,086	-.269*	0,046	0,203
	Sig. (2-tailed)					0,157	0,457	0,025	0,000	0,216	0,982	0,418	0,114	0,000	0,664	0,507	0,034	0,722	0,114
FMIA_I	Pearson Correlation					1,000	.578**	-.371**	0,096	0,176	-0,003	-.400**	-0,207	0,147	-.617**	0,232	.350**	0,131	-0,172
	Sig. (2-tailed)						0,000	0,003	0,460	0,170	0,979	0,001	0,110	0,254	0,000	0,070	0,005	0,310	0,180
FMIP_I	Pearson Correlation						1,000	-0,218	0,112	0,052	-0,048	-.272*	-0,072	0,039	-.383**	0,111	.264*	0,028	0,018
	Sig. (2-tailed)							0,089	0,385	0,687	0,713	0,034	0,583	0,763	0,002	0,392	0,038	0,830	0,887
FOCR_I	Pearson Correlation							1,000	-0,063	-.273*	0,054	0,033	0,046	-0,230	0,071	-.343**	-.904**	0,064	.254*
	Sig. (2-tailed)								0,626	0,032	0,678	0,803	0,727	0,072	0,585	0,006	0,000	0,622	0,047
SOC_I	Pearson Correlation								1,000	0,132	0,088	0,055	-0,223	.442**	0,081	0,117	-0,013	-0,206	-0,211

	Sig. (2-tailed)									0,305	0,495	0,672	0,084	0,000	0,529	0,367	0,918	0,109	0,099
SQ_I	Pearson Correlation									1,000	0,092	0,002	-0,033	0,117	0,051	0,250	0,192	-0,071	-.894**
	Sig. (2-tailed)										0,475	0,990	0,799	0,364	0,694	0,050	0,135	0,582	0,000
CIS-FS_S	Pearson Correlation										1,000	-0,005	-0,143	0,074	-.269*	-.330**	-0,050	-.691**	-0,223
	Sig. (2-tailed)											0,969	0,271	0,567	0,035	0,009	0,699	0,000	0,081
CEQC_S	Pearson Correlation											1,000	.316*	0,106	.403**	0,085	-0,012	0,061	0,007
	Sig. (2-tailed)												0,013	0,415	0,001	0,515	0,927	0,640	0,958
CEQE_S	Pearson Correlation												1,000	-0,156	0,108	-0,074	-0,038	0,013	0,094
	Sig. (2-tailed)													0,231	0,409	0,573	0,773	0,919	0,470
FCS_S	Pearson Correlation													1,000	-0,101	0,004	0,242	-0,140	-0,215
	Sig. (2-tailed)														0,433	0,973	0,059	0,277	0,093
FMIA_S	Pearson Correlation														1,000	.477**	-0,108	0,209	0,096
	Sig. (2-tailed)															0,000	0,404	0,103	0,456
FMIP_S	Pearson Correlation															1,000	0,226	.398**	-0,117
	Sig. (2-tailed)																0,078	0,001	0,365
FOCR_S	Pearson Correlation																1,000	0,001	-0,144
	Sig. (2-tailed)																	0,995	0,264

SOC_S	Pearson Correlation Sig. (2-tailed)																	1,000	0,182 0,157
SQ_S	Pearson Correlation Sig. (2-tailed)																		1,000

*. Correlation is significant at the 0.05 level (2-tailed).

**. Correlation is significant at the 0.01 level (2-tailed).

PE Correlations

		CIS-FS_I	CEQC_I	CEQE_I	FCS_I	FMIA_I	FMIP_I	FOCR_I	SOC_I	SQ_I	CIS-FS_S	CEQC_S	CEQE_S	FCS_S	FMIA_S	FMIP_S	FOCR_S	SOC_S	SQ_S
CIS-FS_I	Pearson Correlation	1,000	0,023	-0,025	.342*	-0,056	0,024	0,136	-.343*	-0,206	0,161	-0,042	-0,250	0,194	0,046	0,059	-0,072	-0,250	0,156
	Sig. (2-tailed)		0,878	0,868	0,015	0,697	0,868	0,348	0,015	0,151	0,265	0,777	0,086	0,177	0,749	0,682	0,620	0,081	0,279
CEQC_I	Pearson Correlation		1,000	.824**	-0,174	0,063	0,006	0,072	-.325*	0,017	-0,262	.590**	0,083	-.307*	-0,187	-0,137	0,049	0,023	-0,080
	Sig. (2-tailed)			0,000	0,236	0,672	0,970	0,626	0,024	0,907	0,072	0,000	0,576	0,034	0,203	0,354	0,740	0,879	0,587
CEQE_I	Pearson Correlation			1,000	-0,051	-0,074	-0,145	0,020	-0,241	0,021	-0,222	.472**	0,013	-0,057	0,062	0,038	-0,063	0,034	-0,081
	Sig. (2-tailed)				0,732	0,618	0,325	0,894	0,099	0,888	0,130	0,001	0,928	0,701	0,675	0,800	0,669	0,820	0,585
FCS_I	Pearson Correlation				1,000	-.497**	-.409**	.506**	-.457**	-.324*	0,087	-0,133	-0,089	0,216	.378**	.336*	0,183	-0,243	0,264
	Sig. (2-tailed)					0,000	0,003	0,000	0,001	0,022	0,549	0,366	0,546	0,132	0,007	0,017	0,203	0,089	0,064
FMIA_I	Pearson Correlation					1,000	.738**	-.402**	.464**	0,159	0,023	-0,113	-0,187	-0,245	-.754**	-0,220	-0,174	0,017	-0,162
	Sig. (2-tailed)						0,000	0,004	0,001	0,270	0,874	0,443	0,204	0,086	0,000	0,124	0,226	0,906	0,260
FMIP_I	Pearson Correlation						1,000	-0,223	.290*	0,017	0,067	-0,117	-0,124	-0,105	-.490**	-.395**	-0,123	-0,130	-0,044
	Sig. (2-tailed)							0,120	0,041	0,905	0,645	0,428	0,400	0,469	0,000	0,005	0,395	0,367	0,761
FOCR_I	Pearson Correlation							1,000	-0,214	-0,228	0,034	0,135	0,093	0,158	0,226	-0,024	.412**	-0,212	0,166
	Sig. (2-tailed)								0,135	0,111	0,816	0,360	0,531	0,275	0,114	0,870	0,003	0,140	0,248
SOC_I	Pearson Correlation								1,000	0,205	-0,135	-0,086	0,118	-0,220	-0,177	0,043	-0,215	.286*	-0,212

	Sig. (2-tailed)									0,153	0,348	0,560	0,424	0,124	0,218	0,764	0,133	0,044	0,139
SQ_I	Pearson Correlation									1,000	0,060	0,210	0,037	-0,061	-0,223	-0,156	0,004	0,219	-.929**
	Sig. (2-tailed)										0,678	0,152	0,803	0,674	0,120	0,278	0,978	0,127	0,000
CIS-FS_S	Pearson Correlation										1,000	-.292*	-0,192	.622**	-0,157	-.280*	0,173	-.632**	0,062
	Sig. (2-tailed)											0,044	0,191	0,000	0,275	0,049	0,228	0,000	0,671
CEQC_S	Pearson Correlation											1,000	.403**	-.333*	-0,069	-0,072	0,088	.288*	-0,251
	Sig. (2-tailed)												0,004	0,021	0,641	0,626	0,552	0,047	0,085
CEQE_S	Pearson Correlation												1,000	-0,210	0,117	0,184	.295*	.306*	-0,012
	Sig. (2-tailed)													0,152	0,430	0,210	0,042	0,034	0,937
FCS_S	Pearson Correlation													1,000	0,141	-0,185	0,153	-.700**	0,190
	Sig. (2-tailed)														0,327	0,199	0,289	0,000	0,185
FMIA_S	Pearson Correlation														1,000	.552**	-0,098	0,061	0,188
	Sig. (2-tailed)															0,000	0,496	0,676	0,191
FMIP_S	Pearson Correlation															1,000	-0,203	.329*	0, 111
	Sig. (2-tailed)																0,157	0,019	0,442
FOCR_S	Pearson Correlation																1,000	-0,184	-0,012
	Sig. (2-tailed)																	0,202	0,933

SOC_S	Pearson Correlation																	1,000	-0,254
	Sig. (2-tailed)																		0,075
SQ_S	Pearson Correlation																		1,000
	Sig. (2-tailed)																		

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

APPENDIX D – Multiple regression analyses of models including CEQE_I

In PE the intercepts of expectancy (CEQE_I) and credibility (CEQC_I) were highly correlated (r = .824, p < .001). As CEQE showed to have a floor effect (see Results section), we decided to only report on a multivariate model with the baseline values of credibility (CEQC_I) in the main text. In this appendix, the results are shown of the multiple regression analysis with expectancy (CEQE_I) included in the model. The explained variance of the model for eMBCT was 34%, for AAF 6%, and PE 11%.

These results and the scatterplot in Appendix B, indicate that high sense of control at baseline has predictive value for a reduction in fatigue severity in eMBCT.

Table D.1. Three-group multiple regression analysis with baseline values on fatigue severity change (n = 164).

	eMBCT (n = 55)		**AAF** (n = 61)		**PE** (n = 48)	
Parameter	β (SE)	p	β (SE)	p	β (SE)	p
CIS-FS_I	0.204 (0.116)	0.080	-0.113 (0.144)	0.432	0.101 (0.153)	0.509
CEQE_I	-0.135 (0.115)	0.239	-0.177 (0.127)	0.163	-0.256 (0.144)	0.076
FCS_I	-0.236 (0.144)	0.103	-0.001 (0.156)	0.994	0.017 (0.186)	0.927
FMIA_I	-0.172 (0.175)	0.327	0.057 (0.160)	0.723	0.092 (0.219)	0.674
FMIP_I	0.175 (0.172)	0.309	-0.058 (0.154)	0.705	0.061 (0.199)	0.760
FOCR_I	0.068 (0.127)	0.592	0.123 (0.148)	0.407	0.045 (0.162)	0.779
SOC_I	-0.466 (0.115)	0.000	0.083 (0.160)	0.604	-0.242 (0.175)	0.167
SQ_I	-0.255 (0.129)	0.049	-0.023 (0.132)	0.861	0.144 (0.144)	0.316
R^2	0.337		0.062		0.118	

Abbreviations: eMBCT = online mindfulness-based cognitive therapy; AAF = ambulant activity feedback; PE = psycho-education; CIS-FS = fatigue severity subscale of the checklist individual strength; SQ = subjective sleep quality scale; SOC = sense of control over fatigue; FOCR = fear of cancer recurrence; FMIA = Freiburg mindfulness inventory acceptance subscale; FMIP = Freiburg mindfulness inventory presence subscale; FCS = fatigue catastrophizing scale; CEQE = expectancy subscale of the credibility and expectancy scale; I = baseline value; p = two-tailed p-value; n = number of participants; β = regression coefficient; SE = standard error; R^2 = explained variance.

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Chapter 7

A phenomenological study on patient experiences of two different therapist-guided web-based interventions for chronic cancer-related fatigue

Based on:

Bruggeman-Everts, F.Z.*, Bruggeman, J.S.* & Van der Lee, M.L. (submitted). A phenomenological study on patient experiences of two different therapist-guided web-based interventions for chronic cancer-related fatigue. * Equal contribution.

