ABSTRACT

Introduction One in five breast cancer (BC) survivors are affected by persistent pain years after completing primary treatment. While the efficacy of psychological interventions for BC-related pain has been documented in several meta-analyses, reported effect sizes are generally modest, pointing to a need for optimisation. Guided by the Multiphase Optimization Strategy, the present study aims to optimise psychological treatment for BC-related pain by identifying active treatment components in a full factorial design.

Methods and analysis The study uses a 2×3 factorial design, randomising 192 women with BC-related pain (18–75 years) to eight experimental conditions. The eight conditions consist of three contemporary cognitive–behavioural therapy components, namely: (1) mindful attention, (2) decentering, and (3) values and committed action. Each component is delivered in two sessions, and each participant will receive either zero, two, four, or six sessions. Participants receiving two or three treatment components will be randomised to receive them in varying order. Assessments will be conducted at baseline (T1), session by session, every day for 6 days following the first session in each treatment component, at post-intervention (T2) and at 12-week follow-up (T3). Primary outcomes are pain intensity (Numerical Rating Scale) and pain interference (Brief Pain Inventory interference subscale) from T1 to T2. Secondary outcomes are pain burden, pain quality, pain frequency, pain catastrophising, psychological distress, well-being and fear of cancer recurrence. Possible mediators include mindful attention, decentering, and pain acceptance and activity engagement. Possible moderators are treatment expectancy, treatment adherence, satisfaction with treatment and therapeutic alliance.

Ethics and dissemination Ethical approval for the present study was received from the Central Denmark Region Committee on Health Research Ethics (no. 1-10-72-309-40). Findings will be made available to the study funders, care providers, patient organisations and other researchers at international conferences, and published in international, peer-reviewed journals.

Trial registration number ClinicalTrials.gov Registry (NCT05444101).

INTRODUCTION

Breast cancer (BC) is the most common cancer type among women, with nearly 2 million yearly cases worldwide.1 With improved survival rates, a growing number of women survive their BC disease.2 This poses a rehabilitation challenge as a significant number of women experience various late effects following their BC diagnosis and treatment, including psychological distress,3 fear of cancer recurrence,4 fatigue,5 sleep disturbances6 and pain. The latter is a prevalent symptom,7–9 manifesting in about 19% of women after BC treatment.10,11 Pain is a multifaceted experience consisting of not only sensory, but also cognitive and affective dimensions.12 The clinical and psychological predictors of pain after BC correspond with the conceptualisation of pain as a multifactorial experience consisting of not only sensory, but also cognitive and affective dimensions.12 The clinical and psychological predictors of pain after BC correspond with the conceptualisation of pain as a multifactorial experience consisting of not only sensory, but also cognitive and affective dimensions.12

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ The present study is guided by the Multiphase Optimization Strategy framework and uses a full factorial design to identify active treatment components in contemporary cognitive–behavioural therapy for pain after breast cancer.

⇒ The study includes session-by-session as well as daily measures of treatment mediators, enabling fine-grained analyses of putative change processes during treatment.

⇒ While the three treatment components were carefully designed with the intention of minimum overlap, they may involve aspects of common psychological processes, which may complicate interpretation of the result (i.e., disentanglement of the components).
where pharmacological and psychological interventions target different aspects of the pain experience. This is supported by studies showing that pharmacological treatments have less than optimal effects on pain after BC treatment. Moreover, pharmacological treatment of pain may be associated with a number of adverse effects such as sedation, nausea, constipation and impaired sexual functioning.

Several meta-analyses have documented the efficacy of psychological treatments on cancer-related pain. For example, a meta-analysis from 2013 found a statistically significant effect of psychosocial interventions on pain after BC, although the effect was smaller (Hedges’ g=0.21) when adjusted for the possibility of publication bias. Another meta-analysis investigated the effect of cognitive–behavioural therapy (CBT) on pain in patients with BC, and revealed a statistically significant medium effect size (Cohen’s d=0.49). More recently, so-called contemporary (‘third wave’) CBTs have increasingly been used to treat persistent pain. Rather than focusing on changing psychological events (eg, realistic restructuring as seen in earlier CBT), these therapies focus on changing the function of those events and the patient’s relationship to them (eg, decentering).

