A Protocol for a feasibility study of Cognitive Bias Modification training (IVY 2.0) countering fatigue in people with breast cancer

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Research Article

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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 2.0) 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 and effectiveness of the IVY 2.0 CBM training in a feasibility wait-list control trial. The effectiveness of the CBM app is measured 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 as well as people in the metastatic phase. The number of target participants is 120 with 60 people in the (neo)adjuvant setting, and 60 in the metastatic setting, both groups divided 1:1 with 30 people in the IVY treatment group and 30 people in the delayed treatment control group. All participants receive the training via the IVY 2.0 app, in which participants categorize words related to vitality with words related to ‘I’ and words related to fatigue with words related to ‘other’. Preliminary effects are measured on 3 levels; (1) self-identity bias is measured with a short computer task based on the Implicit Association Test (IAT), while (2) avoidance and all-or-nothing behaviour, as well as (3) fatigue and vitality levels are measured with questionnaires.

Discussion

This study wants to evaluate the feasibility of a larger-scale multi-centre RCT to investigate this novel eHealth application and to give first indications on the effectiveness of this intervention to counter fatigue in people suffering from breast cancer. Using the IVY 2.0 CBM app requires very little effort, both in time and cognitive load, which could be especially beneficial for fatigue symptoms.

Trial registration:

Retrospectively registered at the Open Science Framework (OSF; https://osf.io/e85g7/) on October 20, 2023.
Background

Introduction

Breast cancer is the most frequently occurring cancer and the leading cause of death in women worldwide (1). In the Netherlands as well, breast cancer is the most prevalent cancer-type with around 14,000 diagnoses per year (2). Healing (curation) can be achieved in most cases. In the curative 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 is cancer related fatigue (CRF; 3). More than 50% of people suffering from 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 characterise cancer-related fatigue 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” (5, 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). Cancer-related fatigue 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 cancer related fatigue 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 also play an important role, possibly especially in the early stage of cancer related fatigue.

Another way that unconscious processes can influence fatigue symptoms are 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). 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 (22). 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).

To our knowledge, our research team is the first to introduce CBM to counter fatigue symptoms. First, to meet the wishes and needs of professionals and individuals with breast-cancer, our research team developed the first IVY 1.0 CBM app using a co-creation approach (31). Next, following the iterative human-centred design framework (32), our research team has investigated this novel eHealth application by researching usability. This has been done with people suffering from breast cancer (33) and from chronic kidney disease (34). Both of these studies evaluated the application with multiple stakeholders (patients and health care professionals) and revealed positive results. Although in this usability study with people suffering from breast-cancer, preliminary data analyses only revealed a trend in altering self-identity bias (33), a pilot study with people suffering from chronic kidney disease revealed strong CBM effects on cognitive bias, and promising results on symptoms and related behaviour (34).

The current study aims to similarly take this next step with people suffering from breast-cancer by evaluating the feasibility of researching this CBM training further and by again investigating the effects of the training on cognitive bias, fatigue and related behaviour in people suffering from breast-cancer. Both patients in the curative as well as the palliative stage are selected for this feasibility study, as these stages involve different contexts that 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 wants to assess the feasibility of doing a larger-scale multi-centre RCT with the IVY 2.0 CBM training with people suffering from breast-cancer. Specifically, the research process will be investigated, such as the recruitment process and retention of people in two cancer-treatment stages, namely people in the curative setting, as well as people in the metastatic phase. Furthermore, first indications of the effectiveness of the CBM training will be measured and analysed 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 was written in accordance with the 2013 SPIRIT guidelines (see the SPIRIT checklist in Additional file 1 and the SPIRIT schedule outlined in Fig. 1).

**Study design**

In this article the study protocol of a multi-centre, waitlist-control feasibility study is described with the IVY 2.0 CBM training to counter fatigue in people suffering from breast-cancer in both the (neo)adjuvant and metastatic phase. This prospective non-randomized intervention study will test the research process (e.g., recruitment, retention) in both patient groups, the design feasibility for a future randomised controlled trial, and give first indications of the effectiveness of the training on implicit bias and self-reports of fatigue, vitality, avoidance, and all-or-nothing behaviour. These objectives will be evaluated with a mixed-methods approach. As this is such a novel research approach, many other interesting topics and possible moderators were also incorporated in the design, such as depressive symptoms, and whether a booster training after follow-up could have a boosting effect. These topics might be beyond the scope of this article and might be addressed in additional articles.

