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STUDY PROTOCOL

Pre- and post-operative psychological interventions to prevent pain and fatigue after breast cancer surgery (PREVENT): Protocol for a randomized controlled trial

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Abstract

Background

Breast cancer is the most common cancer type among women worldwide with over a million new cases each year. More than 40% of these women will struggle with chronic pain and fatigue after surgery, regardless of surgical procedure. These consequences are detrimental and result in distress and disability, including work disability. Few attempts have been made to prevent chronic pain and fatigue after surgery by applying a psychological approach, despite psychological risk factors being crucial in the development of both chronic pain and fatigue. In this study, we aim to develop and test an easily implementable strategy of preventing chronic pain and fatigue after breast cancer surgery. The intervention strategy involves a pre-operative hypnosis session and a web-based post-operative Acceptance and Commitment Therapy (ACT). The hypnosis has previously been found effective in alleviating acute post-operative pain and fatigue in breast cancer patients, while ACT is well suited to cancer populations as it offers a model of healthy adaptation to difficult circumstances. Together they form an intervention strategy with both a preventive and a rehabilitative focus.

Methods/Design

This randomized controlled trial aims to estimate the effects of the pre- and post- operative interventions compared to attentional control and treatment as usual (TAU) and will also include a qualitative process evaluation. Participants will be randomized to receive either a pre-operative brief hypnosis session and a post-operative web-based psychological intervention (iACT) or a pre-operative one-session mindfulness through an audio file and post-operative TAU. Self-reported questionnaire data and biomarker data will be assessed pre-surgery, post-surgery and 3 and 12 months after surgery. In addition, we will assess registry data on sick leave and prescriptions until 2-year follow-up. In the qualitative process evaluation, data will be collected from participants from both study arms (through interviews and a

(contact via https://www.nsd.no/en/find-data). Through this portal, researchers can apply for access to the data. NSD will in collaboration with our data access committee be responsible for reviewing requests and providing access to the anonymous data. The Data Access Committee includes Silje Endresen Reme (siljerem@uio.no), Henrik Børsting Jacobsen (h.b.jacobsen@psykologi.uio.no), Lars-Petter Granan (largra@ous-hf.no) and Tone Marte Ljosså (Tone.Marte.Ljosaa@usn.no).

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Abbreviations: ACT, Acceptance and Commitment Therapy; CPSP, Chronic Post-Surgical Pain; EQ-5D, European Quality of Life– 5 Dimensions; QoL, Quality of Life; RCT, Randomized Controlled Trials; TAU, Treatment As Usual.

diary) and two different analyses performed (socio-narrative and Grounded Theory) with the objective to describe the development of chronic post-surgical pain and fatigue and the potential influence of the interventions on these processes. The study is set-up to demonstrate a minimum difference in pain of 1 point on NRS (0–10) and 3 points on FACIT-F (0–52) between the groups at 3-months follow-up by including 200 breast cancer patients in total.

Discussion

This trial will be the first study to estimate the effect of a combined pre-operative hypnosis with a post-operative iACT to prevent pain and fatigue after breast cancer surgery. The results from our study might i) help the large group of women affected by chronic pain and fatigue after breast cancer surgery, ii) shed light on the mechanisms involved in chronic pain and fatigue development, and iii) serve as a model for other surgical procedures.

Trial registration

Clinicaltrials.gov, registration number NCT04518085. Registered on January 29th, 2020. https://clinicaltrials.gov/ct2/show/NCT04518085.

Background

Late effects from breast cancer

Breast cancer is the most prevalent cancer type among women, with >1 million new cases worldwide every year [1]. Survival rates are increasing [2], but for many patients survivorship is also characterized by disabling psychological and physical late effects [3–5].

Chronic post-surgical pain (CPSP) and chronic fatigue are most prevalent. CPSP has prevalence rates ranging from 25–60% depending on definition, measurement and treatment [6]. In a recent Norwegian study, more than 40% of women treated for breast cancer continued to have pain 2–6 years after surgery [7], while over a third of the women in a large Danish study reported chronic pain 5–7 years after surgery [8].

Chronic fatigue after surgery

Chronic fatigue is the most common symptom associated with cancer and its treatments [9,10], and is usually operationalized as fatigue lasting 6 months or longer [11]. Despite a high prevalence of chronic fatigue, studies on the occurrence of and predictors of fatigue after surgery are scarce. One of the few studies investigating chronic fatigue after breast cancer surgery reported high levels of fatigue in the first two months after surgery, followed by mild-to-moderate levels of fatigue that persisted 12 months after surgery [12]. In another study of breast cancer survivors, a third of the women struggled with chronic fatigue up to 10 years into survivorship [13].

Chronic pain after surgery. Surgery as a major risk factor for chronic pain was first identified in 1998 [14], but has since received increasing attention and priority [15]. Chronic post-surgical pain has been defined as pain that persists at least 3 months after surgery, localized to the surgical site or referred area, and not explained by other causes [16,17]. The pathophysiology of CPSP is still unclear. Presumably, the nature of most CPSP is neuropathic since surgery

(e.g., mastectomy) may involve major nerve damage, and is associated with the highest incidence of such pain [16,18]. However, many patients with CPSP do not show any signs of neuropathic pain, or any sensory changes [3]. It is thus assumed that the distinct pathophysiology reflects both peripheral and central sensitization as well as humoral factors contributing to pain [19], and CPSP is now grounded in the bio-psycho-social model, where psychological and social factors contribute to biological factors in the development of chronic pain [20,21]. Interestingly, there are several shared risk factors between pain and fatigue after surgery, including depression and outcome expectancies [22], implying that the very same processes might influence both post-surgical pain and fatigue.

Risk factors

Documented risk factors for CPSP can be divided into more or less modifiable factors. Female gender, younger age [18] and preoperative pain conditions [16,18,21,23] are the most commonly reported unmodifiable risk factors, along with pre-operative use of opioids [21] which is also on the less modifiable side. However, a preventive intervention could target psychological factors, which are both modifiable, robust, and potent predictors of CPSP and fatigue [20,24]. The most frequent tap into anxiety, such as hypervigilance and pain catastrophizing [24–28]. Other significant predictors involve depression, stress, and optimism [12,20,27].

Theoretical model

Our research group recently developed a theoretical model for CPSP following breast cancer surgery (the surgery outcome expectancy model of CPSP, "SURGE") [19]. The key principles in the SURGE model builds on the cognitive activation theory of stress [29], predictive coding accounts [30], and well-established psychoneuroimmunological processes. The SURGE proposes that pain and stress in response to surgery are appraised through learned patterns of responses and what these responses will accomplish, response outcome expectancies. Negative response outcome expectancies sustain the activation of the physiological stress response and increase the risk of CPSP through pathophysiological mechanisms such as central sensitization, cortisol dysfunction, impairment of corticolimbic connectivity and inflammatory induced sickness behavior.