Examples of contemporary CBTs include mindfulness-based cognitive therapy (MBCT), mindfulness-based stress reduction (MBSR), and acceptance and commitment therapy.

Several randomised controlled trials (RCTs) have demonstrated the efficacy of contemporary CBTs on pain in various populations, with some trials focusing specifically on patients with BC. For example, a trial on the efficacy of MBCT including women treated for BC with persistent pain showed a statistically significant positive effect on pain intensity at 6-month follow-up. Similarly, a trial evaluating the efficacy of MBSR on persistent neuropathic pain in women after BC treatment revealed a statistically significant reduction from baseline to post-treatment on both pain intensity and pain interference.

Similar findings have been detected in studies of contemporary CBTs in other chronic pain populations, including fibromyalgia, pelvic pain, headache, and lower back pain. Taken together, contemporary CBTs appear efficacious in treating persistent pain. However, the effects found are generally modest, thereby challenging the clinical impact of the results and pointing to a need for optimisation.

A prerequisite for treatment optimisation is knowledge about why and how a treatment exerts its effect, that is, which processes account for a therapeutic change. Specifically, to optimise a treatment, it is necessary to identify which specific treatment components catalyse a therapeutic change. For instance, whether a mindfulness exercise enhances the ability to willfully direct one’s attention, which then leads to a favourable outcome. Nevertheless, a challenge in psychological therapy research is that knowledge about how and why psychological therapy works remains limited. The standard approach to investigate therapeutic processes is so-called mediation studies embedded in RCTs, which aim to examine the change processes during an intervention. For example, the previously mentioned RCT on the effect of MBCT on pain after BC treatment found that reductions in pain catastrophising explained a significant proportion of the achieved pain reduction, while other studies report that increases in well-being are preceded by increases in mindfulness skills. However, basing mediation studies on two-arm RCT data poses a limitation, as typical RCTs are not designed to, or suitable for, identifying the active treatment components driving the effects detected. Indeed, RCTs were originally developed to test single-component interventions (eg, drugs), but psychological interventions usually consist of multiple treatment components (eg, mindfulness, psychoeducation and action plans). As such, the psychological treatment components evaluated in RCTs are delivered simultaneously in ‘intervention packages’, the effect of each of the individual components on the outcome and the relationship between components, that is, how they interact, cannot be singled out. As such, the typical RCT is not designed to inform about the effects of individual treatment components or the possible positive or detrimental effects of one component on another.

To improve our knowledge about how multicomponent psychological interventions work, calls for alternative approaches to the conventional RCT set-up. The Multiphase Optimization Strategy (MOST) is a methodological framework, conceptually rooted in engineering, designed specifically for optimisation of multicomponent interventions. Specifically, MOST enables the systematic identification of active treatment components in multicomponent interventions, including how the presence or absence of one or more components affects the performance of other components. Within the MOST framework, optimisation of an intervention is the process of identifying an intervention that provides the best expected outcome obtainable within key constraints imposed by the need for efficiency, affordability and/or scalability. MOST begins with a preparation phase, where mechanisms to be targeted in the intervention and the individual treatment components are selected. In the second optimisation phase, the effects of selected treatment components are tested in a highly rigorous, efficient, randomised trial (ie, factorial experiment) allowing for the estimation of the main effects of each component, and the interactions of all components, with the aim of identifying active treatment components. In a third evaluation phase, the goal is to confirm the effects of the active treatment components, usually with a two-arm RCT, but other experimental designs may also be appropriate (see Tanner et al41). Thus, MOST has the potential to lead to (a) increased efficacy by excluding treatment components with either neutral or detrimental effects on the outcome, and (b) improved cost-effectiveness by excluding treatment components with no or only negligible effects on the outcome, thus reducing costs of the intervention.
This underscores the relevance of the MOST framework for implementation science, that is, the process of translating research findings into treatments, which is often complicated by many interventions being developed with a primary focus on efficacy, but with little consideration of cost, complexity and burden. In contrast, the MOST framework offers the ability to consider implementation constraints when building the intervention, that is, combination and selection of components.

