Pilot and Feasibility Studies

STUDY PROTOCOL

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A protocol for a feasibility study of Cognitive Bias Modification training (IVY) countering fatigue in people with breast cancer

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Abstract

Background Cancer-related fatigue (CRF) is the most prevalent, distressing, and quality of life disturbing symptom during and after cancer treatment for many cancer types including breast cancer. The experience and burden of this symptom can induce a cognitive bias towards fatigue or a fatigue-related self-image, which can further increase the fatigue symptoms and related behaviour. For this, a Cognitive Bias Modification (CBM) eHealth app (IVY) has been developed. The app aims to counter the fatigue-related self-image and to modify it towards vitality, which might translate to less experienced fatigue and more experienced vitality. This study aims to evaluate the feasibility of the IVY CBM training and the research design of a wait-list control trial. If feasibility is judged sufficient, the effectiveness of the CBM app will also be analyzed on (1) underlying mechanisms (cognitive fatigue bias), (2) symptom fatigue (self-reported fatigue and vitality), and (3) related behaviours (avoidance and all-or-nothing behaviour).

Methods This feasibility study addresses individuals being treated for breast cancer receiving (neo)adjuvant treatment or metastatic care. The number of target participants is 120 (60 (neo)adjuvant, and 60 metastatic) patients. Both groups will be randomized with 30 people in the IVY treatment group and 30 people in the delayed treatment control group. All participants will receive the training via the IVY app, in which participants categorize words related to vitality with words related to 'I' and words related to fatigue with words related to 'other'. If feasibility is judged sufficient, the effects of the training will be explored on 3 levels: (1) self-identity bias, which will be measured with a short computer task based on the Implicit Association Test (IAT), (2) avoidance and all-or-nothing behaviour, and (3) fatigue and vitality levels, which will all be measured with questionnaires.

Discussion This study aims to evaluate the feasibility of a larger-scale multi-centre Randomized Controlled Trial (RCT) to investigate a novel eHealth application and, if possible, to give indications on the effectiveness of this intervention to counter fatigue in individuals with breast cancer. Using the IVY CBM app requires very little effort, both in time and cognitive load, which could be especially beneficial for fatigue symptoms.

Trial registration Registered at the Open Science Framework (OSF; https://osf.io/e85g7/) on October 20, 2023.

Keywords Cancer-related fatigue (CRF), Breast cancer, Vitality, Cognitive bias modification (CBM), EHealth application

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Background

Introduction

Breast cancer is the most frequently occurring cancer and the leading cause of death in women worldwide [1]. In the Netherlands, breast cancer is the most prevalent cancer type with around 14,000 diagnoses per year [2]. Most cases are curative. In this setting, in addition to primary treatment (most of the time surgery or radiotherapy), more than 60% of patients are given some form of neoadjuvant or adjuvant systemic therapy, which are treatments, such as chemotherapy or hormone therapy, that are undergone before or after primary treatment to enhance the chance of treatment success and lessen the chance of cancer recurrence [3]. When cancer has spread to different body parts, it has metastasized [4], e.g. metastatic breast cancer, which for most patients means that treatment has become palliative [5, 6].

The most reported and distressing symptom during and after cancer treatment for many patients is cancer-related fatigue (CRF [7]). More than 50% of people with breast cancer in the curative setting, as well as in the metastatic setting, experience fatigue symptoms during their treatment trajectory [8, 9]. One way to characterize 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 functioning' ([10], p. 1014). Fatigue can have many consequences: Next to stress, limitations in daily activities, quality of life, and labour participation as well as comorbidities such as depression and anxiety are frequently reported [7, 11]. CRF is a complex, multifactorial symptom that can have different determinants and clinical expression per individual, which are challenging aspects for diagnosis and treatment [7]. Next to pharmacological interventions, where mixed effects were found on fatigue, some non-pharmacological interventions have found beneficial or promising effects, such as physical exercise, psychosocial interventions, e.g. cognitive behavioural therapy (CBT), psychoeducation or self-management programs, and mind–body programs, e.g. yoga, acupuncture, or mindfulness [8, 12, 13].

Most of these interventions focus mainly on reflective processes targeting fatigue [14], however, in psychology, dual-process models (e.g. the Reflective-Impulsive Model; RIM [15]) are proposed, postulating two integrated systems, one conscious and reflective, one non-conscious and associative [14, 16]. For instance, habit forming initially has a strong unconscious component, which in a later stage might interact with or get changed by conscious processes [17]. Indeed, responding to CRF was found to be predominated by bodily sensations and partly an automatic, habitual, repetitive behaviour requiring minimal reflection [17, 18]. Thus, existing interventions mostly focus on conscious processes to counter fatigue, but unconscious processes are also found to play an important role, especially in the early stage of CRF.