Hypnosis

Hypnosis is a non-pharmacotherapeutic technique that holds promise as a harmless and effective pre-operative intervention to alleviate acute post-surgical pain and fatigue [31,32]. Clinical research with at least 20 different surgical populations has indicated that hypnosis can reduce the need for medication, reduce post-surgical symptoms, and enhance recovery [32]. Furthermore, meta-analyses [33], narrative reviews [34,35], and randomized clinical studies [36–39] all support the potential clinical utility of hypnosis with surgical patients. A rigorous trial from the US demonstrated particularly promising results [40]. In that trial, a brief hypnosis session before breast cancer surgery had an impact on the patients' need for pain medications and the level of postoperative pain, nausea, exhaustion, and discomfort, with moderate to large effect sizes. However, a French study, following a similar protocol but with some deviations from the American study, was not able to reproduce the effects [41]. As such, there is a need for rigorous replication studies in different contexts. Moreover, no studies have so far investigated long-term effects of preoperative hypnosis, and whether it could in fact contribute to prevent acute post-surgical pain from turning chronic.

Acceptance and Commitment Therapy (ACT)

ACT is an evidence-based treatment for chronic pain [42,43] and is also a good fit for treating chronic fatigue [44]. ACT is well suited to cancer populations as it offers a model of healthy adaptation to difficult circumstances and has shown promise in the treatment of opioid misuse [45]. The goal of ACT is to increase psychological flexibility by reducing the influence from cognition and language when it produces an inability to persist or change in the service of long term valued goals. Psychological flexibility has been defined as the process of being in the present moment while persisting or changing behavior in accordance with chosen values [46]. There have been several calls to expand the scope of ACT interventions to the treatment of CPSP [47]. In a recent initiative, ACT was applied as treatment for CPSP in The Toronto General Hospital, with preliminary promising results. Those receiving ACT demonstrated greater reductions in opioid use and pain interference, as well as reductions in depressed mood, compared to those who received treatment as usual [48,49]. In addition to being an evidence-based treatment for pain and fatigue, ACT is also among the very few psychological treatments with documented effects on return-to-work [50]. Moreover, in a recent Norwegian study, a small-scale ACT follow-up intervention consisting of 1–6 phone calls, eased patients transition into the workplace [51].

Even though both CPSP and chronic fatigue are common consequences of breast cancer surgery [7,52], with disabling effects on recovery outcomes and quality of life, hardly any studies have looked at preventive interventions from a psychological perspective. As psychological risk factors are substantial, and the pathophysiology of both conditions largely unknown, interventions focusing on the psychological factors are largely needed.

Methods/Design

Study design

The PREVENT trial is designed as a randomized controlled, surgeon and statistician blinded superiority trial with two parallel groups and a primary end point of self-reported pain and fatigue 3 months after surgery. Randomization will be performed as block randomization with a 1:1 ratio. Participants are randomized to an intervention group including pre-operative hypnosis and post-operative web-based ACT (iACT), or a control group including pre-operative mindfulness and post-operative treatment as usual (TAU). We will thus be able to assess the short-term effectiveness of the pre-operative hypnosis alone, and the long-term effects in combination with the post-operative iACT. The aims are pursued with mixed methods, including an effect evaluation and a process evaluation.

Study setting

The PREVENT trial is a single center trial placed in Oslo, Norway, in a large university hospital (Oslo University Hospital, Aker). In the Department of Breast and Endocrine Surgery, more than 400 breast cancer surgeries are performed every year.

Aims and objectives

The overall aim of the study is to develop and test an easily implementable strategy of preventing chronic pain and fatigue after breast cancer surgery. The intervention strategy involves a pre-operative hypnosis session and a post-operative, internet-based Acceptance and Commitment Therapy (iACT). Together they form an intervention strategy with both a preventive and a rehabilitative focus. The PREVENT trial is designed to answer the following questions:

Primary objectives.

1. Will pre-operative hypnosis + iACT lead to less pain and fatigue 3 months after surgery compared to an attentional control?
2. Is hypnosis more effective than an attentional control in alleviating side effects from surgery? A replication study.

Secondary objectives. The following research questions are exploratory but will be guided by previous findings and our theoretical model targeting secondary effects of treatment. Compared with our attentional control:

1. Will hypnosis impact levels of high sensitive c-reactive protein (hs-CRP) 3–4 weeks after surgery?
2. Will the potential effects of hypnosis in alleviating side effects sustain 3–4 weeks after surgery?
3. Will hypnosis in combination with iACT result in fewer prescriptions for pain and psychotropic medication in the 12 months after surgery?
4. Will hypnosis combined with iACT be favorable in a cost-utility analysis and result in fewer days of sick leave the following year after surgery?
5. Will hypnosis + iACT lead to increased psychological flexibility at 1-year follow-up?

In addition to secondary effects of treatment, we have the following research question exploring potential mechanistic pathways of pain and/or fatigue after surgery:

6. Does long-term stress (hair cortisol concentration), low grade inflammation (hs-CRP) and/or immunological reactivity (TruCulture supernatant) independently or in combination explain the development of chronic pain and/or fatigue after surgery?

Further, the following research questions explore the study cohort in terms of modifiable risk factors and novel predictors of pain and fatigue after surgery: Do biopsychosocial factors predict acute and sub-acute pain in our control group?

7. Do biopsychosocial factors predict acute and sub-acute pain in our control group? More precisely, do surgical procedure, presurgical pain, anxiety, depression, negative response outcome expectancies and low social perceived support predict pain intensity and pain unpleasantness immediately after, and 4 weeks after surgery while controlling for age?
8. Are medical, psychological, or social variables at baseline the strongest predictors of CPSP and chronic fatigue 3 and 12 months after surgery?
9. What is the prevalence of surgical fear? Associations with biological and psychological variables and development of a risk profile.

Finally, the following research questions will be pursued in a qualitative process evaluation:

10. What types of lived narratives are associated with post-surgical pain and fatigue, and what types of narratives are associated with high quality of life and return to life as normal?
11. Are these narratives changed by the interventions, and if so, how?
12. How does pain catastrophizing fit into a person's overall narrative, and (how) is it changed by the interventions?

13. How do different forms of narratives contribute to developing or sustaining post-surgical pain or fatigue?

Hypotheses of efficacy.

1. Compared to attentional control, hypnosis + iACT will be superior in preventing chronic post-surgical pain and fatigue 3 months after surgery.
2. Compared to attentional control, hypnosis will be superior in alleviating side effects from surgery.