A conceptual model for the present study

MOST relies on theory and empirical research to identify processes to be targeted by the treatment components. The Fear-Avoidance Model (FAM) describes core cognitive–behavioural processes, including pain catastrophising, pain-related fear, pain hypervigilance and pain avoidance, which contribute to the transition from acute to persistent pain, including maintaining and exacerbating processes. Since its formulation, FAM has received considerable empirical support, especially from research within musculoskeletal conditions. For instance, studies have shown that pain-related fear and pain avoidant beliefs predict the transition from acute to chronic low back pain. Moreover, a recently published meta-analysis revealed medium-to-large associations between pain catastrophising, pain-related fear and pain vigilance, respectively, and several pain outcomes. While the validity of FAM in BC-related pain is less well documented, there is evidence to suggest that similar processes are involved. A recent meta-analysis has, for example, shown associations between pain catastrophising and post-surgery acute and persistent pain specifically in patients with BC. On this background, we will use FAM as a conceptual model in the present study to identify key pain processes as treatment targets. Given the persistent nature of pain after BC treatment, developing the patient’s ability to cope with the pain rather than eliminating the pain per se is an important clinical goal, pointing to the relevance of contemporary CBTs for targeting these pain processes. In the present study, we hypothesise that the following contemporary CBT components will influence key pain processes, leading to reductions in the primary outcomes of pain intensity and pain interference (see figure 1):

1. **Mindful attention practices** will increase attentional control (ie, the ability to intentionally focus and intentionally shift one’s attention), thereby reducing pain hypervigilance.
2. **Decentring practices** will reduce fusion with thoughts (ie, getting caught up in one’s thoughts and acting automatically in response to thoughts), thereby reducing pain catastrophising.
3. **Values and committed action** (ie, behaviour patterns linked to values and goals) will increase acceptance of discomfort and reduce avoidant behaviour.

Study aim

Guided by the MOST framework, the present study aims to identify active contemporary CBT components for pain after BC treatment. Specifically, consistent with the optimisation phase of the MOST framework, a rigorous randomised experiment (ie, a full factorial design) will be used to evaluate the efficacy and change processes of three contemporary CBT components, namely (1) mindful attention, (2) decentring, and (3) values and committed action. Specifically, a full factorial design supports the estimation of the specific contribution of each component (ie, main effects investigated as interaction effects due to the longitudinal design (ie, time×group)) and how the components perform in the presence and absence of one another (ie, interactions between components (eg, the effect of decentring plus vs minus the effect of mindful attention)). This may provide information to support the decision of how to build optimised psychological interventions for pain after BC treatment, thereby moving the field of BC-related pain research forward.

METHODS AND ANALYSIS

The present study protocol adheres to the Standard Protocol Items for Randomized Trials (SPIRIT) statement.

Study design and experimental conditions

The study uses a 2×3 factorial design, randomising participants to one of eight overall experimental conditions reflecting every possible combination of the three treatment components (see figure 2).

![Conceptual project model](http://bmjopen.bmj.com/)

**Figure 1** Conceptual project model.
The eight experimental conditions consist of one, two or three treatment components:

1. The **mindful attention component** includes a breathing exercise.\(^{35,36}\)
2. The **decentering component** includes a guided imagery exercise.\(^{38}\)
3. The **value-based action component** includes identification of personal values and value-based committed action.\(^{39}\)

Manuals of each treatment component were discussed with regard to face validity between three authors (MJ, MSO, RZ). Based on this iterative process, the treatment components were continuously revised until a consensus on a satisfactory face validity was reached. The manuals were read and commented by two external researchers (Ingeborg Farver-Vestergaard (IFV), ORCID: 0000-0002-5738-4055; Anne Maj van der Velden (AMV), ORCID: 0000-0002-1649-6405). The manuals were concealed, and IFV and AMV were asked to correctly assign the manuals according to the three treatment components. Both assigned the concealed manuals correctly according to the three treatment components.