Abstract

Introduction: Chronic cancer-related fatigue (CCRF) is a considerable burden for cancer survivors. Two Web-based interventions have been developed aimed at reducing fatigue and improve quality of life: (a) Ambulant Activity Feedback (AAF) guided by a physiotherapist encompassing the use of an activity sensor and personal digital assistant (PDA), and (b) online Mindfulness-Based Cognitive Therapy (eMBCT) guided by a psychologist.

Objective: The aim of the present study was to qualitatively evaluate AAF and eMBCT by investigating patient experiences of following AAF and eMBCT in their daily life.

Method: A phenomenological study was performed. In-depth interviews were held with ten eMBCT patients and nine AAF patients at their home. They were asked about the challenges they faced before the intervention, helping and hindering factors of the intervention, and how they were doing now.

Results: We found that the challenges CCRF patients faced were characterized by a *distance* between the *inner world* (lived experience of the affected body) and the *outer world* (expectations based on how it should be), resulting in a *need for reorientation* in their daily life of what they *could do* and *wanted to do*. Both interventions helped reorientation between the inner and outer world by creating insight in their boundaries and pitfalls and recognizing bodily symptoms better. In AAF reorientation was established by changing the outer world, by receiving feedback on physical activity and advice when to rest and when to be physically active. In eMBCT, patients learnt to focus on their inner world and come in contact with the body, and communicating about it with their therapist. Hindering factors such as poor technology usability, mismatch in the amount and content of the exercises, and no personal match with the therapist.

Conclusion: This study provided valuable insights on how two different Web-based interventions contributed to reducing fatigue in cancer survivors.

Introduction

A cancer survivor talking about his experiences with cancer-related fatigue:

"Well, it is really frustrating and you have always been this healthy guy, and you were just working and went to your job and were working hard, because you had a family to take care of, so eh... Money had to be earned and you just continued working. Don't complain, just do it. And suddenly you fall into this black hole. And then you get this, and who was expecting this you know, and what is this? And then you have to return to a base level, and climb up, you want to get back to that level! You want to have it all normal again! And that is harder than you thought… And what I tell you, your body is signaling that it cannot cope, you know? You need to do it differently. And that's the big issue, that is very hard for me. You know…" (crying, unintelligible words, silence) (Man, 48 years)

Almost all cancer patients who undergo cancer treatment, suffer from severe fatigue. In a qualitative study by Wu and McSweeney [1] cancer patients described their fatigue as not just being 'tired', but as a new sensation: you experience an overwhelming depletion of energy, you feel like a 'rag doll', you have an unusual need for rest, but resting or sleep is not refreshing. The unexpected sudden onset of severe fatigue and not being able to explain what is causing this fatigue is upsetting. Also, experiences of one's own body has changed. Characteristics of cancer-related fatigue are feelings of becoming alienated from one's body because it has let you down. The body has become a problematic object as it is incapable of functioning as it did formerly, resulting in distressing and depressing emotions of not measuring up, and losing your identity before you were diagnosed with cancer [1].

About a quarter of the patients who have been successfully treated for cancer keep suffering from fatigue for months or even years after treatment [2]. We call this condition chronic cancer-related fatigue (CCRF). eHealth allows interventions to be available at any time and place, which is especially beneficial for CCRF patients who do not have the energy to travel. Therefore, two different Web-based interventions were developed aimed at reducing CCRF: (1) online Mindfulness-Based Cognitive Therapy (eMBCT) guided by a psychologist, and (2) Ambulant Activity Feedback (AAF) guided by a physiotherapist encompassing the use of an activity sensor. See Patients & Methods section for more information about the content of these interventions. In a previous study it was found that self-reported fatigue severity

significantly reduced in patients who followed eMBCT or AAF, compared to participants receiving weekly e-mails with psycho-education, at 6 months after baseline [3] and one year after baseline [4]. These quantitative results are significant for medical knowledge and supposedly also health insurance companies.

As Web-based interventions are a rather new way of delivering mental healthcare to CCRF patients, qualitative research is needed to understand more about how and to what extent the interventions contribute to wellbeing. Moreover, with an open qualitative view we can look beyond concepts that were theorized beforehand, and possibly learn about new outcomes, which may not be easily captured in quantitative research involving questionnaires [5].

Given the subjective nature of CCRF, a phenomenological approach serves as a useful theoretical framework to capture the lived experience of these patients. Phenomenology of the body was first introduced by Husserl [6]. He described a distinction between the experiences one feels through sense organs such as pain (in German *Leib*), and the experience of the body as a thing, thus the appearance of the body (in German *Körper*). This is also described as respectively the *subject* body and *object* body [7–9].

Merleau-Ponty challenges this dialectic view by describing that the way we experience the world is based on the subjectivity of the lived body [10]. He introduces the term *embodiment*, by which is meant "the body is our general medium for having a world". When applied to healthcare, Leder [11] writes about the way our body shapes our experiences of the world and how the body can feel absent when being healthy. But once you suffer from illness and disability the body then appears as an object, as it loses its taken-for-granted nature [11–13]. Williams [14] adds that illness causes us to feel "dys-embodied, alienated, betrayed and estranged from our bodies" (p.38).

Slatman [13] argues that the lived experience of disability or disfigurements cannot simply be reduced to an individual's physical state, but is related to social context. The way the body is experienced is influenced by the world it shares with others. Slatman therefore introduces "socio-phenomenology of the body" that involves an analysis of embodiment both on the level of the individual and on the level of this individual's social group.

Aim of the study

The aim of the present study was to qualitatively evaluate AAF and eMBCT by investigating patient experiences of AAF and eMBCT. In a retrospective manner and in the everyday context of patients, we investigated what challenges these patients were facing in their daily living activities before applying for the trial, which elements of the interventions were named helpful and which were hindering, and how they were doing after the intervention.

Patients & Method

Setting and interventions

This article reports on the results of a phenomenological study embedded within a 3-armed Randomized Controlled Trial called the *Fitter na kanker* trial, hereafter FNK-trial (translates to *More fit after cancer*) [15,16]. The design of the trial and quantitative results on the effectivity of these interventions compared to patients who received psycho-education, are reported elsewhere [3,16]. To improve readability, the therapist is referred to as female, and the patient as male, though all combinations occurred.

Ambulant activity Feedback (AAF)

The AAF intervention consists of a home-based physiotherapist-guided protocol in which patients use an activity sensor (see Appendix A and B of chapter 3) to gain insight in their physical activity pattern, and increase or balance their daily activities in ways that improve their energy levels. It starts with wearing the activity sensor for one week, receiving no feedback on their physical activity (blind scenario). See Appendix A for a detailed description about the use of the personal digital assistant (PDA) and activity sensor (in Dutch). The PDA and activity sensor were connected via a Bluetooth connection, so the devices needed to be close to each other constantly, or else it would give a sound signal. See Wolvers & Vollenbroek-Hutten [17] for a detailed description of the AAF protocol. When a patient was randomized to AAF, the physiotherapist introduced herself, via e-mail, responded to the baseline physical activity level and the intake, and gave a rough planning about the 9-week protocol. Next, the therapist changed the setting of the PDA, and the patient received hourly feedback messages based on a reference line that followed his baseline physical activity level (see Appendix A of chapter 3). Feedback messages consisted of whether the patient should take rest, should be more active, or that he was on a good level of physical activity. The

patient was invited to write something about himself too, and use the system for a minimum of three days a week to get used to the feedback scenario.

In the second week the therapist called the patient to discuss goals she wanted to achieve with the intervention, and define sub-goals to achieve these goals. Goals could be for example: "Doing groceries without the help of another in week 9" or "Being able to take effective rest moments during the week". The patient was asked to start an 'energy diary' in week 4, and in week 6 he was invited to login to the portal in which he could see past accomplishments (see Appendix B of chapter 3). In week 7 the 'blind scenario' was again activated, so the patient could practice keeping to the goals without the feedback messages. In week 8 the blind scenario week was evaluated, the reference line was adjusted if necessary. In week 9 the intervention was evaluated.

Online Mindfulness-Based Cognitive Therapy (eMBCT)

The eMBCT is a Web-based psychologist guided intervention, which follows the Mindfulness-Based Cognitive Therapy protocol specifically designed for CCRF [18,19]. When a patient was randomized to eMBCT, he received the intervention's terms and conditions by e-mail, and could login to the portal [20]. There, the patient filled in an intake which involved open answer questions such as "Describe what a usual day looks like for you".

The therapist introduced herself to the patient in a personal e-mail, she responded to the intake, and gave a rough planning about the 9-week protocol. She invited the patient to start reading the first week's reader on the portal, download the mindfulness exercises and write down his experiences in the log. The therapist and patient agreed on which day the therapist would respond to the weekly logs via e-mail, thereby guiding the patient through the protocol. See Appendix C of chapter 3 for screen shots of the eMBCT portal.

The first and second week's themes were 'awareness of the body' and 'awareness of the breath', with body scan and breathing exercises. Week 3 was aimed at learning to deal with negative emotions and boundaries, and a 3-minute breathing exercise and yoga exercises were practiced. In week 4 sitting meditation was introduced, practicing recognizing automatic negative cognitions. Week 5 consisted of acceptance exercises. Recognizing and coping with automatic thoughts, feelings and behaviors were the theme in week 6, and compassion, loving

kindness towards oneself, and taking care of oneself were introduced in week 7 and 8, with meditation exercises, such as metta-meditation. In week 9 inner strength was the main theme including how to keep practicing after the intervention had finished. See Bruggeman-Everts et al. [21] for a detailed description of the eMBCT protocol (Appendix A in chapter 2).

Patients and data collection

Between December 2015 and March 2016, 22 patients who had finished eMBCT or AAF, were asked if they were willing to be interviewed about their experiences with doing the intervention. Eventually 19 patients agreed. See Appendix B for demographic information about these patients. Nine patients who had followed AAF were interviewed (2 men, 7 women). Seven of them completed all nine weeks, and two dropped out prior to completion (after week 5 and 6). Ten patients who had followed eMBCT were interviewed (3 men, 7 women). Eight of them had completed all nine weeks, and two dropped out before completion (after week 5 and 8).

The interviews were held at the patient's home, at the kitchen table or in the living room. The interview took 20-70 minutes. In case the patient wanted his or her partner to join the interview, this was encouraged. Patients had finished the online intervention between 1 week to 6 months previously. The interview was recorded using a MP3 recorder device. All patients gave written consent prior to the interview, in which they agreed that the interview could be used for the FNK-trial, and that the audio file would be deleted after being transcribed anonymously.

All interviews followed the interview plan: First, patients were given a brief explanation about the audio recording, the goal of the interview, and were asked if they had any questions. Second, following chronicity of participating the trial, the researcher asked the following questions: (1) symptoms or limitations before assigning to the trial, so in what way did they feel restricted in their daily living activities, (2) expectations before starting the intervention, (3) experiences following the intervention (positive and negative experiences), (4) experiences with doing the exercises/ instructions, (5) current symptoms or limitations (how they were doing now), (6) thoughts on how the intervention had helped them or not, (7) how they had experienced receiving help online, (8) how they had experienced the contact with the therapist, (9) participating in the FNK-trial, (10) other experiences. The researchers were

mindful of the fact that the patients were the experts, and they made sure that all pre-conceptualized sensitizing concepts were discussed. Open-ended questions were asked to yield in-depth responses.

Data analysis

Researcher A performed most of the interviews and conceptualized emerging themes with constant comparison analysis: after each interview, A performed member checking [22] by discussing his conceptualization with the patient after the interview was finished. The patient was asked if he agreed with A's conceptualization or not, and if there were elements missing. These were then included in the final conceptualization, thereby adding credibility to the qualitative study.