Measurements. Patient reported outcome measures (PROM) will be collected through a battery of 10 validated questionnaires, all relevant to the various aspects of breast cancer surgery and the post-surgical trajectories. It will be given to the participating women at baseline and at 3- and 12-months follow-ups. To secure high compliance, participants will receive 4 weekly reminders to fill out the questionnaires. The reminders will be sent both as a text message and through email. Our user representative reviewed an earlier version of the questionnaire package and provided input before it was finalized. Estimated time of completion is 15–20 minutes. See Fig 1 for a detailed overview of the schedule of enrolment, interventions, and assessments.

Primary outcome measures. *Chronic post-surgical pain*. CPSP will be measured through the Numeric Rating Scale (NRS) for pain intensity. The NRS is a discontinuous, self-report measure. It consists of a single item, in which the respondent is asked to rate the intensity of pain. This rate is done on an 11-point scale ranging from 0 (no pain) to 10 (worst pain imaginable). In the context of pain, the NRS has been proven to have good reliability and validity [53,54]. It is a valid measure of pain intensity (0–10) that is less influenced by present mood state [55], and has been widely used to assess post-surgical pain in previous studies of women with breast cancer [3,7,8,56]. In the PREVENT trial, participants will be asked to rate their pain intensity in and around the surgical site and referred area (breast, axilla and arm), in line with the definition of CPSP [16]. They will be given a total of 4 NRS questions about pain intensity in the breast, axilla, arm, or other parts of the surgical area. In the main analyses of efficacy, CPSP will be analyzed as a continuous variable where the worst pain at any site indicates the highest numerical rating scale value (0–10) reported by the patient. This way of operationalizing CPSP after breast cancer surgery is in line with previous studies in the field [26,57].

Chronic post-surgical fatigue. Chronic fatigue will be measured through the 13-item Functional Assessment of Chronic Illness Therapy-Fatigue subscale (FACIT-F). The FACIT-F is a unidimensional self-report scale meant to assess fatigue and its impact on daily life. Consisting of 13 items, the scale asks the respondents to rate their level of symptom intensity on a 5-point scale ranging from 0 (not at all) to 4 (very much) as it applies to the past 7 days [58,59]. FACIT-F is a widely used measure of fatigue in breast cancer trials. It has demonstrated excellent internal consistency, high validity, and sensitivity to pick up change in patients with breast cancer [58]. The total score ranges from 0–52, with higher scores indicating less fatigue. A score of less than 30 indicates severe fatigue. In the PREVENT trial, the main analysis will involve a comparison of the total score (0–52) 3 months after surgery between the intervention and control group.

Secondary outcome measures. *Side effects from surgery*. A range of side effects from surgery will be assessed using the 100mm Visual Analogue Scales (VAS) after surgery, upon discharge, in line with the trial that we are replicating [40,60]. Both pain intensity and pain

	STUDY PERIOD							
	Enrolment	Allocation	Post-allocation					Close-out
TIMEPOINT**	$-t_1$	0	t_1	t_2	t_3	t_4	t_5	t_6
	2-20 days before surgery	2-20 days before surgery	Pre-surgery	Post-surgery	3 weeks	3 months	1 year	2 years
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Allocation		X						
Enrolment: qual. process evaluation					X	X		
INTERVENTIONS:								
Hypnosis			X					
Mindfulness			X					
iACT					—	—	—	—
ASSESSMENTS:								
Sociodemographic + clinical variables	X					X	X	
Biomarker: Hair, cortisol	X							
Biomarker: Blood, stress reactivity	X							
Biomarker: Blood, hsCRP	X				X			
Medical data from surgery				X				
Widespread pain questionnaire	X							
NRS pain expectation	X							
Surgical Fear Questionnaire	X							
Life Orientation Test (LOT-R)	X							
HADS anxiety and depression	X					X	X	
PCS – pain catastrophizing	X							
Bergen Insomnia Scale	X						X	
RTW expectations	X							
Job satisfaction	X					X	X	
AAQ-II	X					X	X	
Social Support	X					X	X	
IEQ – injustice	X					X	X	
EORTC QLQ-BR23	X					X	X	
FACIT-F	X					X	X	
VAS side effects	X			X	X			
PGIC						X	X	
NRS chronic post-surgical pain						X	X	
Registry data, prescriptions & sick leave		—	—	—	—	—	—	—
Usage statistics of the iACT					—	—	—	—
Qualitative interviews/diaries					X	X	X	

Fig 1. Schedule of enrolment, interventions, and assessments.

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unpleasantness will be assessed to capture its sensory and affective dimensions. The VAS is a continuous, self-report measure comprised of either a horizontal or vertical line measured at exactly 100 mm. The line is anchored by verbal descriptors, and the respondent is asked to rate the intensity of their symptom by making a mark on the line. The distance between the end of the line, representing absence of the symptom, and the mark will be measured and a score ranging from 0 to 100 will be recorded. Similar to the NRS, the VAS can be used on a variety of symptoms and will here be used to assess pain intensity, pain unpleasantness, fatigue, nausea, discomfort and emotional upset [53].

The European Organization for Research and Treatment-QOL questionnaire for breast cancer specific module (EORTC QLQ-BR23). The EORTC QLQ-BR23 is a health-related quality of life measure specifically designed for women with breast cancer. It consists of 23 items, each asking the respondent to indicate the extent to which they have experienced certain symptoms or problems on a 4-point scale ranging from 1 (not at all) to 4 (very much) [61]. It has been shown to have high reliability and clinical and cross-cultural validity as a measure of quality of life in patients with breast cancer [61]. This measure was specifically included upon recommendation from our user representative, and is measured at baseline, 3- and 12 months follow-up.

Hospital Anxiety and Depression Scale (HADS). The HADS scale is a measure of anxiety and depression specifically designed for patients with physical illness by excluding somatic items [62]. It includes 14 items that are equally divided into two subscales: depression and anxiety. Respondents are asked to respond on a 4-point scale ranging from 0 to 3. Consequently, each subscale has a possible score of 0–21, and a cutoff score of 8 or more on both subscales has previously been reported to give an optimal balance between sensitivity and specificity ($\sim$0.80 for both subscales) according to DSM-III, DSM-IV, ICD-8, and ICD-9.29 [63]. However, in a recent meta-analysis a HADS-D cut-off value of seven or higher were found to maximise combined sensitivity and specificity [64]. The cut-off will therefore be 7 in the current study. HADS has demonstrated high reliability and validity across studies [63], and is in the current study included at baseline, 3- and 12-months follow-up.