In the present study, each treatment component is operationalised as two sessions of 1-hour duration each, which will be delivered over 2 weeks, that is, one session per week. As such, all participants will receive either zero (experimental condition 1), two (experimental conditions 2–4), four (experimental conditions 5–7) or six sessions (experimental condition 8). Participants who are randomised to experimental condition 1 are offered to receive a treatment component of their own choice (ie, two sessions) at the end of the study.

Each treatment component includes homework between the first and second session and in the week following the second session. For the mindful attention and decentering components, participants receive an audio file with the same exercise as is delivered in sessions (ie, a breathing exercise and a guided imagery exercise, respectively), which participants are then asked to perform one time daily. For the values and committed action component, the first session is dedicated to identifying the participants’ values and generate committed actions, that is, behaviours congruent with identified values, which participants are then asked to complete as homework. In the second session, if the committed actions assigned for homework have been successfully completed, new actions are identified and given as homework assignment. If committed actions have not been successfully completed, reasons for this are explored, and the committed actions are either modified or replaced.

All three treatment components were purposefully designed to be delivered online via the software app Zoom. To facilitate the online delivery format, digital codes of conduct are discussed with participants prior to their first session, including the importance of remaining uninterrupted during sessions.

The treatment components are delivered by psychologists and students in the Master of Science in Psychology, who receive thorough training and supervision throughout the data collection.

**Participant eligibility**

The present study includes women treated for primary BC presenting with pain. Specific eligibility criteria are:

- Women treated for primary BC aged between 18 and 75 years at the time of diagnosis.
- Women who are minimally 6 months post-primary treatment (surgery and chemotherapy).
- Women with a pain score of >3 on at least one out of two Numerical Rating Scales (NRSs) measuring pain intensity and pain interference, respectively.
- Women with a sufficient ability to communicate in Danish.
- Women with sufficient equipment and tech knowledge to participate in online-delivered intervention.

Exclusion criteria are: incurable BC (stage IV), BC recurrence, bilateral BC, other active cancer diseases, other severe primary pain conditions, current psychiatric disorders hindering participation in the study (eg, psychosis), and insufficient equipment and/or ability to participate in online-delivered intervention in Danish.

**Recruitment procedure and randomisation**

Participants are identified through a data extraction from the register of the national Danish Breast Cancer Group (DDBC).\(^{78,79}\) In the present study, the DBCG delivers data extractions for all women in Denmark who were diagnosed and treated for primary BC (stages I–III) during 2018–2019, and who were aged between 18 and 75 years at the time of diagnosis. The data extractions include civil registration number, which allows us to contact all women using a public, secure digital postbox (‘E-boks’). Using E-boks, all women identified from the data extraction will receive an invitation to complete a brief questionnaire (see online supplemental material 1), screening for pain intensity and pain interference, cf. the eligibility criteria.

Eligible women, who consent to be contacted, will receive a phone call from a research assistant, who will screen further for eligibility and inform about the study aim, methods and procedures. If the woman agrees to participate, she is sent a digital letter with an attached Participant Information Folder together with a link to an online informed consent form and a baseline questionnaire (T1). Participant recruitment began in October 2023.
2022 and continues until the required number of participants has been included (see the Statistical power and sample size section below).

**Randomisation procedures**

Study participants are randomised using a computerised randomisation module in REDCap—a research electronic data capture tool hosted at Aarhus University,80 81 which complies with the European General Data Protection Regulation (GDPR). The allocation sequence is generated by an independent biostatistician and set up to randomise a total of 192 participants to eight conditions, that is, 24 per condition. Within conditions with two or three treatment components (ie, conditions 5–8), participants are randomised to receive treatment components in different orders to rule out possible order effects. As in most psychological interventions, it is not possible to blind study participants or the therapists to the assigned conditions.