**Participating centres**

Five hospitals will be asked to recruit patients for this study, namely Ziekenhuis Groep Twente (ZGT) in Almelo and Hengelo, Isala in Zwolle, Franciscus in Rotterdam, Gelre in Apeldoorn and Saxenburgh in Hardenberg.

**Study population**

The total number of targeted patients aimed to be recruited, is 120 (n = 60 (neo)adjuvant setting, n = 60 metastatic setting). Each of the participating centres was asked to recruit 30 patients; 15 in the (neo)adjuvant setting and 15 in the metastatic setting, bringing the total to 150 participants. This was done because of a 20% anticipated drop-out rate (35). Within each patient group, patients are sequentially divided into the active IVY treatment group (n = 30) and the delayed treatment control group (n = 30) by the researchers. Because we are not sure that patients will be equally recruited from the hospitals and because we expect the recruitment, especially in metastatic patients, to be challenging for this study, we did not focus on randomisation yet.
Potential participants are approached by specialists on whether they are interested in participating in the study. The specialist gives a general explanation about the study and, if interested, provides the patient with an information letter. Patients also can first contact the researcher or an independent person to ask 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 or 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 systemic therapy with chemo(immuno)therapy or antihormonal treatment in combination with targeted treatment;

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

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

- The patient owns 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 own a smartphone and has no experience using a smartphone.

**Sample size**

A recent – as yet unpublished – similar study among people with chronic kidney disease (in the predialysis and dialysis stage) shows that large effect sizes are achievable on the cognitive bias ($d = 1.20$ for self-identity bias and $d = 1.14$ for attentional bias; (34)) with only 22 participants. However, meta-analyses on CBM show inconclusive results, from bias reduction effect sizes that are small in pain studies ($d = 0.134$; (22)) to medium (attentional CBM: $g = .049$, interpretational CBM: $g = .058$) in various other clinical samples (anxiety, depression, eating disorders, substance use; 31). The effects on symptoms generally were smaller, e.g., a medium effect on biases ($g = 0.49$) and small effects on anxiety and depression ($g = 0.13$) were found (37). Power calculation (based on repeated measures ANOVA, $N = 60$, 3 time levels, alfa = .05; beta = .80) shows that a small effect size ($f = .17$) is still detectable.

**Intervention**
The IVY CBM training consists of an eHealth application in which participants categorize words into 4 categories: vitality, fatigue, I, and other. 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. In the middle of the screen, a total of 120 stimuli related to the 4 categories are presented randomly and sequentially, such as ‘active’ (related to vitality), ‘exhausted’ (related to fatigue), ‘them’ (related to other), and ‘mine’ (related to I). Participants categorized 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 has been chosen in such a way 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 words 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 receive a link with instructions to download and use the application. The IVY CBM training is incorporated in the TIIM app designed by the BMScLab, part of the University of Twente. The IVY treatment group receives this email in week 4 of the study, the delayed treatment group receives the same email in week 12 of the study. Included in these instructions, participants receive contact details from the investigators and are invited to email or call the investigator if they experience any problems using the application. Next to that, a Frequently Asked Questions page is available on the app. During the first week of the baseline and the training, the participants who did not perform a training by the end of the week, are phoned to ask why no response has yet been registered from them. If they experience difficulties using the IVY CBM app, researchers will support them. Additionally, the IVY treatment group receives so-called booster sessions in weeks 21 to 24. During these weeks, each week three sessions were made available, of which the participant was free to determine when, which, and how many sessions to complete.

**Setting**

As can be seen in Table 1, the two groups both have a baseline phase, a training phase, and a follow-up phase. In addition, the active treatment group also has a booster phase after 5 months (3 months after the last training of the first IVY-CBM app training). The active treatment group has a baseline of 4 weeks with 1 measurement every week (of 5–10 minutes). In the control group, the first 4 weeks are the same as in the active treatment group, after that these patients receive a baseline phase of 8 weeks with measurements every other week. Following the baseline phase (for the active treatment group this is after 4 weeks, for the control group it is after 12 weeks), all patients follow a 4-week IVY CBM training phase with 5-minute IVY sessions 5 days a week. A measurement is also sent every 2 weeks during this training phase. Following this 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. The active treatment group will receive a booster phase of 4 weeks after this follow-up period. During this booster phase, participants are asked to train at least twice a week. Also, during this booster phase,
another measurement is sent every 2 weeks. After the booster phase, this group has a follow-up phase of 4 weeks with measurements every other week.