Subsequently, interviews were transcribed (verbatim transcriptions) by volunteers and researcher B. All transcripts were checked by B for punctuation and spelling while listening to the audio file. In this step every single patients' story was studied in-depth by B. Notes were written in the text file concerning the concepts of interest: a) what challenges the patient faced before assigning to the trial, b) helping factors of the intervention, c) hindering factors of the intervention, d) how the patient was doing now, and e) any notable remarks by B while listening to the interview. These notes were then copied to an excel file, and were given sub-codes (for example 'challenge', 'contact with therapist', 'work', 'the use of the PDA'). For each intervention separately, these sub-codes were then clustered into conceptualization of emerging themes between all patients using constant comparison analysis. These coding steps were first completed for all AAF patients and later for all eMBCT patients, to minimize cross contamination of the emerging themes between the interventions.

Finally, A and B discussed their findings to form a shared conclusion of what *challenges* patients were facing before assigning to the trial, what were hindering and helping factors of AAF and eMBCT, and to what extent the interventions contributed to their wellbeing.

Results

Challenges of cancer survivors who suffer from fatigue; distance between the inner and outer world

The analysis of the 19 interviews resulted in a *complex of challenges* that the patients were facing before assigning to the trial. We outlined bodily challenges that involved feeling fatigued and physically exhausted and having difficulty concentrating and thinking, with an unpredictable frequency and intensity. The bodily challenges also involved a medical history of painful or damaging treatment, that radically changed the relationship with the body. Some patients described how their body was literally destroyed by treatment. The life-threatening experience of being diagnosed with cancer, also in addition to the invasive cancer treatments and insecure period directly after diagnosis, medical side-effects, and medical flaws were still causing distress. They often dared no longer to rely entirely on their body. We call the lived experience of this *affected body* challenges of the *inner world*.

Man, 60 years (AAF): *"The moment that I became a cancer patient, it is like a sort of declaration of death. When you are a heart patient they fix you up with a new heart valve, or new drains. They say you are fixed, and you have done well for yourself, and all people think it is sorted. But with cancer there is this extra thing that you have cancer in your intestine, but you will die of cancer in your ear, you know? That's the picture I have, or had. So I had to deal with fear of death, I had to deal with the treatments, the needling, the cutting, the hassle, being at the mercy of doctors that really try their best. But what can I do? I can do nothing! I can only lay there and hope that everybody is doing a good job. Don't panic, that's obviously no help! But that cost me so much energy, to keep me from panicking, to not declare myself dead already. And to suppress that fear."*

The lived experience of the affected body or thus the *inner world*, was distanced from challenges of the *outer world*. By challenges of the outer world we mean expectations of the social environment (family friends, or colleagues) and society (having a paid job is important for participating in society) about the patient getting his or her life back on track. But this also involves expectations of the patient him of herself, such as wanting to do things, be of value to society and friends, getting the old care-free life back. It is precisely this need for revaluation that conflicts with the inner world, that simply does not admit to meet up to the

expectations of the outer world. This fight for recognition and rehabilitation is not only difficult because it often happens in vain, but also because it is often misunderstood by the outer world, simply because of the invisibility of suffering. This results in the patient having to give up hobbies, core activities, work, and not feeling home in their body and feeling distressed of not knowing what helps to do the things they want. See Table 2 for examples.

Table 2. Examples of thoughts and assumptions that describe the distance between the *inner* and *outer world*, that was found to be characteristic for challenges CCRF patients are facing.

outer world	**inner world**
"I am an active person"	"I cannot cope, I have to take rest"
"I finish what I have started"	"I have too much pain, I have to stop before it is finished"
"I am the one in this household who takes care of the children"	"I have to ask the children to cook, because I cannot"

When being confronted with illness, the balance between the *inner world* and the *outer world* is changed, as meeting up to expectations, concentrating, planning, having energy etcetera, is often accompanied with disappointment and lack of understanding by the social context. The orientation to *what you want to do* and *what you can do* is disturbed. Therefore we describe the challenges of CCRF patients as *in need for reorientation* of the balance between the inner and outer world.

Helping and hindering factors of AAF

Helping factors of AAF

AAF patients said that the advice and PA graph gave insight in their physical activity pattern, and learned them how to better divide their energy during the day. For example they were motivated to take more rest in the morning, to preserve energy for later that day, or to become active after a period of sitting behind the computer. Secondly, the feedback messages were friendly and at the same time not easy to ignore and thereby motivating. It was rewarding being in the correct physical activity 'zone'. Without the PDA feedback, they were able to continue imagining what kind of feedback the PDA would have given them during the day, at that moment, as physical body signals were better recognized. Also the themes in the psycho-education were named as helpful.

Woman 60 years: *"The trial has brought me, that my fanatics, because that's what I have, I have to drop my fanatics in the morning. Uhm, because then they said; 'it's time to read a newspaper'. And that way really an eye-opener for me! [Laughing]. As like: 'Yes, I can also read a newspaper now… I don't have to do anything yet!' I don't have to…" [Smiling].*

The social environment of the patient was engaged to the patient following the intervention. A patient felt supported towards her family to actually take rest when the PDA said so, and the family also pointed her to take rest. The therapist was described as someone who was concerned with the patient's situation, is a professional, knows what he or she is talking about, is supportive, kind, and can be easily trusted. Patients felt there was a personal match, and they were cooperatively searching for ways to reach the pre-set goals of physical activity. Having weekly e-mail contact with the therapist was pleasant. Some patients also had contact with their therapist more than once a week, though the protocol described having weekly contact. The therapist played an important role in matching the intervention as she helped the patient to interpret the feedback messages. Also, she could adapt the reference line straightaway, if this was needed.

Woman, 57 years: *"I just have a sedentary profession, and I am sometimes very busy and then that thing starts to beep and says, why don't you go and do something. And then I think: 'Well, get lost! I am doing something' (…) 'Do you think I am laying on the couch or something?' So there was this irritation, But, well, then he (therapist) said 'I know', and 'that is unfortunately not something he (the activity sensor) can measure so just don't let it bother you'. Well then in time I got used to it and then I could also laugh better about is, that's more useful."*

Hindering factors of AAF

Patients said the PDA and activity sensor were ugly, large and unhandy devices. It was a hassle to remember to charge the battery every night. Because the sensor was worn with an elastic band around the waist, it was difficult to dress nicely when wearing it. Some patients missed the psychological support of the therapist, as the e-mails were mostly about goal setting and physical activity, and not about fear of cancer, and how to get your life back on track. The tone of the e-mails of the therapist were by some described as too pushy or too quickly moving from one goal to the next.

Man, 48 years: *"Look, your physical fitness is a mess and it obviously is… physically you are a mess, but psychologically you are also not all well. Because – I tell you – your body is changed, and you do need to process that for yourself eh? Thus uhm, it needs to change, the pattern must change, and how will I do that? So that is what I missed. So well, a piece of support of eh... how are you going to do that?"*

It was hindering if therapists did reply on the agreed day of the week. Receiving a message on a Sunday evening was interpreted as just a quick message next to their 'real' (i.e. face-to-face) jobs. Some patients said that weekly contact with the therapist was too infrequent. One patient was annoyed and confused about the content of the psycho-educational information, as the themes were not corresponding to the goals in his therapy, and did not match his situation. This psycho-education information was derived from the eMBCT protocol, and was also included in the AAF protocol, so participants in all conditions were given the same psycho-education. Also, it took too much effort for many patients to read the psycho-educational text and to write e-mails to the therapist, as when suffering from fatigue, reading comprehension is a difficult task.

After AAF

After the PDA and activity sensor were returned to the researchers, some patients said they felt relieved of these ugly devices, and were glad the intensive period was over. Others missed the PDA, and searched for other technology that would give them feedback on physical activity. Patients kept thinking of what the PDA would have had advised them to do, and said that if they kept better dividing their activities during the day, they would not be as much fatigued as before. Some chose to avoid stressors in daily life, that prevented them from crossing their boundaries. For many patients, it kept being difficult to create balance in physical activity level during the day.

Woman, 60 years: *"Well, it is not completely gone…. I divide more, more of my activities during the day. And as long as I do that nicely well… then I won't be so totally demolished."*

Helping and hindering factors of eMBCT

Helping factors of eMBCT

eMBCT patients said the exercises – especially the 3-minute breathing exercise and body scan exercise – helped them to create a moment of rest, and become conscious about their thoughts, feelings, and how their body felt. The body scan exercise was often used to fall asleep, or as an alternative way to rest, opposite to going to bed in the middle of the day, and feeling like a sick person.

Woman, 60 years: *"I do feel I have.., I have these antennas sooner…, so that I think like 'Whoa, now there is something happening to me. Now I get stressed, now I need to do that 3-minute breathing exercise', or 'Now I need to just take it easy', or… that kind of things that …or 'Now I need to go for a walk and will I put myself very thoroughly with both my feet on the ground'."*

Patients liked writing about their experiences with doing the exercises and reading back the correspondence with the therapist, as it helped organizing their thoughts. The feedback e-mails of the therapist contained eye-openers in that there is no right or wrong, and that the patient might have been too harsh on himself. It was clear that the therapist was a professional who knew about the problems the patients were facing: The therapist acknowledged the patient's troubles by responding in an understanding and caring way. She gave compliments, and picked out things that were going well, and thereby encouraged to continue. She was not only interested the process of following the protocol but also asked for personal life events and coached the patient. A few patients said they valued that the therapist responded empathically when they could not finish all the assignments of the week.

Woman, 45 years: *"I noticed that she actually had read my writings and that she addressed the content. And she connected next week and eh… so that it was much more personal than I first had expected and that was quite nice. (…) She was just repeating what she had read, like 'Your story seems to me like…'. There was a part of recognition like A; 'Too bad for you', and B; also a kind of compliment like 'I see you are working well on certain things. And here and there you are having difficulty, am I correct?' And eh… from there she asked a few more questions that just made me wonder. And so I could think for myself: 'Is this true or not, or do I need to explore it in more detail for myself, or am I hurrying by these thoughts too quickly,*

because I think I get it'. So I noticed especially from her questions, that I noticed that indeed, that I very much… despite the fact that there was no face-to-face contact."

Patients could ask questions about the protocol and the therapist explained the purpose of the exercises, or how the exercises were intended. The fact that there was weekly personal contact with the therapist, provided regularity in the protocol. The content of the readers was useful. MP3 files and readers were downloaded and saved to read back later. Having the choice between different exercises and also different recordings (male or female voice) was pleasant. It was convenient that they could do the exercises when for example their kids were at school, or postpone the exercises in case of for example holidays. The exercise 'eating with attention' could be easily done without people noticing that they are doing an exercise. Moreover, following the intervention also resulted in discussing their pitfalls with friends.

Hindering factors of eMBCT

The intervention was often described as too intensive as it required cognitive efforts, such as reading comprehension and writing down a coherent story about their experiences after each exercise. It needed discipline and time investment to practice every day for 9 weeks straight. Some said it was not possible to do the exercises during work, so all exercises needed to be done in the evening. They felt pressure of doing the exercises and hand in their writings on the agreed day.

Some patients disliked the content of the MP3 mindfulness exercises. Many patients described the first exercise 'eating a raisin with awareness' as ridiculous, because it was not clear to them how the exercise would help them. Patients found some exercises too woolly, for example the mountain meditation. They were annoyed by the tone of voice of the exercises in general, and the choice of words in the exercises. Focusing on negative feelings made some patients feel more miserable. One patient suffered from polyneuropathy in the feet which made the walking meditation too disturbing. Another patient said she preferred being active to feel better, like walking, and thus the sitting meditation was too passive for her.