Patient Global Impression of Change (PGIC). The Patient Global Impression of Change aims to measure the patient's subjective experience of change in function, symptom and quality of life over time, and are meant to reflect the patient's belief about the efficacy of the ongoing intervention (i.e., "feeling better" or "feeling worse") [65]. The PGIC is constructed of a 7-point scale where patient rate their change as "very much improved", "much improved", "minimally improved", "no change", "minimally worsened", "much worsened" and "very much worsened" and is measured at 3- and 12 months follow-up. In studies of pain populations, it has been demonstrated that the "much improved" and "very much improved" ratings indicate moderately important and substantial improvement [66], and PGIC has also shown clinical relevance in daily clinical practice [67].

Acceptance and Action Questionnaire (AAQ-II). consists of 7 items measuring levels of acceptance and avoidance of unpleasant thoughts and feelings [68]. The items are scored a 7-point scale ranging from 1 (never true) to 7 (always true). The AAQ-II has showed good reliability and validity across a range of linguistic and clinical populations, including Norwegian samples and among patients with breast cancer [69,70], and will be measured at baseline, 3- and 12-months follow-up.

Perceived social support. Perceived social support is operationalized based on the conceptual framework on social relations as described by Due et al. [71] and as formulated as specific questions by Skovbjerg et al [72]. The structure is meant to measure the emotional support and practical assistance expected to be available, by asking the following question "will any of the following people help or support you in everyday life, if you need it?" in regard to

"partner", "family", "friends", "colleagues", or "neighbors". For the current study, we decided to include a sixth option; "others", to the list of possible sources of support. Patient rate the perceived social support of these relations respectively using a 6-point scale ranging from 1 (always) to 6 (never or have none) [72]. Social support will be measured at baseline, 3- and 12-months follow-up.

Injustice Experience Questionnaire (IEQ). The IEQ is a 12-item measure meant to assess the respondent's experience of injustice [73]. Injustice encompasses the degree of blame as well as the magnitude and irreparability of loss related to their health condition. The items therefore consist of thoughts and feelings related to injustice. Respondents are asked to rate their experience of injustice on a 5-point scale ranging from 0 (not at all) to 4 (all the time) [73]. The scale has been translated and validated in Norwegian [74]. In the PREVENT trial we slightly adjusted the wording in the scale instruction to make it fit patients diagnosed with breast cancer. Further, to minimize the burden of filling out long questionnaires in a vulnerable situation, we constructed a short version of the IEQ with 5 items. The 5-item version of the scale ranges from 0–20 and have a mean of 8.3 (SD 5.7). These numbers are based on data from 3170 patients with various chronic pain conditions. As a test of validity, the Pearson correlation between the 5-item version of the IEQ and the total score of the full version of PCS was tested: $r = 0.703$ ($p < .01$). This is similar to the correlation between the full scales of each measure ($r = 0.721$) and is as such an indication of scale validity. IEQ is measured at baseline, 3- and 12-months follow-up.

Bergen Insomnia Scale. The Bergen Insomnia Scale (BIS) will be used to assess insomnia symptoms. This questionnaire consists of six items, of which the first four pertain to sleep onset, maintenance, early morning wakening insomnia, and not feeling adequately rested after sleep, corresponding to the DSM-IV criterion for insomnia [75]. The last two items assess level of daytime impairment due to sleepiness and satisfaction with sleep, corresponding to the DSM-IV criterion B [75]. Each item is rated on average occurrence from 0–7 days per week, giving a possible total sum score from 0 to 42. The Bergen Insomnia Scale has shown high reliability and validity in both patient and community samples [76]. Insomnia will be measured at baseline and 12 months follow-up.

Registry data. Registry data on employment and benefit take-up and medical prescriptions will be obtained from the Norwegian Labor and Welfare Administration (NAV) and the Norwegian Prescription Database (NorPD), respectively. To be able to assess for the effects of the interventions, data from NorPD and NAV will be obtained from two years prior to inclusion in the trial until one year follow-up. The NorPD contains data about dispensed drugs in Norway, while NAV-data contains social security micro data for research. These data will be obtained retrospectively.

Biomarker variables. *Stress reactivity*. The immune functional assay will consist in collecting whole blood samples using the standardized TruCulture system (Myriad RBM, Austin, Texas, USA) directly containing immunogenic stimuli. There are two tubes, one containing a control medium (Null tube) and the other lipopolysaccharides (LPS) at 100 ng/mL (from Escherichia coli O55:B5). Immune function is to be assessed by analyzing the supernatant fluid. TruCulture® reproducibly reveals the induced innate and adaptive immune response in whole blood after stimulation, by quantifying the release of soluble immune activation products (cytokines, chemokines, soluble receptors etc.) in the supernatant and by measuring the transcription level (mRNA) in the circulating blood (immune) cells [77]. TruCulture samples will only be collected pre-surgery and investigated as a possible predictor of chronic pain and fatigue.

Low-grade systemic inflammation (hs-CRP). The high sensitive CRP (hs-CRP) test accurately measures low levels of CRP to identify low but chronic levels of inflammation. It

measures CRP in the range from 0.5 to 10 mg/L. Non-fasting serum samples will be drawn from all participants both pre- and post-surgery (3–4 weeks after surgery) and analyzed at the Department of Laboratory Medicine at Aker Hospital in Oslo, Norway.

Hair cortisol. For a few years now, a new and very different method to measure cortisol exposure in humans has been developed; the extraction of cortisol from human hair, with major advantages involving the non-invasive nature, the standardized sampling, and most importantly, the possibility to use hair as a retrospective biomarker of cortisol exposure [78]. Hair grows approximately one centimeter per month, thus making it possible to show the average long-term activity of the HPA-axis, as well as compare hair segments/months with each other (e.g., before and after stressful events). Another advantage is that hair cortisol reflects the amount of free unbound cortisol, which is unaffected by oral contraceptives [79].

Background variables and clinical characteristics. Besides from demographic characteristics such as age, education, occupational status, marital status and number of children, the following variables will be measured at baseline:

Clinical data. Clinical information prior to surgery will be collected by the study nurses during the inclusion appointment. This includes information on height, BMI, smoking, number of previous surgeries (in breast area, and other areas of the body), previous diagnoses of cancer or any chronic pain conditions. Patient charts will be used to collect data on surgical procedures and potential complications during/after surgery. This will include information about the duration of the surgery, tumor-related variables, severity of acute post-surgical pain, and other relevant intra-operative variables, such as type of surgical procedure (i.e., breast conserving surgery, mastectomy, breast reconstruction, sentinel node biopsy, axillary lymph node dissection, nerve blockage and surgical drain), and if there have been any surgical complications. Further, it is noted if patients have received neo-adjuvant treatment, and if their surgery is performed as a day case or requires post-surgical hospital admittance. Medications used during/after surgery is also recorded. This involves intraoperative use of analgesics for pain control and of sedatives, as well as postoperative use of medications for pain control. These are in line with the outcomes reported in the trial we are replicating [40].