Another way that unconscious processes can influence fatigue symptoms is cognitive biases. Cognitive biases are unconscious, 'quick and dirty' rules of thumb used for fast information processing that can be activated automatically and irrespective of conscious goals [19, 20]. For example, people who survived breast cancer show heightened attention for cancer-related words, regardless of their self-reported fear of cancer recurrence [21]. Furthermore, people with chronic fatigue syndrome show an interpretational and attentional bias towards illness-related or health-threatening information [22]. The adverse effect of a cognitive fatigue bias can be direct, e.g. due to higher sensitivity to fatigue signals, or indirect, e.g. fatigue-related behaviour is unconsciously avoided, resulting in all kinds of self-imposed limitations and decline in physical fitness [22, 23]. Multiple hypotheses and theories exist on the mechanisms behind the emergence of cognitive biases, mostly derived from the pain literature, which is a similarly multifactorial symptom as fatigue [23]. One of these theories is the schema-enmeshment model [24] that proposes that frequent or a continuous experience of pain or fatigue can cause an enmeshment between the schema of that symptom with schemas of the illness and the self. In this way, fatigue can become included in one's self-identity, which could perpetuate and aggravate affective distress (such as frustration) and fatigue-related behaviour, such as avoidance [24].

These cognitive biases are the focus in Cognitive Bias Modification (CBM) interventions. By systematically practicing an alternative way of processing, CBM aims to change cognitive biases towards a more positive interpretation [25, 26]. Looking back at the dual-process model, CBM focuses on the unconscious and automatic side of processing, which is often overlooked in other interventions. CBM has shown beneficial effects in other symptoms such as anxiety, depression, chronic pain, and addiction [27–29], and it is a relatively simple, little time-consuming, and low-burden technique, which could be a particularly important advantage for fatigue symptoms [30].

Given the importance, frequency, and impact of fatigue in breast cancer, it seems likely that fatigue biases also play a role in people with breast cancer. However, to our knowledge, fatigue bias has not been researched in individuals with breast cancer before. CBM targeting cognitive biases related to fatigue has not been tested so far in general. To our knowledge, our research team is the

first to introduce CBM to counter fatigue symptoms. We developed the first IVY 1.0 CBM app using a co-creation approach to meet the wishes and needs of professionals and individuals with breast cancer [31]. Next, following the iterative human-centred design framework [32], our research team has investigated this novel eHealth application by researching usability with people with breast cancer (Geerts, Pieterse, Sniehotta, Siemerink, Bode: Cognitive bias modification training (IVY) to prevent fatigue in people with breast cancer: Pilot study investigating user acceptance and study design, in preparation) and chronic kidney disease (Geerts, Bode, Salemink, Laverman, Waanders, Oosterom, Ten Klooster, Pieterse: Towards vitality: A longitudinal pilot study with a cognitive bias modification e-health Intervention (VitalMe) to reduce fatigue in patients with chronic kidney disease, submitted). Both of these studies evaluated the application with multiple stakeholders (patients and health care professionals) and revealed positive results. Although the usability study with people with breast cancer only revealed a trend in altering self-identity bias (Geerts, Pieterse, Sniehotta, Siemerink, Bode: Cognitive bias modification training (IVY) to prevent fatigue in people with breast cancer: Pilot study investigating user acceptance and study design, in preparation), a pilot study with people with chronic kidney disease revealed strong CBM effects on cognitive bias, and promising results on symptoms and related behaviour (Geerts, Bode, Salemink, Laverman, Waanders, Oosterom, Ten Klooster, Pieterse: Towards vitality: A longitudinal pilot study with a cognitive bias modification e-health Intervention (VitalMe) to reduce fatigue in patients with chronic kidney disease, submitted).

The current study aims to take a next step with individuals with breast cancer by evaluating the feasibility of researching this CBM training with a larger study. Additionally, if feasibility is judged sufficient, the effects of the training on cognitive bias, fatigue, and related behaviour will be investigated. Patients in both the curative as well as the palliative setting are selected for this feasibility study, as these different contexts could have practical implementations (e.g. number of hospital visits) that can significantly influence recruitment and retention. Therefore, it is useful to research the feasibility for both groups.

Objectives

The current feasibility study aims to assess the feasibility of doing a larger-scale multi-centre Randomized Controlled Trial (RCT) with the IVY CBM training with people with breast cancer. Specifically, the research process will be investigated, such as the recruitment process and retention of people undergoing cancer treatment, either in the curative or the metastatic setting. If feasibility is judged sufficient to explore the effects of the training in the current study, the effectiveness of the CBM training will also be tested on (1) the underlying mechanism (fatigue self-identity bias), (2) related behaviour (self-reported avoidance and 'all-or-nothing' behaviour), and (3) the fatigue symptom (self-reported fatigue and vitality).