The online setting of eMBCT was hindering for some patients as they lacked face-to-face contact with their therapist. Working with a computer was exhausting and frustrating for patients, as it was not straightforward how they could download MP3 exercises and save their logfiles. When the internet connection failed while they were writing down their experiences

on the portal, it often failed to save their writings. The reluctance against exercises, together with great time-investment resulted in patients postponing the exercises, which caused stress. The two patients who stopped using the intervention, said that the time-investment was not paying off.

After eMBCT

After the protocol had finished, some patients said the exercises still created a moment of peace during the day, but old pitfalls were returning. Most of them had downloaded all readers, exercises and correspondence with their therapist, but continuing doing the exercises regularly was hard without the therapist 'looking over your shoulder'. Some patients continued doing the 3-min breathing exercise, body scan and eating with attention every now and then, and others said it felt like a relief the intervention was over.

Man, 32 years: *"It is actually quite disappointing that it is hard keep doing those things really in a structured manner. At least, I am struggling with it. But I think that if people are very disciplined, people who are like that by nature and think: 'I want to keep doing that and so am doing that', then it may work. But for me that's not working. And then I really have to force myself, and if I don't have a big stick to keep me disciplined, it gets watered down. Although I know that it might be a good thing to do."*

Conclusion

This phenomenological study showed us that both interventions contributed to the patients well-being, by providing tools for reorientation to the balance between the *inner world* and *outer world*, guided by a professional and acknowledging therapist.

The exercises helped reorientation between the *inner* and *outer world* by creating insight in their boundaries and pitfalls by recognizing bodily symptoms better, and thereby preventing crossing their boundaries that led to psychical exhaustion. In opposite of searching and wandering in how to deal with fatigue and how to prevent physical exhaustion and not feeling understood by their social environment, they felt acknowledged for their challenges and supported by the intervention and therapist in their wandering, and they found ways to incorporate relaxing moments during the day without the feeling of being overwhelmed by physical exhaustion. The exercises and the therapist served as a new *outer world* as new expectations were introduced to the patient. But also, the interventions put more focus on their

inner world, through weekly correspondence with their therapist and writing down their lived experiences (thoughts and feelings) and focusing on bodily experiences.

In AAF particularly, the focus was drawn to the *outer world*, as the feedback on physical activity served as a new 'norm' of when to rest and when to be physically active. This new norm was also made clear to the social environment, as the for example family members would repeat the advice given by the accelerometer. The feedback messages allowed them to take rest, and therefore taking rest was something that prevented physical exhaustion, as a way of self-care, instead of having to take rest because they felt exhausted.

In eMBCT particularly, the focus was drawn to the *inner world*, as thoughts like 'How am I doing?', 'Am I in a hurry?', 'How is my body feeling?', popped up during the day, and served as a way of coming in contact with the body. The feedback of the therapist was acknowledging for their situation and gave insight in how to take care of oneself, and that there is no right or wrong. In that way the *outer world* was also changed. Also, exercises were relaxing and helped to fall asleep.

After the interventions patients would easily return to old habits that resulted in crossing boundaries again. So applying the tools in their daily lives after the interventions had finished, needed constant attention and discipline.

Discussion

This study contributes to the discussion of phenomenology of the body in chronic illness, as it included the social context and provided a new framework to understand the phenomenon of how it is to live with a CCRF. Moreover, these results give insight in how two theoretically different Web-based interventions contributed to wellbeing, but more specifically give insight in how both interventions approached the matter in different ways. Both interventions helped reorientation to the balance between the *inner world* and *outer world*, but in AAF the focus was especially on changing the *outer world*, and in eMBCT changing the *inner world*. So there are *many different ways to Rome*. The results teach us that it is matching these interventions to the needs of the patients, that is of great importance of the success of the interventions. The therapist plays a very important role in this, and we think she should be given the autonomy to personalizing the intervention (e.g. pausing the intervention, having

contact more than once a week, introducing a meeting face-to-face when it is preferred, help to interpret the content of the exercises). Moreover, technology should work flawlessly and intuitively. As these patients often had difficulty with reading comprehension due to fatigue, it is important to provide multiple ways of communicating with the therapist and having access to the psycho-educational information, e.g. via video's or video infographics.

A strength of this study is that we interviewed the patients in the context of their own social environment, so we were able to include the context in which patients had followed the intervention. One limitation of this study design may be that we had asked how patients remembered their complaints retrospectively after having followed the intervention. To study the challenges CCRF patients were facing, it may have been better to interview them before the intervention started to minimize 'bias' of the intervention itself. However, by interviewing after the intervention, we were able to study the patient experiences in the light of evaluating the intervention and to what extent the interventions had contributed to their wellbeing. Moreover, our results of challenges of CCRF patients matched to that of the qualitative study of Wu and McSweeney [1] involving patients undergoing cancer treatment. In their article, they introduce the concept of re-unification as a characteristic of the patients in their study. By re-unification they mean 'the harmony of lived body and object body'. This is in line with our finding, but we included a broader perspective by including the social context and expectations of the *outer world*, as an element of the challenges CCRF patients are facing and called this *in need for reorientation between the inner and outer world*. We propose the re-unification of the lived body and object body, or the reorientation efforts of the balance between the *inner* and *outer world* should be included in the definition of CCRF in NCCN guidelines [23]. And this insight may improve matching interventions to this patient group.

It would be very interesting to include the perspective of the therapist to evaluate the interventions more thoroughly. Therefore, we are currently studying the social practices the online psychologist of eMBCT, to further explore the role of the online therapeutic relationship [24].

Appendices

APPENDIX A – Manual PDA (in Dutch)

Handleiding activiteiten meten

Handleiding activiteiten meten – Fitter na kanker

Model smartphone: HTC Desire S

9 juli 2013

Roessingh Research and Development

Enschede, Nederland

Inhoudsopgave

Onderdelen van het activiteitensysteem

A Smartphone (mobiele telefoon met toegang tot internet)

B Bewegingssensor

C Oplader voor de mobiele telefoon

D Oplader voor de sensor

E Draagtasje voor de mobiele telefoon

F Sensorhouder

G Draagriem

F.1 Riembevestiging

F.2 Clipbevestiging

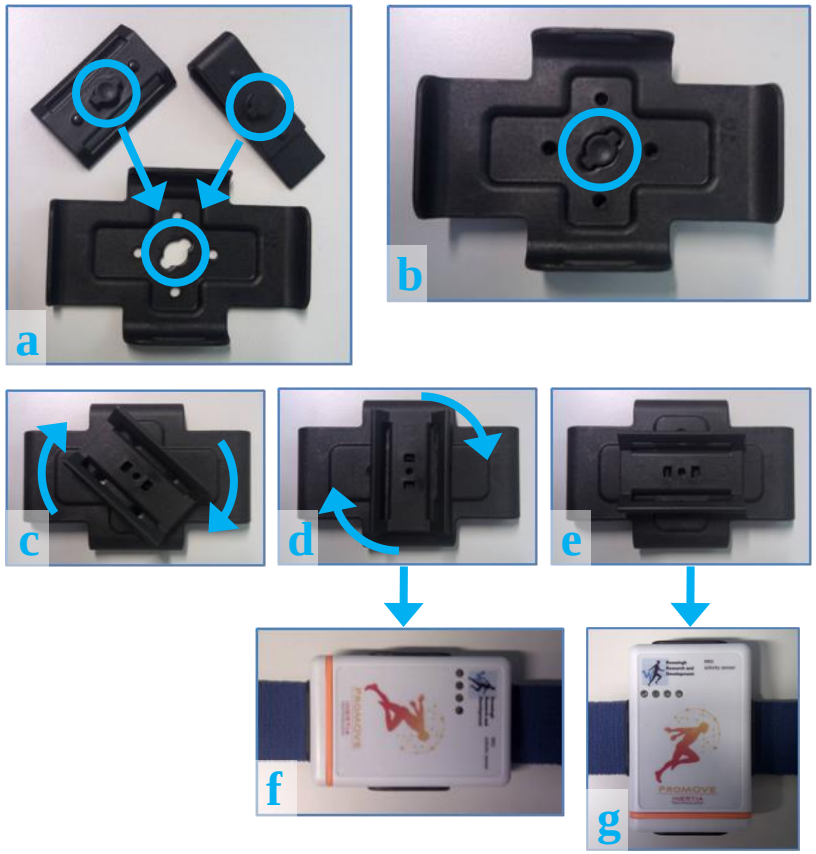
Inleiding

Het systeem voor het meten van uw activiteit bestaat uit een smartphone (mobiele telefoon met toegang tot internet) en een bewegingssensor. Beide apparaten kunt u de gehele dag bij u dragen. De bewegingssensor meet de lichamelijke activiteit over de dag. De metingen worden drie keer per dag over het internet verstuurd naar de onderzoeksdatabase van Fitter na kanker.

Hoe draag ik het systeem?

Bij het systeem wordt een sensorhouder (figuur F) geleverd waar u de sensor in kunt klikken en een draagtasje (E) voor de mobiele telefoon. Zowel de sensorhouder als het tasje kunt u bevestigen aan een broekriem of aan de bijgeleverde draagriem (G). Voor een betrouwbare meting moet u de sensor aan de **zijkant van uw heup** dragen. Het maakt niet uit of dat aan de linkerkant of de rechterkant is. De telefoon kunt u dragen op een plek die u comfortabel vindt.

Hoe werkt de sensorhouder?



In de afbeeldingen hierboven ziet u hoe de sensorhouder werkt. Bij de houder horen twee bevestigingen, waarvan u er een kunt kiezen. De houder wordt het stevigst bevestigd aan een riem, waarvoor u de riembevestiging neemt (linksboven in afbeelding a). Deze past ook op de bijgeleverde draagriem. Als u geen riem draagt, of uw riem is te breed, dan kunt u de clipbevestiging nemen (rechtsboven in afbeelding a). De houder zelf heeft een uitsparing in het midden waar de bevestiging in past

(zie de cirkels in afbeelding a en afbeelding b). In afbeelding c ziet u de achterkant van de sensorhouder. Door de bevestiging te draaien klikt deze vast, zoals in afbeelding d. In deze positie draagt u de sensor horizontaal (f). Eventueel kunt u de bevestiging nog een kwartslag verder draaien (e), zodat u de sensor verticaal draagt (g). De clipbevestiging is verder niet afgebeeld, maar werkt op dezelfde manier.

Hoe gebruik ik de draagriem?

De draagriem is elastisch en is voorzien van klitteband waarmee u de riem op maat kunt maken. Zowel het tasje voor de mobiele telefoon als de sensorhouder kunt u aan deze riem bevestigen. In de afbeeldingen hierboven ziet u hoe dat werkt.