Widespread pain questionnaire. As a measure of pre-existing pain we used a modified version of the Fibromyalgia Survey Diagnostic-2016 criteria (FSD-2016 criteria) [80] translated and validated for Norwegian participants [81]. The modified questionnaire asks about pain in the four quadrants of the body (left upper, left lower, right upper, right lower), if this has persisted for more than 3 months and if it is bothersome, it also covers head and visceral pain to exclude this from the picture, giving a short and pragmatic index of chronic widespread pain.

The Pain Catastrophizing Scale (PCS). The PCS is a self-report measure of catastrophizing. The scale assesses elements of rumination, magnification, and helplessness in response to pain [82]. Responders rate items on a 4-point Likert scale ranging from 0 (not at all) to 4 (all the time). To decrease responder burden, this study uses the short version of the scale (PCS-4). PCS-4 has been validated in surgical [83] and chronic pain populations [84].

Pain expectations. A single item is used to assess how much pain the women expect to have after surgery. A single-question approach has previously shown high predictive validity after cesarean delivery [85]. The participant will be asked to rate the intensity of pain she expects to have after surgery on an 11-point scale ranging from 0 (no pain) to10 (worst pain imaginable).

Return to work expectations (RTW). Return-to-work expectations (RTW-expectations) is assessed by asking participants to respond to the following statement: "I expect to return to work within the next few weeks". Responses are given on a five-point Likert scale ranging from "strongly agree" to strongly disagree". In line with previous studies, we will trichotomize the variable in to positive, uncertain, or negative RTW-expectations [86,87]. This single item measure of RTW-expectations has been demonstrated to be a strong predictor of non-RTW in

populations with similarities to the current, such as people on sick leave due to chronic low back pain [88], and people struggling with work participation due to common mental disorders [86].

Job satisfaction. Job satisfaction will be assessed with two single items used in several previous trials [e.g., 89]. The first item asks participants how satisfied they are with their overall job situation, where they indicate their response on a Likert scale from "very satisfied" to "not satisfied at all" or "not currently working". The second item asks what job they would choose if they could choose again, with the alternatives "would choose my current job", "would choose not to work at all" or "would choose a different job than the one I have now". Job satisfaction is measured at baseline, 3- and 12-months follow-up.

The Surgical Fear Questionnaire (SFQ). The SFQ is a reliable and valid self-report instrument designed to assess fear of surgery, and it consists of 8 items which is scored on an 11-point scale ranging from 0 (not at all afraid) to 10 (very afraid) [90]. The items target different fears concerning surgery, namely fear of operation, anaesthesia, postoperative pain, side effects, health deterioration, failed operation, incomplete recovery, and long duration of rehabilitation. The structure of the SFQ can best be described by a two-factor model, in which two subscales can be distinguished: fear of immediate consequences of surgery and fear of the long-term consequences. We translated the scale to Norwegian through a forward-back-translation procedure.

Life Orientation Test–Revised (LOT-R). The LOT-R is a 10 item self-report test meant to assess dispositional optimism. The respondents are asked to rate their agreement to various statements on a 5-point scale ranging from 0 (strongly disagree) to 4 (strongly agree). Three of the items assess optimism, three assess pessimism, and the remaining four are filler items that are not meant to be included in the scoring [91]. A validated Norwegian version of the scale will be used in the current study [92].

Data collection and procedure

A flow chart detailing the data collection and procedure of the trial is presented below (Fig 2).

Before surgery. Patients scheduled for breast cancer surgery at the Department of Breast and Endocrine Surgery, Oslo University Hospital, Aker, receive oral and written information about the PREVENT trial from the doctors or nurses responsible for their treatment. This usually happens at their first regular consultation at the hospital, following diagnosis. If patients are interested in participating, they immediately or within the first following days and prior to surgery receive a consultation with a study nurse. The study nurse provides the patients with information about the study and go through the inclusion- and exclusion criteria. Patients who are eligible and want to participate sign the informed consent form, in which case the study nurse introduces the patients to the online data collection platform, VieDoc^{TM}, which includes the questionnaires (PROMs) that must be filled out (once before surgery, 3- and 12 months after surgery). The questionnaires can be filled out at home using the patient's own electronic devices (VieDocME^{TM}). In VieDoc^{TM}, patients are automatically randomized (ratio 1:1) to one of two groups: Intervention (Pre-surgical clinical hypnosis and post-surgical iACT), or Control (pre-surgical mindfulness and post-surgical TAU). Further at this point, the study nurse collects hair and blood samples from the patients. At the day of surgery, patients in the intervention group are met by a trained specialist in clinical hypnosis, who provides the 20-minute hypnosis session. Patients in the control group are met by a study nurse, who plays a pre-recorded mindfulness session (13 minutes) delivered on an iPad with headphones. All treatments (hypnosis, mindfulness and iACT) take place in an undisturbed designated room at the hospital ward. The patients will receive the hypnosis/mindfulness sitting in a chair or