**Table 1**  
*Schematic overview of the study design*

<table>
<thead>
<tr>
<th>Group</th>
<th>Month 1</th>
<th>Month 2</th>
<th>Month 3</th>
<th>Month 4</th>
<th>Month 5</th>
<th>Month 6</th>
<th>Month 7</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Active IVY-treatment</strong></td>
<td>Baseline</td>
<td>IVY training</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>IVY booster</td>
<td>Follow-up</td>
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<tr>
<td>Measurements</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>2</td>
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<tr>
<td>Trainings</td>
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<td>20</td>
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<tr>
<td><strong>Delayed IVY control</strong></td>
<td>Baseline</td>
<td>Baseline</td>
<td>Baseline</td>
<td>IVY training</td>
<td>Follow-up</td>
<td>Follow-up</td>
<td>Follow-up</td>
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<tr>
<td>Measurements</td>
<td>4</td>
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<td>Trainings</td>
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</table>

Both a training session and a bias measurement session take no more than 5 minutes at a time. Taking the patient-reported outcomes to be administered into account (self-reported fatigue, vitality, and behaviour), the time needed will be relatively little (about 10 minutes). Thus, the burden on patients remains very low, despite the high frequency of sessions. In addition, we give patients a lot of freedom in determining the moment of participating. Patients are free to do the measurement at a for them suitable time during that week. Similarly, during the booster phase, patients have the option to decide at what moments during the week the booster training sessions are performed. For the normal training sessions as well, the sessions are available in the morning, but the participants are free to do them at a time that suits them best.

Specifically, on Monday morning, participants receive a digital message that their measurement is ready. Those who have not yet completed the measurement on Wednesday will receive a reminder. During the training phase, participants receive a digital invitation to do a session every weekday morning at 8:00 am. Those who have not yet completed the training will receive a reminder at 7:00 PM that same day. During the booster phase, participants are asked to do the training sessions at least twice a week. On Monday morning, 3 training sessions are made available for that entire week. On Friday morning the participants receive a reminder for these booster training sessions. In both the normal training phase and the booster phase, participants in training weeks 2 and 4 also receive a measurement. This is also sent on Monday morning with a reminder on Wednesday morning. These procedures are inspired by a previous study with people suffering from chronic kidney disease (34).

**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 end of June 2022 to end of February 2023, thus
in this time 120 participants are expected to be recruited, which means 15 participants per month in total, 3 per participating centre. Specifically, the recruitment and enrolment will be assessed by obtaining percentages of people willing to participate from the by the care practitioners judged as eligible people for the study. 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. 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, preliminary analyses of the effectiveness of the training to counter fatigue on bias, symptoms and behaviour will be conducted.

Materials

To measure self-identity bias, the study was conducted using the platforms Qualtrics (38) and Inquisit (39). During each measure, using Qualtrics, participants were automatically sent forward to Inquisit where they performed the Implicit Association Test (IAT; 35) 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 categories fatigue, vitality, I and other by using the ‘E’ and ‘I’ keys on the keyboard. 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. Next, four questionnaires are presented. The first questionnaire is the shortened version of the Cognitive and Behavioural Responses Questionnaire (CBRSQ; 36). It 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 are 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 .76 for the avoidance / resting subscale and a Cronbach’s alpha of .85 for the all-or-nothing subscale (42).

Next, using The Dutch Vitality measure (Vita-16; 38), vitality was 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 are averaged and higher scores indicate higher vitality. The scale has excellent reliability with a Cronbach’s Alpha of .90 for the full scale, a Cronbach’s Alpha of .90 for the energy subscale, a Cronbach’s Alpha of .89 for the motivation subscale, and a Cronbach’s Alpha of .90 for the resilience subscale.

Following, participants filled in the Checklist Individual Strength (CIS; 39) 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’ were answered. Scores are 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 .92, a Cronbach’s Alpha of .90 for the full scale, and Cronbach’s alphas of .88 (fatigue severity), .92 (activity), .82 (concentration), and .87 (motivation) (44, 45), reliability of the CIS is excellent.

Lastly, with the Hospital Anxiety and Depression Scale (HADS; 41), 7 items of the depression subscale were used to research possible depressive symptoms. Four of these items (e.g., ‘I still enjoy things I enjoyed earlier’) could be answered using a four-points frequency scale (1 = the same as earlier, 4 = not at all), and three items could be answered using another four-points frequency scale (1 = not at all, 4 = mostly), of which one had a reversed answer order. Higher scores indicate higher depression symptoms. With a Cronbach’s alpha of .86, the depression subscale of the HADS has good reliability. Completing these questionnaires took approximately five minutes each week.