**Outcome measures**

Table 1 provides an overview of all assessment points and outcome measures. Data are collected and managed in REDCap.80 81

**Assessment points**

Assessment points include (1) at study enrolment (baseline (T1)), (2) session by session (Ts1–6), (3) every day for 6 days following the first session in each treatment component (Td1–18), (4) at post-intervention (T2) and (5) at 12-week follow-up (T3) (see figure 3).

**Primary outcomes**

The present study includes two primary outcomes, namely pain intensity and pain interference, as is generally recommended.82 Pain intensity during the last week is measured using an 11-point NRS,83 with a higher score indicating more pain. The NRS has been validated in patients with BC.46 Pain interference is measured using the Brief Pain Inventory (BPI) interference subscale,84 (Danish version 86), which assesses pain interference during the last week across seven domains, namely general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life. The total score is calculated as the mean across the seven items (range: 0–10), with a higher score indicating more pain interference. The BPI interference subscale has been proven reliable (α=0.92).87 To minimise participant burden in daily measures, pain interference is measured with a single aggregated item assessing pain interference during the last 24 hours across the seven domains measured with the BPI (‘On average, to what extent did your pain interfere with your daily life (eg, your general activity, your mood, your walking ability, your normal work, your relations with other people, your sleep and your enjoyment of life) during the last 24 hours?’).

**Secondary outcomes**

Additional pain measures, tapping into other relevant aspects of the pain experience, include pain burden capturing the affective–motivational dimension of pain.88 Aligning with a previous trial with women reporting pain after BC,46 pain burden is measured with an 11-point NRS,83 with a higher score indicating higher perceived pain burden. Pain quality is measured with the pain descriptors from the Short-Form McGill Pain Questionnaire (SF-MPQ-2),89 which assesses pain quality using four subscales, that is, continuous pain, neuropathic pain, intermittent pain and affective pain, respectively, where in particular neuropathic pain is a frequent type of pain reported by women treated for BC.11 90 For each subscale, higher scores indicate more pain. The SF-MPQ-2 has previously been used in patients with BC46 and has proven to have good internal consistency in pain populations (α=0.73–0.95 for subscales88). Pain frequency is measured with a single item (ie, ‘How often do you feel pain’), with a higher score indicating higher pain frequency.

Other secondary outcomes include outcomes that have been shown to be related to the pain experience, namely pain catastrophicising,16 17 psychological distress,91 well-being92 and fear of cancer recurrence (FCR).93 Pain catastrophicising is measured with the Pain Catastrophizing Scale (PCS),94 with a higher total score indicating more pain catastrophising. The PCS has previously shown good psychometric properties (α=0.87).94 Psychological distress is measured using the Hospital Anxiety and Depression Scale (HADS),95 with a higher total score indicating more psychological distress. Several studies with patients with cancer, including patients with BC, indicate that the HADS total score is a sensitive measure of global psychological distress,96–98 with good internal consistency (α>0.87).99 Well-being is measured with the WHO Well-Being Index (WHO-5),100 with a higher score indicating more well-being. The WHO-5 has been validated in several clinical populations,101 has been used in patients with BC46 and has proven to have good internal consistency (α=0.82).102 Finally, FCR is measured with the Fear of Cancer Recurrence Inventory Short Form (FCRI-SF).103 104 with a higher score indicating more FCR. The FCRI-SF consists of the nine-item FCRI severity subscale from the full version of the FCRI, which has good psychometric properties (α=0.89)105 and has been translated into Danish and validated in patients with cancer.106 To minimise participant burden, none of the secondary outcomes are included in the session-by-session or daily measures.