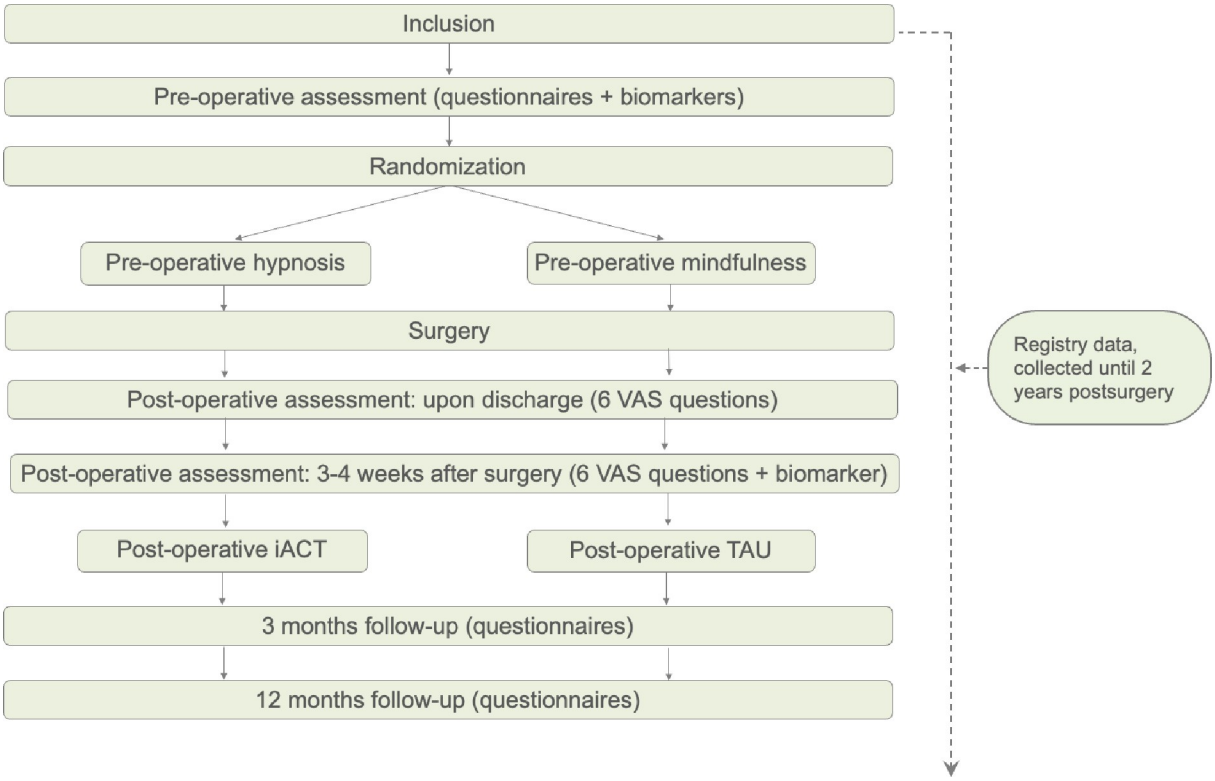

Fig 2. Flow chart of the study logistics and data collection.

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lying in a bed, depending in their own preference. Immediately after the treatment, patients are taken to the operating room receiving their anesthetic and surgical procedures.

Immediately after surgery. Post-surgery, after waking up and before discharge, the patient fills out six VAS questions on pain intensity, pain bothersomeness, fatigue, nausea, discomfort, and emotional distress. This is filled out with pen and paper, and the questions are identical to the questions used in the trial we are replicating [40].

3–4 weeks to 12 months after surgery. 3–4 weeks after surgery, as a part of a regular outpatient consultation at the hospital, a study nurse repeats blood samples and the six VAS questions. After the questions (PROMs) are answered, patients in the hypnosis + iACT group are introduced to the post-operative intervention (iACT) and instructed on how to use the iACT platform. Patients in this group can access the platform from home during the complete one year follow up period. All patients are reminded via e-mail to use VieDocME^{TM} to answer the follow up questionnaires 3- and 12-months after surgery. The 3-month timepoint where patients provide PROMs was chosen as this aligns with the time when CPSP is diagnosed. The 12-month timepoint of PROMs collection was chosen to align with previous studies on long-term follow-up.

Allocation. The allocation sequence is computed-generated by VieDoc^{TM}, where patients are randomized (ratio 1:1) to one of two groups: Intervention (Pre-surgical clinical hypnosis and post-surgical iACT), or Control (pre-surgical mindfulness and post-surgical TAU). Block sizes will vary between 4, 6 and 8. The study nurses in charge of enrollment do not have information about block sizes. As soon as a patient is enrolled and has completed the baseline questionnaire (PROMs), the allocation of that patient is generated automatically in VieDoc to the study nurse who then assign the patient to the intervention and inform about the procedure.

Blinding. Blinding of participants is not possible due to the character of the interventions. However, the following personnel will be blinded: The surgeons performing the surgery, the anesthesiologists and nurses, and the trial statistician, who is also the outcome assessor. The person who accompanies the patient to the surgical ward is instructed not to reveal the allocation to the health care personnel at the surgical ward. The participant is also instructed not to reveal which pre-operative intervention they received.

Drop-out and strategies for PROM data retention. Participants who no longer wish to participate in the study can inform the research group of their decision by notifying the study nurse, the trial coordinator, or the PI. The trial coordinator or the study nurse will in any case contact participants who drop out by phone and ask if they are willing to report the reason for withdrawal. If reasons are provided, these will be registered on a dedicated drop-out form. They will then be presented with the following options: First, they will get the option of discontinuing the interventions only but keep receiving the questionnaire follow-ups. If they do not wish to hear from us again, they will be registered as dropouts from the trial, but we will ask for permission to use already collected data, as well as follow them up with registry data. Lastly, if they wish to be completely excluded from the trial and have all their data deleted, we will adhere to that. Through this differentiated strategy we hope to retain as much PROMs data as possible from participants who drop out from the trial. Participants who drop out of the study will still be included in the intention-to-treat (ITT) analyses, unless they required all their data deleted.

Data management. Data from all sources will be entered and stored on a secure server. The University has an approved system for that which we will use (TSD). When recruitment and data collection is concluded, data will be extracted from VieDoc and imported in to TSD where a designated data manager will clean the data and prepare them for analyses. A detailed data management plan is available for download [93].

Interventions

Pre-operative hypnosis. The pre-operative hypnosis protocol is identical to the study we are replicating [40]. The scripted session includes a relaxation-based induction, suggestions for pleasant visual imagery, suggestions to experience relaxation and peace, and specific symptom-focused suggestions. The intervention has been thoroughly translated and piloted in a previous study that showed both feasibility and acceptability of hypnosis in this context [94]. Trained psychologists and last-year psychology students will provide the hypnosis in a dedicated room in the hospital. Patients will be encouraged to use self-hypnosis on their own following the treatment session. The hypnosis lasts for 15–20 minutes and is provided within 2 hours prior to surgery. The patients will be invited to either sit in a comfortable chair or lay down in a bed during the hypnosis. After the session, the therapist or the study nurse follows the patient to the surgical ward.

Active control condition. Patients randomized to the control group will receive a mindfulness before surgery. The mindfulness session will be delivered through a pre-recorded audio file on a mobile phone with headphones. The audio file guides listeners through a 13-minute mindfulness session where they are invited to sit/lay down and pay attention to their surroundings, before being invited to notice their breath. The subsequent invitation is to count inhales and exhales until you reach 10, and then starting over again. The counting is prompted throughout the rest of the session until 13 minutes have passed. Recorded mindfulness meditation have shown significant effects on chronic pain and fatigue in breast cancer patients [95]. However, the referred studies all entail numerous sessions of mindfulness with some degree of therapist involvement. We therefore believe a single session of mindfulness delivered through an audio file, constitute an active and ethically sound control condition. The

patients will be invited to either sit in a comfortable chair or lay down in a bed during the mindfulness session. After the session, a therapist or the study nurse follows the patient to the surgical ward.