**Statistical analysis**

The feasibility outcomes recruitment and retention will be monitored and assessed using Excel. The feasibility outcome variability will be researched with the Descriptives analyses on SPSS. Next to that, to research the variability in more detail as well as the effect 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.

These visualisations will be supplemented by generalized piecewise linear regression analyses (PLMs). PLM is an analysis method suited for time-series data that are segmented into phases (47, 48). The dataset is split at certain break points (the phases) and regression parameters (intercept, trend, level, and slope) are calculated separately for each phase, and compared with each other (47, 48). In this model, the intercept refers to the outcome at the start of the study, the trend effect refers to the trendline in one phase, the level effect refers to the instant and constant effect of the intervention, and the slope effect is an indication of the effect of the intervention by comparing the trendline (trend) at baseline to the trendline during the intervention (47, 48). Averages for each measurement will be investigated with the PLM, yielding beta weights for trend, level, and slope effects, as well as a P value (with P < .05 as cut-
off for significance) and $R^2$ effect sizes (47). This analysis will be done in SPSS and with the scan package in R.

Next to these analyses, the design allows for two other ways of analysing the intervention effect, which has a positive and verifying influence on the power. First, the effect of the training will be analysed using Linear Mixed Models (LMM) by looking at both groups’ pre- to post- comparisons. Second, the effect of the training will be analysed 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 is analysed both with between and within-comparisons.

**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. As CRF is an often experienced but complex symptom, interventions looking at different approaches to fatigue are useful both alone standing as well as combined with other interventions. Such a different approach is Cognitive Bias Modification (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 phone or tablet, 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, as well as the analysis of preliminary effects of the training.

The data collection for this study started in August 2022 and will end in the end of October 2023. Writing this protocol article was delayed because we first wanted to analyse the findings in the study conducted with people suffering from CKD. As the study with patients suffering from 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 to continue with this article.

Another consideration that we would like to mention is the choice for non-randomisation. We described the reasons (expected recruitment difficulties with the metastatic group and different recruitment rates per hospital) for making this decision, however, a counterargument is that a feasibility study should test
all aspects of the prospective RCT, which includes randomisation (49). We could have investigated further whether it was possible to randomise even with the constrictions of the current study. Next to that, other feasibility studies often describe criteria for success for recruitment and retention (e.g., (50,51). Because our study investigates such a novel intervention, we decided to judge the feasibility a posteriori.

Nevertheless, this study describes a protocol for a feasibility study to investigate a novel and innovative intervention countering fatigue in people suffering from breast cancer. This CBM intervention focuses on unconscious processes, which is 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 suffering from 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 chronic kidney disease), 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 people suffering from breast cancer.

**Abbreviations**

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ALU</td>
<td>Adviescommissie Lokale Uitvoerbaarheid Wetenschappelijk Onderzoek</td>
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<tr>
<td>ANOVA</td>
<td>Analysis of Variance</td>
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<tr>
<td>CBM</td>
<td>Cognitive bias modification</td>
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<tr>
<td>CBRSQ</td>
<td>Cognitive and Behavioural Responses to Symptoms Questionnaire</td>
</tr>
<tr>
<td>CBT</td>
<td>cognitive behavioural therapy</td>
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<tr>
<td>CIS</td>
<td>Checklist Individual Strength</td>
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<tr>
<td>CKD</td>
<td>Chronic Kidney Disease</td>
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<tr>
<td>CMO</td>
<td>Commissie Mensgebonden Onderzoek</td>
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<tr>
<td>CRF</td>
<td>Cancer related fatigue</td>
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<td>HADS</td>
<td>Hospital Anxiety and Depression Scale</td>
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<td>IAT</td>
<td>Implicit Association Test</td>
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<td>IVY</td>
<td>Implicit VitalitY</td>
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<td>LMM</td>
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Declarations

Consent for publication

Not applicable

Availability of data and materials

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.

Competing interests

The authors declare that they have no competing interests.

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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.

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References


50. Marley J. Study protocol for a feasibility study of an online educational programme for people working and living with persistent low back pain. 2023;


Figures
Figure 1

SPIRIT schedule of enrolment, interventions, and assessments

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<th>TIMEPOINT</th>
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See image above for figure legend

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