Methods

This protocol is written in accordance with the 2013 SPIRIT guidelines (see the SPIRIT checklist in Additional file 1 and the SPIRIT schedule outlined in Table 1).

Study design

This article describes the protocol of a multi-centre, wait-list-control feasibility study with the IVY CBM training to counter fatigue in people with breast cancer in both the (neo)adjuvant and metastatic setting. This prospective intervention study will test the research processes (e.g. recruitment, retention) in both patient groups and the design feasibility for a future RCT. If feasibility is judged sufficient in the current study, the effectiveness of the training on implicit bias and self-reports of fatigue, vitality, avoidance, and all-or-nothing behaviour will also be explored. These objectives will be evaluated with a mixed-methods approach. As this is such a novel intervention, many other interesting topics and possible moderators are also incorporated in the design, such as depressive symptoms, and whether a booster training after follow-up could have a reinforcing effect. These topics are beyond the scope of this article.

Participating centres

It is intended that five hospitals will be recruiting sites: Ziekenhuis Groep Twente (ZGT) in Almelo and Hengelo, Isala in Zwolle, Franciscus in Rotterdam, Gelre in Apeldoorn, and Saxenburgh in Hardenberg.

Study population

It is intended that each of the participating centres recruit 30 patients: 15 in the (neo)adjuvant setting and 15 in the metastatic setting, bringing the total to 150 participants. We expect that 120 (60 (neo)adjuvant and 60 metastatic) patients will be included in the study. As the recruitment rate of the participating centres is also informative for the feasibility of the study, hospitals are allowed to recruit more than the intended number of participants regardless of the number recruited in the other hospitals. Within each patient group, the researchers will randomize patients into the active IVY treatment group ($n=30$) and the delayed treatment control group ($n=30$).

Table 1 SPIRIT schedule of enrolment, interventions, and assessments

	Enrolment	Allocation	Close-out				
TIMEPOINT	$-t_1$	0	$t_{1(baseline)}$	$t_{2(training)}$	$t_{3(follow-up)}$	$t_{4(booster)}$	$T_{5(follow-up\ 2);\ month\ 7}$
ENROLMENT:		X					
Eligibility screen	X						
Informed consent	X						
Allocation		X					
INTERVENTIONS:							
Active IVY- treatment group			X	X	X	X	X
Delayed treatment control group			X	X	X		
ASSESSMENTS:							
Demographics			X				
Self-identity bias			X	X	X	X	X
Fatigue			X	X	X	X	X
Vitality			X	X	X	X	X
Behaviour (all-or-nothing & avoidance)			X	X	X	X	X

Potential participants will be approached by their health care providers (HCP) on whether they are interested in participating in the study. The HCP will give a general explanation about the study and, if interested, provides the patient with an information letter (PIF). In the PIF, patients can find contact details of the researcher or an independent person (a specialist in a different department in one of the participating centres) for questions before deciding to participate. If interested in participating, the patient can register via the registration form that is sent to the researcher. On the registration form, only a name, phone number, and email address are asked. After registration, the researcher will contact the patient. An informed consent form is completed in duplicate if the patient agrees to participate, one of which is returned to the patient, and the other is archived. The patient can contact the researcher, the independent person, or the primary practitioner at any time for questions.

Inclusion criteria

- Patients with breast cancer who undergo curative treatment for breast cancer with (neo)adjuvant chemo(immuno)therapy and patients who undergo palliative system therapy with chemo(immuno)therapy or antihormonal treatment in combination with targeted treatment.

- Adequate speaking- and reading skills in the Dutch language.

- The patient has access to a smartphone and must be able to operate it (download, start and run an app).

- The patient has access to a computer with internet and has experience working with one.

Exclusion criteria

- Patients in the adjuvant setting who undergo immunotherapy treatment only.

- Patients in the metastatic setting who are being treated with an anti-hormonal treatment only.

- Insufficient speaking- and reading skills in the Dutch language.

- The patient does not have access to a smartphone or computer and has no experience using a smartphone or computer.

Sample size

A recent—as yet unpublished—similar study among people with chronic kidney disease shows that large effect sizes are achievable on cognitive bias ($d=1.20$ for self-identity bias and $d=1.14$ for attentional bias (Geerts, Bode, Salemink, Laverman, Waanders, Oosterom, Ten Klooster, Pieterse: Towards vitality: A longitudinal pilot study with a cognitive bias modification e-health Intervention (VitalMe) to reduce fatigue in patients with chronic kidney disease, submitted) with only 22 participants. However, meta-analyses on CBM show inconclusive results, from bias reduction effect sizes that are small in pain studies ($d=0.134$ [23]) to medium (attentional CBM: $g=0.049$, interpretational CBM: $g=0.058$) in various other clinical samples (anxiety, depression, eating disorders, substance use [33]). The effects on symptoms generally are smaller, e.g. a medium effect on biases ($g=0.49$), and small effects on anxiety and depression ($g=0.13$) were found [34]. Power calculation (based on repeated measures ANOVA, 3 time levels, alfa = 0.05; beta = 0.80) shows that a small effect size ($f=0.17$) is still detectable with the sample size ($n=60$) in our study.