Comparison of interventions. *Pre-surgery intervention versus active control*. Hypnosis and mindfulness are commonly regarded as supplements or integrative parts of an ACT intervention [43]. They both start by focusing the patient's attention in similar ways but proceed to utilize that focused state into different means. The pre-operative hypnosis here is used with a specific purpose and intent of lessening pain and promote coping. The pre-operative one-session mindfulness has a specific purpose and intent to focus on one thing like the breath, sounds or the body. Thus, both techniques guide the patients experience and use suggestion, but the end goals are fundamentally different.

Criteria for discontinuing allocated interventions. Before the hypnosis and mindfulness session, patients are informed that they at any point, and without stating any reason, can disrupt the session. They are informed about the harmless nature of the interventions, with few or none reported side effects, but they are also informed that if they should experience any discomfort or other adverse events and wish to terminate the session, the treatment will be immediately terminated. The occurrence of potential adverse events will be registered by the therapist administering the treatments, as well as registered through PROMs (PGIC) at 3- and 12-months follow-up.

Post-surgical intervention. The post-surgical intervention is comprised of a web-based ACT intervention (iACT) with the cognitive activation theory of stress as theoretical vantage points [29]. The intervention consists of videos in combination with a work booklet targeting three main processes derived from the ACT hexaflex model [46], and delivered in a web based interface where a specific order of viewing is suggested, but not enforced. In the suggested order, the intervention has several videos that is built to involve the patient in a broadening of their perspective of what can constitute maintaining and debilitating factors when experiencing chronic pain and/or fatigue. These initial videos involve a biopsychosocial explanation of pain and fatigue, alongside an introduction to mindfulness, values-based living, and stress reduction through cognitive behavioral techniques.

The post-surgical intervention also involves the use of a hand-out booklet that serves as an addition to numerous videos presented to the participants. The videos are sorted in three categories aimed to communicate the six processes in a commonsensical way. The three categories are referred to as the tri-flex in the Focused ACT model [96], and consists of Aware (present-moment awareness and self-as-context), Open (Accept and defusion) and Engaged (values and committed action). Within the booklet there are written tasks corresponding to different videos and scenarios shown in the online intervention to approximate previous trials showing efficacy on chronic pain from a similar intervention [97].

Following the call of Bewick and colleagues [98] for a more standardized reporting of intervention content, iACT can be described as a web-based intervention targeting women undergoing breast cancer surgery. It is delivered in secondary care, free of charge, but currently only for this research project. Participants choose how much time to spend on the intervention and can use it for as long as they like (up to a year). Each video lasts approximately between 5 and 25 minutes. It has a strong theoretical foundation, based on the CATS-model as well as the ACT model. The interventions are not tailored and includes no counselor involvement. In terms of information architecture [99], the intervention has a matrix design (participants can navigate freely), with topically organized content.

After the last PROMs data collection, at 1 year follow-up, participants in the control group will be offered access to the iACT platform.

Adherence to intervention protocols. Regular supervision will be conducted with the therapists conducting the pre-operative hypnosis to secure compliance to the protocol, and every second hypnosis session is audio recorded for quality assurance. We plan to review a random selection of audio recordings, at least 20% in total, to assess adherence to the hypnosis script. To assess adherence to the post-operative intervention, we will have statistics on each participant's program use, measured by what videos/audio files they have seen/listened to, and how many times they have accessed the various content.

Concomitant care. All participants in the trial will receive care as usual in addition to the interventions that they receive in the PREVENT trial. This could involve medical treatment such as chemotherapy, radiation, endocrine treatment etc., as well as psychological treatment and support. There are no treatment restrictions attached to participation in the PREVENT trial. Concomitant treatment will, however, be registered.

Participants. The study will recruit and randomize 200 participants amongst patients from the Department of Breast and Endocrine surgery at Oslo University hospital (see sample size calculations for justification).

Inclusion criteria

Patients must fulfill the following criteria to be eligible for inclusion in the study:

- Women diagnosed with breast cancer and scheduled for surgery
- Be able to provide informed consent
- Over the age of 18

Exclusion criteria.

- Insufficient Norwegian speaking or writing skills to participate in the interventions and fill out questionnaires
- Over the age of 70
- Cognitive and psychiatric impairment or other serious malignancies

Sample size and power

Sample size is estimated for both primary outcomes. Previous trials with similar interventions have demonstrated moderate/large effect sizes on pain and fatigue [60,100]. However, compared to these studies, we expect more heterogeneity in our data as our study population will undergo several medical treatments during the trial (e.g., radiotherapy or chemotherapy after surgery). We thus expect a minimum difference that is clinically relevant to be 1 point on NRS (0–10) and 3 points (which corresponds to patients reporting being "slightly better") on FACIT-F (0–52). Based on previous studies, it is expected that the control group scores 5 (SD 2.4) on NRS at 3 months follow-up [101], and 18 (SD 7) on FACIT-F [60]. With a power of 0.80 and a two-tailed α of .05, the number needed in each group to detect the difference in pain is n = 92, and in fatigue n = 87. To account for attrition and loss to follow-up, we plan to include 100 patients in each group.

Statistical analyses

Effect analyses of primary and secondary outcomes will be performed according to both the intention-to-treat principle (the primary analysis) and per protocol. The efficacy analysis of the primary outcomes will involve a comparison of mean pain and fatigue levels at 3 months follow-up by use of independent sample t-test. This will constitute the main analysis of the

primary outcomes. Additionally, they will be analyzed using linear mixed models (also referred to as multilevel models) at the 3 different time points (post-surgery, 3- and 12-months follow-up). Multilevel modelling is a flexible statistical approach that can handle non-balanced data with missing entries and repeated observations [102].

Sub-group analyses. Any significant main effects between the intervention and control group may allow for subgroup analyses. The following pre-defined subgroups will be investigated: Surgical procedure (breast conserving vs mastectomy), axillary lymph node dissection (yes/no), pre-existing pain condition (yes/no) and clinically relevant anxiety. All these variables have been shown to predict CPSP and other late effects from breast cancer surgery and could as such act as moderators of any treatment effect.

Handling of missing data. For the analyses of secondary outcomes, we plan to apply mixed effects models by use of Maximum Likelihood Estimation (MLE) which is a recommended approach to handle complex structures of missing data. In MLE, there will be a robust adjustment for missing observations, accounting for complex structures of missing data [103]. Due to the considerable number of secondary outcome measures in the PREVENT trial, alpha inflation is a concern, and these analyses will as such be interpreted with caution.