**Change processes**

Putative change processes during treatment include (1) mindful attention, (2) decentring, and (3) values and committed action. Mindful attention is measured with the Mindful Attention Awareness Scale (MAAS) total score,107 with a higher score indicating higher levels of mindful attention. The MAAS has been translated into Danish and has proven a good internal consistency (α=0.88).107 Decentring is measured with the 11-item decentring subscale of the Experiences Questionnaire (EQ),108 with a higher score indicating higher levels of
decentring. The EQ decentring subscale is internally consistent ($\alpha=0.90$).\(^{108}\) Values and committed action is measured with the Chronic Pain Acceptance Scale (CPAS), consisting of the two subscales ‘pain willingness’ and ‘activity engagement’, with higher scores indicating more acceptance and activity engagement, respectively.\(^{109}\)

Studies have revealed acceptable to excellent internal consistency ($\alpha=0.72–0.91$).\(^{110}\)

To minimise participant burden, only two items from each scale (MAAS, EQ, CPAS) are included in the session-by-session measures. In the selection of these two items, three authors independently identified the two items with the highest face validity among the five items from each scale with highest factor loadings in validation papers.\(^{108} 109 111\) Discrepancies were discussed and agreed on for all items.

Given the frequency of the daily measures (Td1–18), only a single item from each scale (MAAS, EQ, CPAS) is administered. In the selection of these single items, three authors consensually selected the item with the highest face validity out of the two items included in the session-by-session measures (Ts1–6).

For session by session (Ts1–6), post-intervention (T2) and follow-up (T3), homework is assessed with four items related to the extent to which participants conducted homework since the last session. For daily measures (Td1–18), homework during the last 24 hours is assessed with a single item.

BPI, Brief Pain Inventory; CPAS, Chronic Pain Acceptance Scale; EQ, Experiences Questionnaire; FCRI-SF, Fear of Cancer Recurrence Inventory Short Form; HADS, Hospital Anxiety and Depression Scale; MAAS, Mindful Attention Awareness Scale; No, number; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale; SF-MPQ-2, Short-Form McGill Pain Questionnaire; Td1–18, daily measures, days 1–18; Ts1–6, session-by-session measures, sessions 1–6; WAI-RS, Working Alliance Inventory Revised Short Form; WHO-5, WHO 5-item Well-Being Index.

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**Table 1** Overview of outcomes and assessments

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Scale</th>
<th>N. of items</th>
<th>Answer format range</th>
<th>T1 (baseline)</th>
<th>Ts1–6</th>
<th>Td1–18</th>
<th>T2 (post-intervention)</th>
<th>T3 (follow-up)</th>
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<tbody>
<tr>
<td>Primary outcomes</td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Pain intensity</td>
<td>NRS</td>
<td>11</td>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>0–11</td>
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<td>X</td>
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<td>0–11</td>
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<td>X</td>
<td>X</td>
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<td>X</td>
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<td>Pain catastrophising</td>
<td>PCS</td>
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<td>Secondary outcomes</td>
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<td>Pain acceptance and activity engagement</td>
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<td>EQ</td>
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<td>1–5</td>
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<td>X</td>
<td>X</td>
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<tr>
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<td>CPAS</td>
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<td>0–6</td>
<td>X</td>
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<td>X</td>
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<td>1–5</td>
<td>X</td>
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<td>X</td>
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<td>Homework§</td>
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<td>Different formats</td>
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<td>X</td>
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<tr>
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<td>WAI-RS</td>
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<td>1–7</td>
<td>X</td>
<td>X</td>
<td>X</td>
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</table>

*For daily measures (Td1–18), pain interference is measured with one aggregated item assessing pain interference during the last 24 hours within the seven domains measured with the BPI, that is, general activity, mood, walking ability, normal work, relations with other people, sleep and enjoyment of life.

†To minimise participant burden, only two items from each scale (MAAS, EQ, CPAS) are included in the session-by-session measures (Ts1–6). In the selection of these two items, three authors independently identified the two items with the highest face validity among the five items from each scale with highest factor loadings in validation papers.\(^{108} 109 111\) Discrepancies were discussed and agreement was reached for all items.

‡Given the frequency of the daily measures (Td1–18), only a single item from each scale (MAAS, EQ, CPAS) is administered. In the selection of these single items, three authors consensually selected the item with the highest face validity out of the two items included in the session-by-session measures (Ts1–6).

§For session by session (Ts1–6), post-intervention (T2) and follow-up (T3), homework is assessed with four items related to the extent to which participants conducted homework since the last session. For daily measures (Td1–18), homework during the last 24 hours is assessed with a single item.