Intervention

The IVY CBM training is incorporated in the TIIM app designed by the BMSlab, part of the University of Twente. The training consists of an eHealth application in which participants categorize words into 4 categories: Dutch translations of vitality, fatigue, I, and others. The categories 'fatigue' and 'other' are presented at the top of the screen, while the categories 'vitality' and 'I' are presented at the bottom of the screen (see Appendix 1). In the middle of the screen, a total of 120 stimuli related to the 4 categories are presented randomly and sequentially, such as the Dutch translation of 'active' (related to vitality), 'exhausted' (related to fatigue), 'them' (related to other), and 'mine' (related to I; see Appendix 2). Participants categorize the stimuli to their categories by swiping up (for fatigue and other) or down (for vitality and me) as quickly as possible. The bottom-top position is chosen in such a way so that the swipe movement corresponds to a 'toward me' (approach) or 'away from me' (avoidance) principle, which reinforces this association task [31]. Moreover, by having 'avoid' words zoom out (become smaller), and 'approach' words zoom in (become larger), this effect is further enhanced. Categorizing the 'vitality' and 'I' stimuli together is thought to reinforce connections between self-image and vitality and weaken associations between self-image and fatigue.

A week before the training phase, participants will receive a link with instructions to download and use the application. Included in these instructions, participants receive contact details from the researchers and are invited to email or call the researchers if they experience any problems using the application. If the participant is not registered to the app at the appropriate moment, the researcher will call to ask why they are not registered yet and help them register. A Frequently Asked Questions page is available on the app. If participants experience difficulties using the IVY CBM app, the researchers will support them. Participants who are registered to the app but do not do any training during the first week will be called to ask why they missed the training sessions and to help them.

All participants will train 5 days a week with 5-min IVY sessions for 4 weeks. Every weekday at 8:00 a.m., participants will receive a digital notification that a new training is available via the app. Those who have not yet completed the training will receive a reminder at 7:00 p.m. that same day. The participants are free to do the training at a for them convenient time during the day. Additionally, 3 months after the first training phase, the IVY treatment group will receive so-called booster sessions for 4 weeks. During this booster phase, three sessions are made available each week and participants are asked to train at least twice a week. On Monday morning, three training sessions are made available for that entire week. On Friday morning, the participants receive a reminder for these booster training sessions. Participants are again free to do the training sessions at a for them convenient moment in the week.

Setting

As can be seen in Table 2 and in the research schedule that will be provided to participants (Appendix 3), the two groups both have a baseline, training, and follow-up phase, while the active treatment group also has a booster phase. The baseline phase for the active treatment group contains 4 weeks with 1 measurement every week (of 5–10 min). The baseline phase for the control group contains the same first 4 weeks added by an additional 8 weeks with measurements every other week. After the baseline phase (for the active treatment group, this is after 4 weeks; for the control group, it is after 12 weeks), all participants follow the 4-week IVY CBM training phase. A measurement is sent every 2 weeks during this training phase. Following the training phase, both groups receive the follow-up phase with weekly measurements for the first 4 weeks and measurements every other week for the following 8 weeks. After this follow-up period, the active treatment group will receive the 4-week booster phase. During this booster phase, measurements are sent every 2 weeks. After the booster phase, this group has a follow-up phase of 4 weeks with measurements every other week.

A measurement (including the IAT and the questionnaires) takes about 10 min. As this is a relatively small time investment, the burden on patients remains low despite the high frequency of sessions. Patients are free to do the measurement at a for them suitable time during that week. Specifically, on Monday morning, participants will receive an email directing them to the measurement. Those who have not yet completed the measurement on Wednesday will receive a reminder. During the first weeks of the baseline, the participants who do not respond to the study will be phoned to ask why no response has yet been registered from them. These procedures are inspired by a previous study with people with chronic kidney disease (Geerts, Bode, Salemink, Laverman, Waanders, Oosterom, Ten Klooster, Pieterse: Towards vitality: A longitudinal pilot study with a cognitive bias modification e-health Intervention (VitalMe) to reduce fatigue in patients with chronic kidney disease, submitted).