Implementation

The project is administered from the Dept of Psychology, University of Oslo, but data will be collected, stored, and analyzed at Oslo University Hospital through VieDoc which is an established and secure system for data collection, storing and management approved by the hospital. The trial runs at the hospital in the Department of Breast and Endocrine surgery. Two study nurses are employed and currently work in the out-patient department and on the ward with patient recruitment, follow-up, and biomarker assessments. A research assistant is responsible for practical aspects of the trial as well as administering the web-based platform where the iACT is delivered. An experienced psychologist with expertise in hypnosis is responsible for delivering the pre-surgery hypnosis and supervising the other therapists (psychologists/last-year psychology students). They have all gone through didactic and practical training in the specific hypnosis intervention used in the trial, as well as completed supervised practice as part of their training. The iACT was developed under the leadership of the co-PI of the study (Jacobsen), with input from our national and international partners (Linton & Flink), and user representatives. The user representatives have also provided valuable feedback upon completion of the post-operative intervention that has led to several adjustments and modifications.

To disseminate the results to patients, clinicians, policy makers and the public, we are planning to co-host a seminar with the Norwegian Cancer Society for stakeholders and collaborators to present results from the trial. The Cancer Society will also communicate the research findings through their channels, which are well organized and far reaching.

Process evaluation

Participants. Participants in the RCT will also be invited to contribute to the qualitative process evaluation. We expect to include 6–16 participants in the process evaluation, with an equal number of participants from each study arm. With qualitative methodology, the general rule is that quality is more important than quantity–that is, having many participants is less important than ensuring high quality of the data and the analysis [104]. Furthermore, the final number of participants can rarely be decided upon in advance, but rather, the decision to stop inclusion depends on the quality of the data collected and the needs of the analysis. Patients participating in the process evaluation will sign a separate informed consent relating to participation in this ancillary study.

Participants will be recruited in two waves. In the first wave of recruitment, participants will be purposively selected on the basis of maximum variation on expectedly important parameters [105], such as age, type of operation, and whether the cancer is recurrent or new. In the second wave, participants will be selected based on their scores on the pre-operation questionnaire in the quantitative part of the study, specifically their scores on pain catastrophizing. We will purposefully select some participants who score high on pain catastrophizing and some who score low, with the purpose of unpacking this predictor qualitatively and understanding how it may be changed by the interventions.

Form of data collection. Data will be collected through individual, semi-structured interviews and a diary. The interviews may be conducted face-to-face, over the telephone, or via Zoom, and the participants will be asked about her thoughts and feelings about the past, present, and future in relation to the cancer diagnosis, the treatment, and quality of life. At the first interview, around 4 weeks after surgery, participants will be given a diary to record their thoughts and feelings pertaining to the illness, treatment, symptoms, their situation, and the future. The diary will be collected before the next interview, which will take place some months later.

Analyses. Data will be transcribed by the researcher and analyzed with two separate analyses: (socio)narrative analysis [106,107] and Grounded Theory [108]. The different analyses are expected to result in different, complementary perspectives on the development of CPSP and fatigue and how the intervention strategy influences these processes. In reporting from the process evaluation, we will follow the journal reporting standards for qualitative research [109].

Confidentiality

PROMs will be completed electronically using the ViedocMe functionality available in Viedoc. Study staff will create a ViedocMe account for each participant in the participant's Clinic View in Viedoc and provide a unique log-in profile (username, pin-code, and ViedocMe web-address) for each participant.

Data protection and management

All data will be stored on a secure server at University of Oslo (TSD). This is a platform for collecting, storing, analyzing, and sharing sensitive data in compliance with the Norwegian privacy regulation. A detailed plan for data management has been developed in collaboration with both Oslo University and the University of Oslo that shares the responsibility for data management in this study. Only the PI, the co-PI and the data manager will have access to all the collected data. Other researchers will be granted limited access according to their need of data for their research. TSD has a system in place for differentiated access.

Dissemination policy

The results will be disseminated to the international academic community through publications in peer-reviewed scientific journals, adhering strictly to the Vancouver Protocol.

In collaboration with our user representative in the research team, we will strategize a plan to communicate the findings more broadly. This could involve seminars, workshops and lectures for health care providers and other stakeholders, articles in the broader news media, and feature articles in specific user magazines or websites and conferences for health workers, health authorities, policy makers, and researchers. Our group follows an active media policy, providing that results have been published in scientific journals, with presence on several social

media platforms. We have developed a website dedicated to the PREVENT trial where we will communicate information about the project's key findings and conclusions.

Finally, we plan to share anonymous README files as well the statistical codes for the main analysis in an open repository (e.g., Open Science Framework) to ensure transparency and reproducibility.

Discussion

Breast cancer is the most common form of cancer among women [1], and a majority of women report persistent psychological and physiological symptoms after breast cancer surgery [3–5]. Chronic post-surgical pain and fatigue are the most common sequelas [6,13]. This is a both a major clinical problem, with prevalence rates ranging up to 60% [6], and a socioeconomic burden on the health care system [110]. Studies on preventive interventions are scarce, and those that have been carried out have not been sufficiently replicated.

This study will to our knowledge be the first study to investigate the combined effects of a pre-operative hypnosis intervention and a web-based post-operative ACT intervention in women about to undergo breast cancer surgery. It will also be among the very few attempts worldwide to prevent the incidence of pain and fatigue after breast cancer surgery applying a psychological approach. This study design has several strengths. The outcome measures are valid and reliable, involving both self-report measures, objective registry data, and biomarker data, as well as a qualitative process evaluation sub study, and the study will contribute to the need of rigorous clinical trials within this field of research. The project results will be highly relevant to all health care personnel involved in breast cancer care, but also to the larger community of clinicians and researchers within the field of chronic pain and fatigue.

Trial status

The trial started recruitment in October 2020 and is still collecting data for the primary endpoint.

Supporting information

S1 Spirit checklist. The completed SPIRIT checklist with reference to where in he manuscript the different points are addressed.
(DOC)

S1 File. Study protocol approved by IRB. The written confirmation that the study protocol has received an approval from the Regional Ethical Committee of South-Eastern Norway.
(PDF)

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Ethics approval and consent to participate

The study will comply with good clinical practice, including the most recent version of the declaration of Helsinki, as well as all relevant rules and regulations of Norway. The study has been approved by the Regional ethical committee (reference number 67725), the Data

Protection Officer at Oslo University Hospital (reference number 20/00831), and the Norwegian Social Science Data Services (project number: 219790). We follow the institutional guidelines for collecting and storing sensitive data, as well as registration of the project in the University's research data base (FORSKPRO). Prior to inclusion, all participants receive oral as well as written information about the trial, the randomization process, personal confidentiality, and the right to withdraw from the project at any time. They also sign declarations of informed consent and voluntary participation. Important protocol modifications will be reported to the ethical committee as well as the data protection officers.

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Writing – review & editing: Alice Munk, Marianne Therese Smogeli Holter, Ragnhild S. Falk, Henrik Børsting Jacobsen.

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