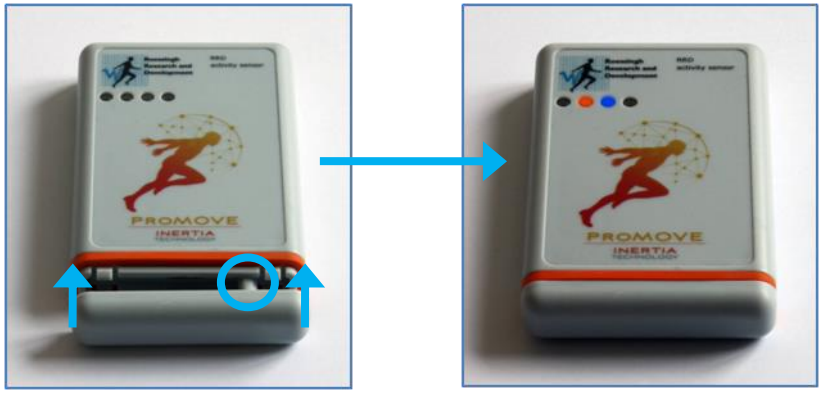
1. Maak het klitteband los aan de zijde die u ziet in afbeelding a.
2. Verwijder de sluiting van de riem (b).
3. Schuif de sensorhouder en het tasje voor de mobiele telefoon op de riem (c).
4. Schuif de sluiting terug op de riem (d).
5. Maak het klitteband weer vast (e). In afbeelding f ziet u hoe het er aan de voorkant uitziet.
6. Bind de riem om uw middel en klik de sluiting vast.
7. Verstel de riem eventueel met het klitteband, zodat hij goed past.
8. Verschuif de sensor naar de zijkant van uw heup en verschuif de mobiele telefoon naar een plek die u comfortabel vindt.

Wat meet het systeem?

De sensor meet veranderingen van snelheid en bepaalt zo hoeveel u beweegt en hoeveel rust u houdt op een dag. Een snelheidsverandering treedt op als u bijvoorbeeld vanuit stilstand gaat bewegen of als u heen en weer beweegt. Telkens als u een stap zet, tilt u uw been op en beweegt het naar voren. Dat zijn allemaal snelheidsveranderingen, die door de sensor op uw heup te meten zijn. De sensor is dan ook erg geschikt om uw activiteit te meten tijdens bijvoorbeeld wandelen.

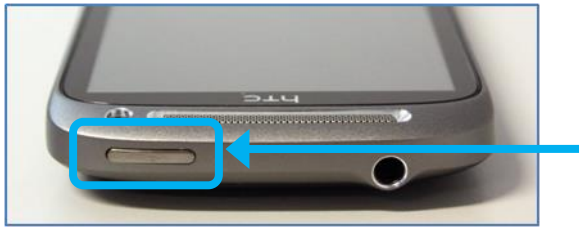
Opstarten van het activiteitensysteem

1. **Aanzetten van de sensor**
   Schuif de losse onderkant op de sensor. Zorg dat het lange pinnetje in het gaatje valt. Er gaan kort een rood en een blauw lampje branden: de sensor start op.

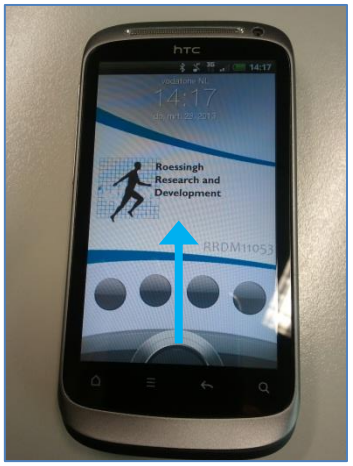


De sensor start

2. **Aanzetten van de mobiele telefoon**
   Druk op de aan/uit-knop op de bovenkant. Het scherm gaat aan en de telefoon begint met opstarten.



Schermvergrendeling



Ontgrendel het scherm door de ring naar boven te schuiven met uw vinger.

Wanneer u het scherm een tijd niet heeft gebruikt, zal het scherm vergrendeld worden. De knoppen op het scherm worden dan tijdelijk afgeschermd, zodat ze niet worden ingedrukt wanneer u bijvoorbeeld de telefoon in uw broekzak draagt. Om het scherm weer te gebruiken, moet u het eerst ontgrendelen. Schuif hiervoor met uw vinger de ring onder in beeld omhoog. Gebruik daarvoor uw vingertop, niet uw nagel.

Als u het scherm een langere tijd niet hebt gebruikt, zal het scherm helemaal uit gaan. Uw activiteit wordt gewoon gemeten. U kunt het weer aanzetten door kort op de aan/uit-knop te drukken.

U kunt ook zelf het scherm vergrendelen door kort op de aan/uit-knop te drukken. Zo spaart u de batterij en voorkomt u dat u per ongeluk iets indrukt.

De meting starten

Als u na het opstarten van de telefoon het scherm ontgrendeld heeft, is het mogelijk dat u een van de schermen ziet die hieronder beschreven worden.

1. 

Dit scherm wordt direct na het opstarten van de telefoon getoond. Na ongeveer een minuut verschijnt in dit scherm vanzelf de knop **Starten** (scherm 2).

2. 

Dit scherm ziet u als de mobiele telefoon klaar is om de meting te starten. Druk met uw vinger op de knop **Starten**. Na een minuut start de meting vanzelf, ook als u niet op de knop hebt gedrukt. Daarna kan korte tijd het scherm op afbeelding 3 verschijnen en zult u ten slotte in het hoofdscherm komen.

3. 

Dit scherm kan korte tijd zichtbaar zijn terwijl de mobiele telefoon verbinding maakt met de sensor. Zodra er een verbinding is, verdwijnt dit scherm vanzelf en komt u uiteindelijk in het hoofdscherm.

Als dit niet gebeurt: zie pagina 19 van deze handleiding.

Gebruik van het activiteitensysteem

Als u het activiteitensysteem heeft opgestart, zoals beschreven in de vorige hoofdstukken, zal het hoofdscherm verschijnen.

U ziet in het hoofdscherm het logo van Roessingh Research and Development en de tekst "Aan het meten".

Er is nu verbinding met de sensor. Als er geen verbinding is, ziet u:

Batterij van de mobiele telefoon.

Het hoofdscherm tijdens de meetperiode.

Wanneer draag ik het systeem?

Draagt u het systeem alstublieft:

- op 7 achtereenvolgende dagen tijdens zowel voor- als nameting (zie ook B en D op Bijlage 1 van de Informatiebrief),
- en op 3 zelfgekozen dagen van week 3, 6 en 9 van de e-therapie.

Wij zullen u hier telkens aan herinneren per e-mail.

Hieronder kunt u eventueel voor uzelf bijhouden wanneer de verschillende metingen zullen plaatsvinden.

	Startdatum	Aantal meetdagen	
Voormeting (B)		7	☐ ☐ ☐ ☐ ☐ ☐ ☐
Start e-therapie (week 1)		0	
Week 3		3	☐ ☐ ☐ ☐ ☐ ☐ ☐
Week 6		3	☐ ☐ ☐ ☐ ☐ ☐ ☐
Week 9		3	☐ ☐ ☐ ☐ ☐ ☐ ☐
Nameting (D)		7	☐ ☐ ☐ ☐ ☐ ☐ ☐

Afsluiten

Als u klaar bent met meten en u hoeft de rest van de dag niet meer te meten, dan kunt u het systeem uitzetten en opladen voor de volgende dag. Zorg er eerst voor dat het scherm ontgrendeld is. Hoe dat werkt, kunt u nalezen op pagina 11 (Schermvergrendeling).

1. Druk op de aan/uit-knop (op de bovenrand van de telefoon) en houd de knop ingedrukt, totdat u dit scherm ziet.

2. Druk op **Uitschakelen**. De telefoon wordt nu uitgeschakeld.

3. Zet ook de sensor uit. Verwijder de onderkant van de sensor. De sensor is nu uit. Bewaar de onderkant van de sensor in de sensorhouder.

Verwijder de onderkant van de sensor.

Bewaar de onderkant van de sensor in de sensorhouder.

Opladen

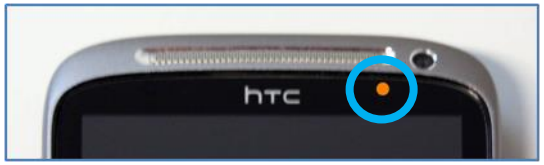
Zorg ervoor dat zowel de mobiele telefoon als de sensor zijn opgeladen aan het begin van de dag. U kunt het beste elke avond als u het systeem afsluit, de apparaten aan de lader leggen. *Sluit u alstublieft de telefoon helemaal af wanneer u deze 's nachts oplaadt.*

De telefoon wordt opgeladen.

De sensor wordt opgeladen.

Sluit de opladers aan zoals hierboven weergegeven.

Op de telefoon gaat een oranje lampje branden:



Als de telefoon helemaal opgeladen is, dan wordt dat lampje groen:

Op de sensor gaat een geel lampje branden en dat lampje gaat uit als de sensor is opgeladen.

Problemen oplossen

Er is geen verbinding met de activiteitensensor.

Als de verbinding met de sensor wegvalt, wordt het sensoricoontje grijs en verschijnt na enige tijd dit scherm:

Dit kan verschillende oorzaken hebben:

- De sensor is uit. Waarschijnlijk is de batterij van de sensor leeg en moet u de sensor opladen.
- U draagt de sensor niet meer bij u. Zodra de sensor weer in de buurt van de telefoon is, wordt de verbinding hersteld.

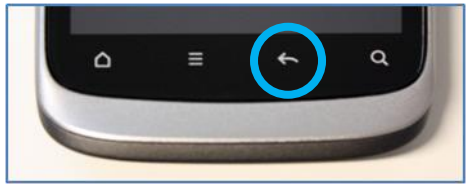
Er is een storing in de verbinding. Dit moet vanzelf na enige tijd hersteld worden. Gebeurt dat niet, dan kunt u het beste de mobiele telefoon opnieuw opstarten, door deze eerst af te sluiten en vervolgens weer aan te zetten (zie pagina 16,

- **Afsluiten**).

Ik zie een onbekend scherm en ik kan het niet afsluiten.

Door het ingedrukt houden van een knop, kan het soms gebeuren dat er een onbekend scherm verschijnt, zoals dit:

U kunt zo'n scherm sluiten door op de 'terug'-knop te drukken:



Er knippert een rood lampje op de sensor

Dit lampje knippert langzaam als de batterij bijna leeg is. Als het lampje stopt met knipperen en helemaal uit gaat, dan is de batterij leeg en moet u de sensor opnieuw opladen.