Study outcomes

The feasibility of the study will be informed by recruitment and retention rates per participating centre and per patient group. Recruitment will take place from the end

Table 2 Schematic overview of the study design

Group	Month 1	Month 2	Month 3	Month 4	Month 5	Month 6	Month 7
Active IVY-treatment	Baseline	IVY training	Follow-up	Follow-up	Follow-up	IVY booster	Follow-up
Measurements	4	2	4	2	2	2	2
Trainings		20				8	
Delayed IVY control	Baseline	Baseline	Baseline	IVY training	Follow-up	Follow-up	Follow-up
Measurements	4	2	2	2	4	2	2
Trainings				20			

of June 2022 to end of February 2023. At this time, 150 participants are expected to be recruited, of which 120 are expected to be included, which means 15 participants per month in total, 3 per participating centre. Specifically, the recruitment and inclusion will be assessed by obtaining percentages of people willing to participate from the people judged as eligible for the study by the care practitioners. Retention will be assessed with the number and percentage of people dropping out of the study, as well as completion rates of the training and measurement sessions. People who drop out will be asked for their reasons to drop out. Moreover, feedback from participants will be recorded via the open-ended question at the end of each measurement and by monitoring moments of contact with the researcher. Furthermore, variability in demographic data and the outcome measures, such as the range of given answers and floor and ceiling effects, will be investigated. Lastly, if the above feasibility assessments are judged as sufficient, analyses of the effectiveness of the training to counter fatigue on bias, symptoms, and behaviour will be conducted.

To judge the feasibility to proceed to a full trial, criteria are identified (see Table 3). In the recruitment phase, a recruitment rate of 80% is already predicted (hospitals are requested to recruit a total of 150 patients, to arrive at 120 included participants). Secondly, a 20% dropout rate [35] will be used as the retention criterium, i.e. if more than 20% of included participants dropout after baseline, retention strategies should be re-evaluated before continuing with a full trial. Thirdly, if the feedback from participants indicates serious concerns for acceptance, these should be addressed before continuing with a full trial. Lastly, if effects can be explored in this study, at least a medium effect of the intervention (compared to control) on the CBM mechanism (cognitive bias) is expected. If smaller or negative effects are found, then the design and intervention should be re-evaluated before continuing with a full trial.

Table 3 Schematic overview of the recruitment, inclusion and retention feasibility criteria

Feasibility criteria	n (%)
Recruitment	150 (100)
Inclusion	120 (80)
Retention	96 (80)[a]

[a] Retention is based on the number of participants included

Materials

The measurements in this study will be conducted with the platforms Qualtrics [36] and Inquisit [37]. During each measure, using Qualtrics, participants are automatically sent forward to Inquisit where they perform the Implicit Association Test (IAT [38]) to measure the self-identity bias. Similar to the training (which was inspired by the IAT), participants are asked to categorize stimuli related to the Dutch categories 'fatigue', 'vitality', 'I', and 'other' by using the 'E' and 'I' keys on the keyboard (see Appendix 2). The IAT contains seven blocks: five practice blocks and two measurement blocks. Participants start with practicing the 'I' vs. 'other' categories ($n=20$), then the 'fatigue' vs. 'vitality' categories (n = 20) and then the combinations 'I or fatigue' vs. 'other or vitality' ($n=20$), after which these combinations are measured ($n=40$). Then the categories are switched; where 'I' was first on the left side of the screen (corresponding with the 'E' key), now, 'I' is on the right side of the screen (corresponding with the 'I' key). This switch is practiced with 'I' vs. 'other' ($n=20$) and with the combinations 'I or vitality' vs. 'other or fatigue' ($n=20$). Then these combinations are measured ($n=40$) as well. By comparing the reaction times on these two measurement blocks, the D-score can be calculated, which in this case represents the strength of a self-identity towards fatigue versus vitality.

After completion of the IAT, participants are automatically sent back to Qualtrics to fill in questionnaires, which in the first measurement starts with questions about demographic data such as age, marital status, and education level. Four Dutch questionnaires are presented. First, the shortened version of the Cognitive and Behavioural Responses Questionnaire (CBRSQ [39]) is used to measure behavioural responses such as avoidance / resting, and all-or-nothing. The avoidance / resting

subscale contains eight items (e.g. 'I sleep during the day to keep my fatigue under control') and the all-or-nothing subscale contains five items (e.g. 'When it comes to doing things, I'm an 'all or nothing' kind of person'). These items are answered using a five-points frequency scale (0 = never, 4 = always). Scores of the subscales will be added, and higher scores indicate more frequent avoidance / resting or all-or-nothing behaviour. The scales have been shown to have acceptable to good internal consistency with a Cronbach's alpha of 0.76 for the avoidance / resting subscale and a Cronbach's alpha of 0.85 for the all-or-nothing subscale [40].