BPI, Brief Pain Inventory; CPAS, Chronic Pain Acceptance Scale; EQ, Experiences Questionnaire; FCRI-SF, Fear of Cancer Recurrence Inventory Short Form; HADS, Hospital Anxiety and Depression Scale; MAAS, Mindful Attention Awareness Scale; No, number; NRS, Numerical Rating Scale; PCS, Pain Catastrophizing Scale; SF-MPQ-2, Short-Form McGill Pain Questionnaire; Td1–18, daily measures, days 1–18; Ts1–6, session-by-session measures, sessions 1–6; WAI-RS, Working Alliance Inventory Revised Short Form; WHO-5, WHO 5-item Well-Being Index.
and MJ, independently identified the two items with the highest face validity among the five items from each scale with highest factor loadings in validation papers.\textsuperscript{108, 109, 111} Discrepancies were discussed and agreement was reached for all items. Given the frequency of the daily measures, only a single item from each scale (MAAS, EQ, CPAS) is administered. In the selection of these single items, CB, MSO and MJ consensually selected the item with the highest face validity out of the two items included in the session-by-session measures.

**Moderators**

Treatment expectancy is assessed using a single question (‘To what extent do you believe that participation in the present study will reduce your pain and increase your overall well-being?’). A higher score indicates a stronger expectation that the intervention will lead to a positive outcome. For session by session (Td1–6), post-intervention (T2) and follow-up (T3), homework is registered using the following four items: (1) ‘Have you conducted homework since the last session? (yes/no), (2) ‘Which exercises did you use in your homework?’ (mindful attention/decentring/values and committed action), (3) ‘How many days did you conduct homework during the last week?’ and (4) ‘On average, how many minutes did you perform homework?’ For daily measures (Td1–18), homework during the last 24 hours is assessed using a single question (‘To what extent did you conduct your homework during the last 24 hours?’). Therapeutic alliance is measured at post-intervention (T2) using the Working Alliance Inventory Revised Short Form (WAI-RS) total score,\textsuperscript{112} with a higher score indicating a stronger therapeutic alliance. The WAI-RS total scale has proven good internal consistency (\(\alpha=90\)).\textsuperscript{113}

**Demographic and clinical outcomes**

In addition to the self-report measures, participants’ clinical data will be obtained by data extractions from the DBCG, including age, menopausal status, disease characteristics (e.g., tumour size, endocrine receptor and HER2 status) and treatment-related characteristics (e.g., type of surgery and adjuvant therapy).
Treatment adherence

Video recordings of all treatment sessions will be used to rate the integrity of the treatment components. Two trained raters will independently code 25% randomly selected sessions of each of the three components, that is, mindful attention, decentering, and values and committed action. A treatment fidelity sheet assessing the extent to which a therapist adheres to the treatment component will be used.

Data analysis

The primary analyses will evaluate the main effect of the three individual treatment components (ie, time×group). This will be tested based on the intent-to-treat sample using multilevel models, with pain intensity and pain interference as the primary outcomes across time (from baseline (T1) to post-intervention (T2), including session-by-session measures). Main effects will be tested as repeated measures two-way interactions, that is, time×group, where group is operationalised as the conditions in which a given component is given (+) versus conditions in which a given component is not given (−) (cf. figure 2). Accordingly, the main effect (ie, time×group) of, for example, the mindful attention component, is established by the mean of conditions 1–4 (minus (−) mindful attention) compared with the mean of conditions 5–8 (plus (+) mindful attention) over time (figure 2), and the same subject will thus be a control subject for one factor and a treatment subject for another factor.

In secondary analyses, we will investigate the effects on secondary outcomes, and it will be explored if the detected effects on both primary and secondary outcomes are contingent upon the proposed moderators, as well as relevant demographic and clinical outcomes, including age, menopausal status, and disease-related and treatment-related characteristics. We will also evaluate the main effects (ie, time×group) of specific combinations (eg, mindful attention and decentering), order of components (eg, first mindful attention, then decentering, or the other way around) and number of components (ie, 1, 2 or 3), and we will examine whether possible effects of the components are maintained over time (ie, from baseline (T1) to follow-up (T3)).