APPENDIX B – Demographics of participants

ID	gender	education	age	living situation	completed to week no.	cancer type	suffering from fatigue since	treatment at baseline	treatment type	paid job	time since last treatment	oncological revalidation	help received psychologist before
AAF1	woman	high	57	with partner and child(ren)	9	Breast	1 - 2 y	HT	OP + CT + HT + RT	yes	1 - 2 y	no	no
AAF2	man	low	48	with partner and child(ren)	9	Digestive system	6 m - 1 y	no	OP + CT + RT	yes	6 m - 1 y	no	no
AAF3	man	middle	60	with partner living apart	9	Digestive system	1 - 2 y	no	OP	no	1 - 2 y	yes	yes
AAF4	woman	middle	69	with partner	6	Urinary tract + Digestive system+ Blood, bone marrow, Hodgkin's disease (not leukemia)	unknown	no	OP + CT	unknown		no	no
AAF5	woman	middle	57	with partner	9	Breast	6 m - 1 y	HT+AD	OP + CT + RT + HT	no	6 m - 1 y	no	no
AAF6	woman	high	47	with partner and child(ren)	9	Breast	3-5 m	no	OP + CT +RT	no	6 m - 1 y	no	no

AAF7	woman	middle	60	with partner and child(ren)	9	Digestive system	> 5 y	no	OP + RT	yes	> 5 y	yes	yes
AAF8	woman	middle	60	with partner	9	Head and neck	6 m - 1 y	no	OP	yes	2 - 5 y	no	no
AAF9	woman	high	54	with partner	5	Blood, bone marrow, Hodgkin's disease (not leukemia)	1 - 2 y	no	CT + RT + IT	no	2 - 5 y	yes	no
eMBCT1	woman	middle	53	with partner	9	Leukemia	2 - 5 y	no	CT + RT + ST	yes	2 - 5 y	yes	no
eMBCT2	woman	high	42	with partner and child(ren)	9	Reproductive organs	2 - 5 years	no	OP + CT + RT	no	2 - 5 y	yes	yes
eMBCT3	man	middle	67	with partner	9	Digestive system	1 - 2 y	no	CT + RT	no	1 - 2 y	no	no
eMBCT4	man	high	32	with partner	9	Blood, bone marrow, Hodgkin's disease (not leukemia)	> 5 y	no	OP + CT	no	> 5 y	no	yes
eMBCT5	woman	high	60	with partner and child(ren)	9	Breast	> 5 y	HT	OP + HT + RT	yes	2 - 5 y	yes	no
eMBCT6	woman	middle	57	with partner and child(ren)	8	Breast	6 m - 1 y	no	OP + CT + RT	no	6 m - 1 y	yes	no

eMBCT7	woman	high	45	with children	5	Breast	> 5 y	HT	OP + CT + RT + HT	no	> 5 y	no	yes
eMBCT8	woman	middle	43	with partner and child(ren)	9	Breast	1 - 2 y	HT	OP + HT	no	1 - 2 y	yes	no
eMBCT9	man	middle	62	with partner	9	Blood, bone marrow, Hodgkin's disease (not leukemia)	2 - 5 y	no	CT + RT	no	> 5 y	no	no
eMBCT10	woman	high	44	with partner	9	Breast	2 - 5 y	HT	OP + CT+ HT+ RT+ IT	no	2 - 5 y	yes	yes

Abbreviations: OP = operation; CT = chemotherapy; HT = hormone therapy; ST = stem cell transplantation; IT = immunotherapy; y = year; m= months

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Chapter 8

General Discussion

Principal findings

Two different Web-based interventions were developed aimed at reducing CCRF: a physiotherapist-guided ambulant activity feedback (AAF) therapy encompassing the use of an accelerometer, and a psychologist guided Web-based mindfulness-based cognitive therapy (eMBCT). To improve the quality and accessibility of Web-based interventions for cancer survivors who suffer from CCRF, this dissertation comprises the investigation of the following research questions in a 3-armed RCT:

1. The effectiveness of two different types of Web-based interventions (AAF and eMBCT) for reducing CCRF compared to an unguided active control condition receiving psycho-educational e-mails;
2. Specific and generic predictors and working mechanisms of these interventions;
3. Patient experiences with following these interventions.

Concerning the first research question, we found that in AAF and eMBCT fatigue severity significantly reduced more than in the psycho-education condition. Fatigue severity substantially reduced (clinical relevant improvement) in 62% of the participants in AAF, 49% in eMBCT and 12% in PE. Moreover, mental health increased in all three conditions.
Concerning the second research question, we found that high *sense of control* (feeling capable of changing fatigue) at baseline was a predictor for fatigue reduction in eMBCT, and an increase in *sense of control* was a generic working mechanism for fatigue severity reduction in both eMBCT and AAF. Concerning the third research question, we found that the interventions were helpful as they were provided with tools that gave insight in their boundaries and pitfalls. This helped reorientation between the inner world (lived experience of fatigue) and the outer world (expectations). While they were guided by a professional and caring therapist, reorientation of what they wanted and could do, was established. The supporting role of the online therapist was very important for feeling acknowledged for their challenges, and that the therapist was able to personalize the protocol to the patient.

When combining our quantitative and qualitative findings, we can conclude that both AAF and eMBCT were effective in reducing fatigue by providing helpful tools while being supported by a caring professional. The interventions led to feeling more capable of changing fatigue (sense of control), or as the interviews suggested, the interventions helped creating

insight in boundaries and pitfalls and facilitated reorientation of the balance between the inner world and the outer world.

The interviews brought nuance to the quantitative findings that both interventions were effective in reducing fatigue: in the interviews patients said that the extreme fatigue severity was reduced after the interventions, but fatigue was still a burden in daily life. Thus, fatigue was not gone, but it helped fatigue severity become bearable. This learns us that an intervention that shows to be effective in a RCT design helps *managing* fatigue, resulting in that fatigue severity reduces to a clinical meaningful lower level (for example [1]), in contrast to lack of evidence of disease [14] (p. 275). The NCCN guidelines [2] also hold information about effective interventions that help management of fatigue.

Suggestions for improvement of AAF and eMBCT

Based on the findings presented in this dissertation, we provide suggestions for improvement of AAF and eMBCT. In order to improve the interventions further and minimize dropout, designers should focus on matching and personalizing the eHealth interventions to the specific needs of each patient. Especially eHealth has great possibilities to match the intervention to the specific needs. Tailoring interventions and letting the patient choose which modules to follow, shows to be promising [4–8]. The NCCN guidelines also mention that interventions should be "tailored to the specific needs of patients and their families"[2] (p. SFAT-5).

As both AAF and eMBCT have shown to be effective, a combination of both interventions may be provided to all patients within the same setting. This would allow the patient to change to an alternative Web-based intervention when in practice it turns out that the intervention does not match. This may prevent discouragement and frustration when dropping out, as was often the case in non-adherent participants in this trial. Secondly, in future versions of AAF and eMBCT technology should work flawlessly and intuitively, and the intervention should be easily applicable in everyday life of the patients. For example, it should be made easier to save the correspondence with the therapist from the eMBCT portal on the computer. Also, efforts should be made to provide a nicer looking activity sensor and PDA, which is easy to handle and has a long life battery, so AAF patients indeed like to wear and use it. Furthermore, as our patients often had difficulty with reading comprehension due

to fatigue, it is important to provide multiple ways of communicating with the therapist and consuming the psycho-educational information, e.g. via video's or video infographics. In both interventions, there were patients who said they preferred face-to-face contact, so it is advised to consider starting with a face-to-face introduction, video conversation, or offer the interventions in a blended design. Many patients said it was too intensive to write down experiences, so video or audio messages can help these patients to discuss their experiences with their therapist. Yet, other patients found it helpful to write down their experiences, so this must remain an option.

Methodology

Strengths and limitations of the study design

Our 3-armed RCT design has several strengths. One major strength of the study design is that we used an active control condition that consisted of psycho-education. As psycho-education was found to be effective for cancer-related fatigue [5], comparing AAF and eMBCT to PE is a strict way of evaluating these interventions. We performed latent growth curve analysis (see chapter 5). This technique allows individuals to have an individual growth trajectory over time (with individual variance) and compensates for missing data in an elegant way. Also, individual time of filling in the questionnaire (timescores) was included in the statistical model. Another strength is that by randomization into three groups, we were able to study treatment specific and generic working mechanisms and predictors. In addition, we used both quantitative *and* qualitative research methods, and thus this dissertation entails a comprehensive view on the clinical relevance of these interventions.

We experienced several limitations of the RCT design for evaluating interventions, as a few characteristic aspects of the RCT design influenced the translation from research to clinical practice (external validity). Firstly, one downside of an RCT design, is that at some point technology catches up in time, and the interventions under study become outdated. In our study, new nicer looking small accelerometers came to the (commercial) market and became soon affordable, and eMBCT was not compatible with an iPad. But we decided not to update the interventions during the trial because then we would have to split our research groups into the old and new version which asks for many more participants to include to gain enough statistical power. Or, with the use of Bayesian statistics more power can be generated with the

use of prior information which is incorporated in the model that is being tested [9,10]. However, we decided to conservatively stick to our original research protocol and not update the versions of the interventions during the trial.

Secondly, another limitation of the RCT design were general aspects of a research setting. Filling in questionnaires simultaneously to following the interventions was an extra task for the patients. One solution to minimize this effect may be planned missing-data designs. In this design some parts of data are purposely not collected and thus a way to minimize the burden of filling in questionnaires [11]. The missing data is then imputed by using various sophisticated statistical models such as multiple imputation and maximum likelihood estimation. However, this method asks for larger sample sizes (about 400 or more) [12], so this was not possible for the FNK trial. Moreover, having frequent contact with the researchers was different from clinical practice, and the attention may have been helpful on itself. One could minimize the contact with the researchers, but in my experience having close contact with the participants also reduced missing data. Furthermore, based on our contact with the patients, we noticed that the motivation to participate in this trial was mostly because the patients wanted to help improving healthcare for fatigued cancer survivors, rather than mainly to follow an intervention for their complaints. This is expected to be different in clinical practice, where patients would apply for an intervention to help dealing with their complaints.

Despite the above mentioned limitations, in evidence-based medicine (EBM) an RCT is high in the hierarchy of experimental evidence. EBM, which advocates clinical decisions are based on experimental evidence, has brought better methodology that has allowed us to distinguish between helpful and harmful treatments, identify the major problems with publication bias, and surface and address industry conflicts of interest (such as big pharma companies) [13]. Critics on EBM are concerned that the importance of experimental evidence could devalue knowledge based on clinical experience [14]. The ‘quality mark’ of EBM has it’s downsides as statistically significant findings may be marginal in clinical practice, evidence-based guidelines often map poorly to complex multimorbidity, and these inflexible quality marks of a specific protocol may produce care that is management driven rather than patient centered [14].

To minimize the gap between research and the clinical setting in our trial, we already made several choices within the RCT design to retain the characteristics of clinical practice and also retain the rigor of randomization (thus eliminate selection bias). In that way this trial can be called a pragmatic trial. Pragmatic trials contrast explanatory trials in which the aim is to test whether an intervention works under optimal situations [15]. In explanatory trials, patients with co-morbid diseases – which could also explain fatigue severity – would be excluded from the trial. In this study, we chose not to exclude patients for that reason, so our sample would better represent the population that would apply for these interventions in a clinical setting. We registered co-morbidities and checked whether these variables were equally divided between groups, and it turned out so. A second choice in the design to increase external validity was that we let patients self-refer to the trial. Patients were recruited via social media, regional newspapers, patient societies, medical specialists, and walk-inn centers. It was expected that via these channels our sample would represent the population which suffers from the long term consequences of cancer and who would apply for Web-based interventions in a clinical setting. Thirdly, we did not interfere in the clinical expertise and professional autonomy of the therapists, as this would result in less personalized care and would hinder the full potential of the intervention [16]. Patients said it was helpful that the therapist responded more than once a week, and that they could postpone the exercises in case it suited them better (see chapter 7). From a methodological point of view this may be considered a limitation, but it narrows the gap between research and clinical practice, and has supplied us with valuable insights.

Recommendations for future research

In this paragraph I highlight the main lessons learned from the methodology of the FNK trial, to help future research continue.

In the FNK trial, we started with quantitative research, followed by qualitative research to see if the results of these two different methodologies would overlap. The FNK trial is in fact a mixed method design [17]. Though this design did supply valuable knowledge (see ‘Principal findings’ in this chapter), I suggest that in future studies one starts with qualitative research about the patient’s challenges in daily life. In that way, insight in what would be valuable outcomes can be derived from for example diary studies of in-depth interviews. Also, based

on my experience, the researchers will understand their patients under study better after these interviews, which is knowledge that hardly is possible to derive from reading literature.