Second, using the Dutch Vitality measure (Vita-16 [41]), vitality is measured with sixteen items on three subscales: *energy* ($n = 5$), e.g. 'I have enough energy to fulfil my daily tasks', *motivation* ($n = 6$), e.g. 'I make plans for the future', and *resilience* ($n = 5$), e.g. 'I can handle setbacks'. Items are answered using a 7-point Likert scale (1 = never, 7 = always). Answers will be averaged, and higher scores indicate higher vitality. The scale has excellent reliability with a Cronbach's Alpha of 0.90 for the full scale.

Third, participants will fill in the Checklist Individual Strength (CIS [42]) containing 20 items on 4 subscales (*fatigue severity*, *activity*, *concentration*, *motivation*). Using a 7-point Likert scale (1 = No, incorrect, 7 = Yes, correct), items such as 'I feel fit' are answered. Scores will be added together on a range of 20–140 where higher scores indicate high fatigue and low motivation, concentration, and physical activity levels. With a Gutman split-half reliability coefficient of 0.92, and a Cronbach's Alpha of 0.90 for the full scale, the reliability of the CIS is excellent.

Fourth, with the Hospital Anxiety and Depression Scale (HADS [43]), 7 items of the depression subscale are used to research possible depressive symptoms. Four of these items (e.g., 'I still enjoy things I enjoyed earlier') can be answered using a four-points frequency scale (1 = the same as earlier, 4 = not at all), and three items can be answered using another four-point frequency scale (1 = not at all, 4 = mostly), of which one is mirrored. Higher scores indicate higher depression symptoms. With a Cronbach's alpha of 0.86, the depression subscale of the HADS has good reliability. Each measurement will end with an open-ended question 'Do you have any further comments?' that participants will be free to answer.

Statistical analysis

The feasibility outcomes recruitment and retention will be monitored and assessed using Excel. The feasibility outcome variability will be researched with descriptive analyses on SPSS by assessing demographic characteristics, and the range of scores in each research phase. Additionally, to research the variability in more detail as well as potential effects of the training, the data will be explored visually by presenting the averages on the primary (self-identity bias) and secondary outcomes (behavioural and clinical outcomes) as time-series graphs, with the measurement timepoints on the horizontal axis, the outcome variables on the vertical axis, and phase changes presented as vertical lines.

If the feasibility is judged sufficient in the current study, i.e. enough power and no ceiling or floor effects are detected, the effects of the training will also be investigated. The design allows for two ways of analyzing the intervention effect, which has a positive and verifying influence on the power. First, the effect of the training will be analyzed using Linear Mixed Models (LMM) by looking at the control group's pre- to post-comparisons. Second, the effect of the training will be analyzed using LMM by comparing the active and delayed-treatment groups in the first 3 months of the study (treatment vs control). In this way, the effect of the training will be analyzed both with between and within comparisons. LMM is chosen for the analyses as it can inherently deal with randomly missing data on the outcome variables as well as data that have a multilevel nature with measurements nested in individuals over time [44]. With many missing data, measurements will be averaged per phase.

Ethical approval

The Committee of Human Research [Commissie Mensgebonden Onderzoek, CMO] judged this study to not be applicable to the Medical Research Involving Human Subjects Act [Wet medisch-wetenschappelijk onderzoek met mensen, WMO] and thus redirected us to local ethical committees (file number: 2021–13261). Subsequently, the study was approved by the ethical committee of the Faculty Behavioural, Management and Social Sciences of University of Twente (file number 220004) and the Advice Committee Local Practicality Scientific Research [Adviescommissie Lokale Uitvoerbaarheid Wetenschappelijk Onderzoek, ALU] at Hospital Group Twente [Ziekenhuisgroep Twente, ZGT] (case number: ZGT22-09). The data management plan was included in these applications and can be requested from the first author if necessary.

Discussion

In this article, the protocol is described of a wait-list control feasibility study exploring a novel mechanism to counter CRF in people with breast cancer. As CRF is an often experienced but complex and undertreated

symptom, interventions looking at different approaches to fatigue are useful. Such a different approach is CBM which focuses on the often-overlooked unconscious component of fatigue. In the IVY CBM training, offered as an application to be downloaded on a smartphone, with simple repetitive tasks, participants are trained to direct their self-identity to vitality instead of fatigue. In this study, the feasibility to test IVY in a large-scale RCT is described. Furthermore, if the feasibility is judged sufficient, the analysis of the effects of the training is planned.