If main effects (ie, time×group) are detected, they will be followed by lower-level mediation analyses, testing if the effects on outcomes are statistically driven by the corresponding processes (ie, expecting that the effect of mindful attention is mediated by mindful awareness (MAAS), the effect of decentering is mediated by decentering (EQ), and the effect of values and committed action is mediated by pain acceptance and activity engagement (CAPAS)).

For the daily measures, multilevel models (MLMs) will evaluate associations between on the one side daily practice and targeted processes and pain outcomes on the other.

Statistical power and sample size

The criteria for a treatment component to be considered efficacious are (1) a statistically significant (p<0.017) effect (ie, time×group) on at least one of the two primary outcomes, (2) corresponding to an effect size of d≥0.30, cf. previous effect sizes found in meta-analyses.25 30 31

The online software G*power115 116 was used to calculate statistical power. To reach a statistical power of 0.90 to detect an effect (ie, time×group), with an effect size of d=0.30 and adjusting the α level for three primary tests (ie, multiple comparisons; one test per treatment component), the number needed to include is 185 (including an anticipated dropout rate of 20%). With reference to the eight conditions, cf. figure 2, we thus aim to include 192 participants, corresponding to 24 per condition.

Patient and public involvement

Prior to submission of the present study protocol, a feasibility study was conducted with the aim of evaluating the feasibility, acceptability and pre/post-changes (ClinicalTrials.gov Registry: NCT04841928) (manuscript under preparation). The feasibility study included both qualitative data (individual semistructured interviews) and quantitative data (self-report questionnaires; using the same outcomes and assessment points as in the present study, with the exception of the 3-month follow-up (T3), which was not included in the feasibility study). The qualitative data were included to obtain in-depth data on participants’ experiences with study participation and evaluate the treatment components by identifying (1) helpful and unhelpful intervention elements, and (2) whether participants experienced the treatment components as intended. No major adjustments of the treatment components and the study set-up were implemented based on the results of the feasibility study.

ETHICS AND DISSEMINATION

Ethics and registration

The present project is preregistered at ClinicalTrials.gov (NCT05441401). Ethical approval of the study was obtained from the Central Denmark Region Committee on Health Research Ethics (reference number: 1-10-72-309-20). The project is registered at Aarhus University’s internal register of research projects, and data are handled with legal basis in GDPR Article 6, pc 1, litra (e) and the Danish Data Protection Law § 10, pc 1. Participants in the project receive information about the legal basis for handling data in accordance with the duty to report in GDPR Article 13 and Article 14.

Adverse events

While participation in the project may give rise to mild, temporary discomfort during the sessions by focusing on bodily sensations, we expect that each of the three treatment components will have a positive effect on pain. All included participants are screened for suicidal risk. If a participant shows unexpected severe discomfort and/or risk of suicidal behaviour, the study coordinator (CB) will evaluate whether study participation needs to be
suspended and, if necessary, advise the participant to contact her general practitioner.

**Dissemination**

Findings will be made available to the study funders, care providers, patient organisations and other researchers at international conferences and in international, peer-reviewed journals.

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**Contributors**

CB is the study coordinator, drafted the present manuscript and revised the manuscript based on feedback. MJ led study concept and design, obtained funding for the study, wrote the initial study protocol and co-drafted the present manuscript. RZ is the principal investigator of the study, and RZ and MSO contributed to the development of study concept and design, and provided critical revision of protocol drafts. ABJ, AHW, AS, YF and CJ contributed conceptual and methodological insights and decisions, and provided critical revision of protocol drafts. All authors read and approved the final manuscript.

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**Disclaimer**

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**Competing interests**

None declared.

**Patient and public involvement**

Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

**Patient consent for publication**

Not required.

**Provenance and peer review**

Not commissioned; externally peer reviewed.

**Supplemental material**

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