We also learned that it is very complicated to investigate the therapeutic relationship quantitatively (chapter 6). A substantial proportion of patients said it was too early for them to judge their relationship with their therapist based on one or two online contact moments. Many were also annoyed by the questions, as they had confidence that the working alliance would develop, but simply could not answer the questions so early in treatment. However, as the therapeutic alliance showed to be of great importance (chapter 7), and supported by other studies [4,18–21], future research should focus on how a good therapeutic bond is formed in Web-based intervention, and possibly teach new eHealth therapists how to improve this bond and match the intervention to the needs of the patient.

Concerning the research question on what causes change in interventions, many interesting quantitative methodologies continue to evolve, as computers are increasingly able to process more and more data simultaneously and faster. Social network analysis [22,23] has gained popularity in the past decades, and is performed to understand how illness evolves over time, or how an interventions helps reducing symptoms. It is characterized by networked structures in terms of nodes (individual factors, constructs, level of fatigue) and edges (relationships or interactions) that connect them.

Trying to capture the complexity of measurement in a latent variable – which means a variable that is derived from multiple measures and that acknowledges measurement error, and variance between measurements – has shown to be a valuable research method in this FNK trial. Using latent variables is a type of Structural Equation Modeling (SEM) [24]. We performed latent growth curve analysis to study the longitudinal development of fatigue during the study (see chapter 5). This statistical method allows individuals to have an individual growth trajectory over time (with individual variance) and compensates for missing data in an elegant way. Also, individual time of filling in the questionnaire (timescores) was included in the statistical model. In another study of the FNK trial (not included in this dissertation), we performed latent class analysis and identified subpopulations (latent classes) with homogeneous physical activity level and total time spent in moderate-to-vigorous intensity physical activity (MVPA) (see Wolvers et al. [25]). These latent classes indicated heterogeneity within our sample and identified subgroups that may help in personalizing

interventions based on physical activity levels. We therefore recommend to continue using SEM and latent variables as research methods in complex constructs in psychosocial research.

Recommendation for future eHealth designers and eHealth therapists

Based on my experiences with evaluating Web-based interventions with an RCT design, and writings of others [26–28], designing eHealth should start with good *user research* through stakeholder mapping, empathizing with the users, and plenty of iteration cycles of concept versions of the interventions (for example Design Thinking [29–31]). By looking at eHealth interventions as a design challenge, dropping out of the intervention – with the patient being left empty handed, and possibly demoralized if any intervention would help him – is no longer the only alternative when there is mismatch. Instead, the next step is to adapt the intervention further (iterative development process) so that it matches to different patients at different phases in the process.

By personalizing the interventions based on good *user research*, the interventions will most likely better match to the patient's needs, and the interventions will subsequently be more easily implemented. Previous research showed that implementation of eHealth interventions often fails despite this evidence of success in an RCT design [32]. Therefore, if one wants to contribute to delivering valuable Web-based interventions for CCRF patients, one should first focus on good predesign research, market research, and then as the final step investigate if an intervention is effective in a controlled trial design. Thus, based on my experiences and inspired by writings of others [26–28,33], I reckon that studying the effectiveness of interventions should not be too early after the first prototype, but first multiple iteration cycles should be carried out, match the intervention to the patient's needs, and then investigate the if-question.

Concluding remarks

Thorough user research should precede investigating the effectiveness of interventions in large controlled trials. In research methodology, it all comes down to finding a good balance between a) concise, systematic, not ambiguous, standardized, categorized derived in quantitative research, and b) detailed, rich, complex, particular data, derived from qualitative

research. I advise researchers to start with the rich and complex data (inductive research), followed by quantitative hypothesis testing (deductive research). This mixed method approach asks for statisticians and qualitative researchers working together, and I would say, please do so in the future. And after an intervention has found to effectively help to manage symptoms, efforts should continuously be made to personalize and match the intervention to each particular patient, as one size does not fit all. An acknowledging and professional therapist can guide the patient through the process of matching the right intervention or modules to the needs is essential, and both therapist and patient being supported by quantitative results.

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Chapter 9

Summary

About a quarter of cancer survivors suffer from chronic cancer-related fatigue (CCRF). CCRF may persist for many years after treatment and has a considerable impact on a patient's life because of its interference with daily activities and because it hinders patients to participate optimally into the society and work [1–7]. Fortunately, physical activity interventions and psychosocial interventions seem effective in reducing these fatigue complaints [8–12]. Moreover, eHealth allows interventions to be available at any time and place, which is especially beneficial for CCRF patients who do not have the energy to travel. Therefore, two different Web-based interventions were developed aimed at reducing CCRF: a physiotherapist-guided ambulant activity feedback (AAF) therapy encompassing the use of an accelerometer, and a psychologist guided Web-based mindfulness-based cognitive therapy (eMBCT).

To improve the quality and accessibility of Web-based interventions for cancer survivors who suffer from CCRF, this dissertation comprises the investigation of the following research questions in a 3-armed RCT:

1. The effectiveness of two different types of Web-based interventions (AAF and eMBCT) for reducing CCRF compared to an unguided active control condition receiving psycho-educational e-mails (PE);
2. Specific and generic predictors and working mechanisms of these interventions;
3. Patient experiences with following these interventions.

This project is called the 'Fitter na kanker' trial, or FNK trial, and concerns applied research initiated by two research departments in clinical psycho-oncology practice centers: the Helen Dowling Instituut (www.hdi.nl) and Roessingh Research and Development (www.rrd.nl).

Chapter 1 holds a short introduction about CCRF and Web-based interventions aimed to help reducing CCRF. In chapter 2 it was investigated whether cancer-related fatigue was significantly reduced after eMBCT intervention compared to before in a clinical setting (pre-post measurement). It was found that in 35% of the patients fatigue severity was clinically relevant improved after the intervention. In addition, results showed acceptability of this form of treatment by CCRF patients was sufficient. The findings suggested that individual eMBCT may be effective in reducing fatigue in cancer survivors, but as this help a pre-post measurement design, a randomized controlled study with a large sample and longer follow up is needed.

In chapter 3, the research protocol of a 3-armed randomized-controlled trial was presented. This trial design paper was published before analyzing the data, and is therefore in line of the Open Science movement [13], which strives to make science more transparent during the research process. Severely fatigued cancer survivors were recruited via online and offline channels, and self-registered on an open-access website. After eligibility checks, 167 participants were randomized via an embedded automated randomization function into: AAF (n=62), eMBCT (n=55), and PE (n=50). All interventions were 9 weeks. Our primary outcome measure was fatigue severity, measured with the fatigue severity subscale of the Checklist Individual Strength. Our second outcome was mental health, measured with Positive and Negative Affect Scale (PANAS) and Hospital Anxiety and Depression Scale (HADS). Fatigue severity and mental health were assessed before, during (week 3,6 and 9), and after the interventions. Also other constructs of interest such as expectations about the interventions, the level of mindfulness and sense of control over fatigue were assessed to investigate working mechanisms and predictors of fatigue severity change. Physical activity was monitored before, during and after the interventions using an accelerometer. Moreover to investigate qualitatively how these interventions attuned to the patients' needs, we carried out semi-structured interviews.

To investigate whether, or to what extent, mindfulness skills are a working mechanism in mindfulness-based interventions, there is a need for reliable and valid tools to measure mindfulness. We chose to investigate a Dutch translation of the Freiburg Mindfulness Inventory [14] (FMI-14) as it is short and measures the aspects of mindfulness that are thought to be of great importance in medical psychology research and practice, namely *Awareness* and *Presence*. In chapter 4 we indeed found this two component structure and concluded that the Dutch FMI is an acceptable instrument to measure mindfulness in patients who experienced a life-threatening illness in a Dutch speaking population.

In chapter 5, we present the results of the effectivity of both AAF and eMBCT compared to PE between baseline and 6 months later. Using latent growth curve modeling (LGM) we visualized the course of fatigue severity over time, and found that this course of fatigue severity (thus the slope of fatigue severity change) was significantly steeper than the slope in PE. Moreover, fatigue severity substantially reduced (clinical relevant improvement) in 62% of the participants in AAF, 49% in eMBCT compared to 12% in PE. Furthermore, mental

health increased in all three conditions. Reducing the intensity of eMBCT and improving usability of the accelerometer in the AAF may reduce dropout rates.

To increase our knowledge on how change in AAF and eMBCT may be established, in chapter 6 the predictive value of (1) the baseline values (predictors) and (2) the slope factors (working mechanisms) for fatigue severity change were investigated in two separate multiple group regression analyses. We found that (1) patients with high *sense of control* at baseline benefit from eMBCT, (2) patients with high *credibility* of psycho-education about CCRF benefit from PE, (3) an increase in *sense of control* was a generic working mechanism for fatigue severity reduction in both eMBCT and AAF, and not in PE, and (4) a decrease in *fatigue catastrophizing* was a specific working mechanisms in PE. Interestingly, the pre-hypothesized constructs *expectancy*, *mindfulness (acceptance and presence)*, *sleep quality*, *fear of cancer recurrence*, and baseline *fatigue severity* had no significant predictive value for fatigue severity reduction in all three conditions, neither were they found to be working mechanisms.

And finally, in chapter 7 we report on a phenomenological study that aimed to understand CCRF patient experiences with following AAF or eMBCT. We found that CCRF is characterized by a *distance* between the *inner world* (affected body and mind due to invasive and insecure cancer treatment feelings of fatigue, pain, feeling alienated in the body) and the *outer world* (expectations of themselves, social environment and society about living care free, having high energy, maintaining a job, hobbies). This distance resulted in *need for reorientation* of what they could and what they wanted to do in their daily life. eMBCT and AAF were helpful in a sense that patients were given useful insights in their boundaries and pitfalls, while being guided by an acknowledging, professional and caring therapist. In AAF reorientation was established by changing the outer world, by receiving feedback on physical activity that advised them when to rest and when to be physically active, thereby providing them with a new norm of what is the right behavior and what was expected. In eMBCT patients learnt to focus on their inner world, and communicating about it with their therapist. Hindering factors such as poor technology usability and mismatch in the amount and content of the exercises, and no personal match with the therapist, led to frustration and/or dropout.

In conclusion, AAF and eMBCT are effective interventions for reducing fatigue and improve mental health, as they help increasing sense of control of fatigue through providing helpful

tools and being guided by a professional and caring therapist. The interventions helped patients' reorientation of their identity as they gained insights in their boundaries and pitfalls.

In chapter 8 (discussion) we further elaborate on the results of this dissertation and we give recommendations for improvement of the interventions, and recommendations future research.

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Chapter 10

Nederlandstalige samenvatting

Zeker één op de vier patiënten met kanker heeft last van aanhoudende vermoeidheid zelfs lang nadat de behandeling succesvol is afgerond. Deze vermoeidheid heeft een grote invloed op het leven van de patiënt doordat het dagelijkse bezigheden enorm kan beperken en re-integratie kan frustreren [1–7]. De vermoeidheid wordt door patiënten ervaren als beperkend, onaangenaam en beangstigend en kan leiden tot minder welbevinden. Dit wordt ook wel kanker-gerelateerde chronische vermoeidheid genoemd (*chronic cancer-related fatigue*; CCRF).

De afgelopen jaren zijn er verschillende bewegingsprogramma's en psychologische interventies ontwikkeld speciaal gericht op deze langdurige vermoeidheid na kanker. Uit onderzoek blijkt dat deze interventies helpen de CCRF aanzienlijk te verminderen [8–12]. Niet alle patiënten hebben op dit moment toegang tot deze interventies. Daarnaast werken de interventies niet voor iedereen en is nog niet duidelijk welke interventie het beste werkt voor wie.