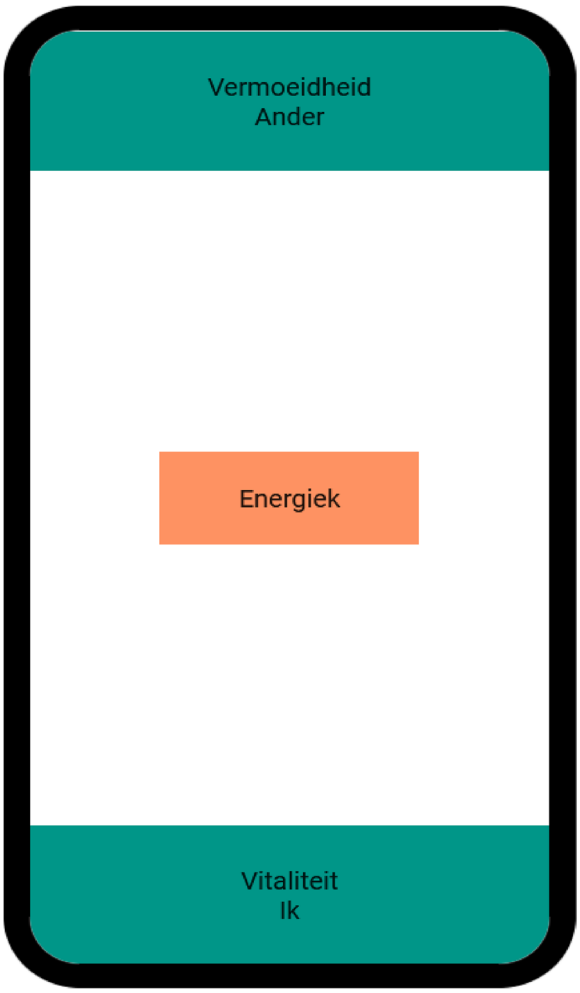
The data collection for this study started in August 2022 and will end at the end of October 2023. Writing this protocol article was delayed because we first wanted to analyze the findings in the study conducted with people with CKD (Geerts, Bode, Salemink, Laverman, Waanders, Oosterom, Ten Klooster, Pieterse: Towards vitality: A longitudinal pilot study with a cognitive bias modification e-health Intervention (VitalMe) to reduce fatigue in patients with chronic kidney disease, submitted). As the study with patients with CKD similarly investigates CBM principles targeting fatigue, it was useful to wait for these findings, both for the sample size calculations, as well as for more evidence for this mechanism, before continuing with this article.

Even though it is not common or recommended in feasibility studies [45], we also aim to analyze the effectiveness of the training. Multiple considerations brought us to this decision: As recruitment in hospital settings is recognized as one of the most challenging aspect of medical research [46], we would like to use the gathered data to the fullest. Additionally, for novel interventions such as the training investigated in this study, any preliminary estimates of effectiveness are very valuable and informative for the decision to continue with a larger trial. This includes making more informed decisions on the sample size needed to detect meaningful effects. As described, we only aim to continue with effect testing when key feasibility criteria are fulfilled. This, together with the combination of multiple analyses, in our view, makes the effect findings more reliable and justified.

This study describes a protocol for a feasibility study to investigate a novel and innovative intervention countering fatigue in people with breast cancer. This CBM intervention focuses on unconscious processes, which are largely overlooked in current treatment but theorized to be an important facilitator of fatigue. Therefore, the CBM training could be a good addition to the already available intervention options targeting fatigue for people with breast cancer. Previous studies on this intervention followed the iterative human-centred design process by developing the application by using co-creation, researching the usability among two patient groups (breast cancer and CKD), and by now describing the protocol for the next step in the iterative human-centred design process: a feasibility study to investigate this intervention further with individuals with breast cancer.

Appendix 1

Screenshot of IVY training



Appendix 2

Stimuli used in the IVY training and the IAT measurement: original Dutch and English translations

Target concepts				
	Dutch	English	Dutch	English
N	Vitaal	Vital	Moe	Tired
1	Energiek	Energetic	Uitgeput	Exhausted
2	Levenslustig	Full of life	Slap	Weak
3	Fit	Fit	Lusteloos	Apathetic

4	Wakker	Awake	Traag	Slow
5	Actief	Active	Duf	Dull
6	Alert	Alert	Slaperig	Sleepy
7	Krachtig	Powerful	Krachteloos	Powerless
8	Sterk	Strong	Vermoeid	Fatigued
9	Snel	Quick	Futloos	Lifeless
10	Vitaal	Vital	Moe	Tired
Attributes				
	Dutch	**English**	**Dutch**	**English**
N	**Ik**	**I**	**Ander**	**Other**
1	Zelf	Self	Hen	Them
2	Mijn	Mine	Ander	Other
3	Mij	Me	Hun	Their
4	Ik	I	Anderen	Others
5	Mezelf	Myself	Jullie	You

Appendix 3
Research schedule for participants

Overview research breast cancer related fatigue. Active treatment group

When	What	Length
		Measurement: 15 min **Training: 5 min**
Start 1 week before start of the study	Week 0: Information and sign-up	-
Baseline 1 x per week	Week 1: Measurement 1 Week 2: Measurement 2 Week 3: Measurement 3 Week 4: Measurement 4	4 weeks in total
Training Each working day	Week 5: IVY Training sessions in the app Week 6: IVY Training sessions in the app + Measurement 5 Week 7: IVY Training sessions in the app Week 8: IVY Training sessions in the app + Measurement 6	4 weeks in total
Follow-up 1 x per week	Week 9: Measurement 7 Week 10: Measurement 8 Week 11: Measurement 9 Week 12: Measurement 10 Week 13: - Week 14: Measurement 11 Week 15: - Week 16: Measurement 12 Week 17: - Week 18: Measurement 13 Week 19: - Week 20: Measurement 14	12 weeks in total
Booster 2 x per week	Week 21: IVY Training sessions in the app Week 22: IVY Training sessions in the app + Measurement 15 Week 23: IVY Training sessions in the app Week 24: IVY Training sessions in the app + Measurement 16	4 weeks in total
Follow-up 2 1 x per week	Week 25: - Week 26: Measurement 17 Week 27: - Week 28: Measurement 18	4 weeks in total

Overview research breast cancer related fatigue. Control group

When	What	Length
		Measurement: 15 min **Training: 5 min**
Start 1 week before start of the study	Week 0: Information and sign-up	-
Baseline 1 x per week	Week 1: Measurement 1 Week 2: Measurement 2 Week 3: Measurement 3 Week 4: Measurement 4 Week 5: - Week 6: Measurement 5 Week 7: - Week 8: Measurement 6 Week 9: - Week 10: Measurement 7 Week 11: - Week 12: Measurement 8	12 weeks in total

When	What	Length
Training Each working day	Week 13: IVY Training sessions in the app Week 14: IVY Training sessions in the app + Measurement 9 Week 15: IVY Training sessions in the app Week 16: IVY Training sessions in the app + Measurement 10	4 weeks in total
Follow-up 1 x per week	Week 17: Measurement 11 Week 18: Measurement 12 Week 19: Measurement 13 Week 20: Measurement 14 Week 21: - Week 22: Measurement 15 Week 23: - Week 24: Measurement 16 Week 25: - Week 26: Measurement 17 Week 27: - Week 28: Measurement 18	12 weeks in total

Abbreviations

ALU	Advice committee Local Feasibility Scientific Research (Adviescommissie Lokale Uitvoerbaarheid Wetenschappelijk Onderzoek)
ANOVA	Analysis of variance
CBM	Cognitive bias modification
CBRSQ	Cognitive and Behavioural Responses to Symptoms Questionnaire
CBT	Cognitive behavioural therapy
CIS	Checklist Individual Strength
CKD	Chronic kidney disease
CMO	Committee Human Research (Commissie Mensgebonden Onderzoek)
CRF	Cancer-related fatigue
HADS	Hospital Anxiety and Depression Scale
HCP	Health care provider
IAT	Implicit Association Test
IVY	Implicit VitalitY
LMM	Linear mixed models
OSF	Open Science Framework
PIF	Patient information letter
RCT	Randomized Controlled Trial
RIM	Reflective-impulsive model
TIIM	Twente Intervention and Interaction Machine
WMO	Medical Research Involving Human Subjects Act (Wet medisch-wetenschappelijk onderzoek met mensen)
ZGT	Hospital group Twente (Ziekenhuisgroep Twente)

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40814-024-01571-8.

Additional file 1: SPIRIT checklist.

Acknowledgements
The authors would like to thank all caretakers in the collaborating hospitals for their interest in this study and their help with recruiting patients. The authors would like to thank the BMSlab of the University of Twente for their contribution in the design, availability, and maintenance of the software used in the intervention of this study.

Authors' contributions
Authors JG, MP, CB, FS, and ES have made substantial contributions to the conception and design of the work and have drafted or substantially revised the work. Next to that, ES has made substantial contributions to the acquisition and recruitment of hospitals and patients, while author JG included the patients. Authors JG, MP, and CB also have made substantial contributions to the creation of new software used in the work. Author LL has made substantial contributions to the conception and design of the work by providing the patient perspective.

Funding
This work was supported by unrestricted grants from Hospital group Twente [Ziekenhuisgroep Twente, ZGT], Novartis, and the Faculty Behavioural, Management and Social Sciences of the University of Twente.

Data availability
The datasets generated and/or analysed during the current study are not publicly available due to privacy restrictions but are available from the corresponding author on reasonable request. Results will be communicated by informing funding parties, by publishing to scientific journals, and by presenting at conferences.

Declarations

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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Received: 27 October 2023 Accepted: 29 October 2024
Published online: 18 December 2024

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