Een veelbelovende vorm van begeleiding voor mensen met aanhoudende vermoeidheid is een interventie die patiënten vanuit huis kunnen volgen, ondersteund door internet en e-mail. Online interventies worden door een grote groep mensen als prettig ervaren vanwege de relatieve anonimiteit en het feit dat je het in eigen tijd vanuit vertrouwde omgeving kunt doen. Het feit dat er niet gereisd hoeft te worden is een extra voordeel dat zwaar weegt voor deze vermoeide groep, voor wie het reizen al te veel kan zijn.

In het huidige onderzoek genaamd *Fitter na kanker*, zijn twee verschillende interventies voor het verminderen van CCRF geëvalueerd die mensen vanuit huis kunnen volgen:

1) Een op afstand begeleid bewegingsprogramma gericht op het beter leren doseren van energie om zo vermoeidheid te doen verminderen (*Ambulant Activity Feedback;* AAF). Deze 9 weken durende therapie wordt begeleid door een fysiotherapeut en is gericht op gedragsmatige aspecten van CCRF. De deelnemer heeft wekelijks contact met de fysiotherapeut en ontvangt informatie over CCRF. De deelnemer draagt een bewegingsmeter op de heup en kan zijn bewegingspatroon inzien op de bijgeleverde smartphone (*personal digital assistant;* PDA). Op de PDA ontvangt de deelnemer ieder uur persoonlijke feedback over het al dan niet aanpassen van beweeg- en rustgedrag.

2) Een online aandachtgerichte cognitieve therapie gericht op het zich bewust worden van automatische reacties die de vermoeidheid versterken (eMBCT: *online mindfulness-based cognitive therapy*). Deze 9 weken durende therapie wordt begeleid door een psycholoog. Via een online omgeving kunnen deelnemers oefeningen, opdrachten en informatie downloaden gericht op de psychologische aspecten van CCRF. Deelnemers wordt bijvoorbeeld gevraagd om mindfulnessoefeningen te doen onder audiobegeleiding (MP3-bestanden) en hun ervaringen op te schrijven bij het doen van de oefeningen. De psycholoog reageert wekelijks op deze berichten, en begeleid zo de deelnemer door de therapie.

Om de kwaliteit en toegankelijkheid van deze twee verschillende interventies voor CCRF te verbeteren, hebben wij middels een 3-armige gerandomiseerde gecontroleerde studie ontwerp, onderzocht of deze interventies effectief zijn in vergelijking met een controlegroep die slechts wordt ondersteund met psycho-educatie over chronische vermoeidheid na kanker met no-reply e-mails (eerste doelstelling). Door twee interventies tegelijkertijd te onderzoeken konden we ook bestuderen welke factoren van de interventies van belang zijn voor het verminderen van vermoeidheid en of er specifieke (voor één interventie) of generieke (voor meerdere interventies) factoren zijn die invloed hebben op het effect. Op die manier kunnen we inzicht krijgen in welke factoren belangrijk zijn voor het verminderen van CCRF, opdat wij de interventies kunnen verbeteren (tweede doelstelling). En om beter inzicht te krijgen in de helpende en belemmerende factoren van de interventies en hoe de interventies konden worden verbeterd, zijn patiëntervaringen onderzocht (derde doelstelling).

Derhalve worden in dit proefschrift drie onderzoeksvragen behandeld:

1. Wat is de effectiviteit van AAF en eMBCT in het verminderen van CCRF vergeleken met het ontvangen van e-mails met psycho-educatie over CCRF (PE)?
2. Wat zijn specifieke en generieke voorspellende factoren, en werkingsmechanismen van AAF en eMBCT?
3. Wat zijn de patiëntervaringen bij het doen van AAF en eMBCT?

Als eerste stap hebben wij onderzocht of ervaren vermoeidheid significant afnam na het volgen van eMBCT bij het Helen Dowling Instituut (reguliere zorg). Wij vonden (hoofdstuk 2) dat 35% van de patiënten klinisch relevant verbeterd was. Dat houdt in dat deze mensen een significante daling in vermoeidheid hadden en daarnaast ook onder een afkapwaarde van

vermoeidheid kwamen. Maar zonder een controlegroep mee te nemen in deze analyses, weet je niet of deze resultaten komen met verloop van tijd of dat de verandering in vermoeidheid echt is toe te schrijven aan de interventie.

In hoofdstuk 3 presenteren wij het onderzoeksontwerp van de *Fitter na kanker* studie: de inclusiecriteria, het aantal deelnemers dat wij wilden werven voor de studie, welke vragenlijsten wij zouden meenemen, en met welke meetmomenten wij onze primaire vraag wilden beantwoorden. Ook hebben we hiermee vastgelegd op welke wijze we onze data willen analyseren; een goede stap richting het vergroten van transparantie in wetenschappelijk onderzoek (zie bijvoorbeeld *Open Science movement* [13]).

In hoofdstuk 4 presenteren wij de psychometrische eigenschappen van een Nederlandse vertaling van een van origine Duitstalige mindfulness vragenlijst: de *Freiburg Mindfulness Inventory* [14]. Wij concludeerden dat je met deze vragenlijst verandering in de constructen van mindfulness ‘acceptatie’ en ‘presentie’ kunt meten in doelgroepen met een levensbedreigende medische aandoening (hartpatiënten en kankerpatiënten). We concludeerden dat deze vragenlijst geschikt is om te gebruiken in verder onderzoek naar werkingsmechanismen in onze studie.

In hoofdstuk 5 presenteren we de resultaten van de effectiviteit van zowel AAF als eMBCT vergeleken met patiënten in de actieve controlegroep die psycho-educatie ontvingen. Met behulp van latente groeimodellen van de vermoeidheidsscores tussen het moment van de start van de interventies en 6 maanden later, konden we het verloop van de vermoeidheid in de loop van de tijd visualiseren, en bovendien bekijken of de verandering in vermoeidheid verschillend was tussen de drie condities. Wij vonden dat zowel AAF als eMBCT effectief zijn in het verminderen van ervaren vermoeidheid vergeleken met de controlegroep. Het verminderen van de hoeveelheid opdrachten van eMBCT, en het verbeteren van de bruikbaarheid van de bewegingsmeter in de AAF zou het aantal mensen dat stopte met de interventies kunnen verminderen.

Om te onderzoeken welke gemeten constructen van belang waren voor afname in vermoeidheid, hebben wij in hoofdstuk 6 onderzocht welke constructen correleerden met verandering in ervaren vermoeidheid tussen baseline en een half jaar later. We vonden dat (1) patiënten met een hoog gevoel van controle over vermoeidheid bij baseline baat hebben bij

eMBCT, (2) patiënten die een grote geloofwaardigheid toeschrijven aan PE ook hiervan profiteren, (3) een toename van het gevoel van controle over vermoeidheid een generiek werkingsmechanisme is voor vermindering van ervaren vermoeidheid in zowel eMBCT en AAF, en niet in PE, en (4) een afname van catastroferen over vermoeidheid is een specifiek werkingsmechanisme in PE. Verwachtingen over de werkzaamheid van de interventies die patiënten vooraf hebben, hadden geen significante voorspellende waarde voor de vermindering van ervaren vermoeidheid in alle drie de condities, en een verandering in deze verwachtingen bleek ook niet samen te hangen met vermindering van ervaren vermoeidheid. De baseline score van mindfulness (acceptatie en presentie), slaapkwaliteit, de mate van angst voor terugkeer van kanker en ernst van vermoeidheid, hadden geen voorspellende waarde voor vermindering van ervaren vermoeidheid. Ook was de verandering in mindfulness, slaapkwaliteit en angst voor terugkeer van kanker geen werkingsmechanisme.

Tenslotte, in hoofdstuk 7, rapporteren we over een fenomenologisch onderzoek middels semigestructureerde diepte interviews bij negen AAF deelnemers en tien eMBCT deelnemers. In deze interviews vroegen wij a) met welke uitdagingen de patiënten geconfronteerd werden voordat ze zich inschreven voor de *Fitter na kanker* studie, b) wat ze helpende en belemmerende aspecten vonden van de interventies en c) hoe het nu met hen ging na afloop van de interventies. Op die manier hebben we onderzocht of de interventies overeenstemden met de behoeften van de patiënten en hoe de interventies konden worden verbeterd. We ontdekten dat chronische vermoeidheid na kanker wordt gekenmerkt door een afstand tussen de binnenwereld (geleefde ervaring van het beschadigde lichaam) en de buitenwereld (verwachtingen hoe het lichaam zou moeten zijn), resulterend in een behoefte aan heroriëntatie in hun dagelijkse leven van wat zij wel en niet konden doen. Beide interventies hielpen in deze behoefte aan heroriëntatie door inzicht te verschaffen in grenzen en valkuilen en om lichamelijke symptomen beter te herkennen. Bij AAF werd de heroriëntatie vanuit de buitenwereld benaderd, namelijk door feedback te ontvangen over fysieke activiteit en advies wanneer ze moesten rusten en wanneer ze fysiek actief moesten zijn. In eMBCT leerden patiënten zich juist te concentreren op hun binnenwereld en om in contact te komen met hun lichamelijke en psychologische ervaring en erover te communiceren met hun therapeut. Belemmerende factoren die werden genoemd waren voor AAF slechte gebruiksvriendelijkheid van de technologie, en voor eMBCT een te grote tijdsinvestering (te intensief) door de hoeveelheid oefeningen. Het niet aansluiten van de inhoud van de

oefeningen en geen persoonlijke match met de therapeut waren belemmerende factoren in beide interventies.

In hoofdstuk 8 (discussie) gaan we verder in op de resultaten van dit proefschrift en geven we aanbevelingen voor verbetering van de interventies en aanbevelingen voor toekomstig onderzoek.

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Chapter 11

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Chapter 12

Publication list

Published at peer-reviewed journals:

Bruggeman-Everts, F.Z., Van der Lee, M.L. & De Jager Meezenbroek, E. Web-based individual mindfulness-based cognitive therapy for cancer-related fatigue - a pilot study. *Internet Interventions* (2015) 2(2):200-213. DOI: 10.1016/j.invent.2015.03.004

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Submitted:

Bruggeman-Everts, F.Z., Van der Lee, M.L, Wolvers, M.D.J., Van de Schoot, R. & Vollenbroek-Hutten, M.M.R. Understanding change in online Mindfulness-Based Cognitive Therapy for Chronic Cancer-Related Fatigue.

Bruggeman-Everts, F.Z.*, Bruggeman, J.S.* & Van der Lee, M.L. A phenomenological study on patient experiences of two different therapist-guided web-based interventions for chronic cancer-related fatigue. * Equal contribution.

Chapter 13

About the author

Fieke studied Biomedical Science and the research master Neuroscience and Cognition at Utrecht University. Her interest grew towards how patients cope with disease and medical treatment. Therefore, she followed a second master in Clinical and Health Psychology at Utrecht University. When searching for a scientific internship, she came in contact with the Helen Dowling Instituut and she was fond of the place instantly. The hospitality and personal care patients received there, inspired her.

Her professional interest focuses on trying to understand how patients manage to cope with a disease, and how developers of (e-health) interventions and therapists can best attune interventions to the needs of patients. By combining her empathic and analytic skills she hopes to continue improving the quality of healthcare by being a translator of patient knowledge.