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Protocol for the REPAT study: role of emotional processing in art therapy for breast cancer palliative care patients

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ABSTRACT

Introduction Patients with breast cancer (BC) cope with depression which is linked to functional limitations in survivorship and to physical symptoms. Pain and fatigue are prominent symptoms that affect the well-being of cancer survivors. Emotional processing has been associated with improved physical and psychological health in survivors. Art therapy is a form of psychotherapy that involves the use of visual art-making for expression and communication. It encourages emotional processing and has been linked to symptom reduction in patients with cancer. This protocol is designed to examine two mechanistic changes: emotional processing (awareness, expression and acceptance) and cholinergic anti-inflammatory processes (heart rate variability and cytokine expression) through which an art therapy intervention may reduce depression, pain and fatigue. In addition, we will examine ethnocultural differences in the effect of art therapy in women from different ethnocultural backgrounds.

Methods and analysis A randomised controlled study with careful controls will randomise 240 patient with BC (50% Jewish and 50% Arab) to an 8-week group art therapy intervention or an 8-week Mandala colouring comparison group. This design will test the mechanisms of art therapy on the targeted outcomes beyond the effects of time with a group, focus on a task and engagement with art materials. We will examine two potential mechanisms: emotional processing and cholinergic anti-inflammatory processes; of the intervention effects on depression, pain and fatigue and compare these effects in Arab versus Jewish women.

Ethics and dissemination Participants will sign informed consent before participation and will be informed that they can leave the study at any point in time without effect on their medical treatment. The Helsinki committees of each participating hospital have approved the study. Data collected in this study will be published in peer-review journals, and we will use the platform of the study website (http://repat.haifa.ac.il/en/) for further dissemination to the general public.

Trial registration number The study is registered in ClinicalTrials.gov: NCT03377816; Pre-results.

Strengths and limitations of this study

- Design: Participants blind to group allocation is relatively rare in psychotherapy studies and will provide us with the opportunity to obtain a close look at the psychological and physiological effect of art-making as part of a therapeutic relationship, tailored at promoting emotional processing as opposed to using engagement with art materials as an activity.
- The fact that we can examine mechanisms of art therapy in a clinical setting, as opposed to a laboratory, ensure that the intervention is very similar, if not identical, to what patients with breast cancer (BC) and survivors can receive in other clinical settings.
- We have the unique opportunity to examine the mechanism of emotional processing in an ethnocultural minority population in which cultural differences are a barrier to receiving support and treatment for psychological and physical symptoms related to BC.
- One of the main challenges in operationalising a complex study of this kind, will be the multilingual nature of the study, required to examine ethnocultural differences in psychological constructs that are language based.
- Recruitment is another challenge that we are likely to encounter, and we will attempt to minimise burden by maintaining a flexible data collection plan in which time points for data collection can be flexible within study design limitations.

INTRODUCTION

Over 200 000 women are diagnosed with breast cancer (BC) in the USA annually,[1] one-third of whom experience depressive disorders[2 3] linked with functional limitation in survivorship,[4] physical symptoms[5] and increased mortality.[6 7] Development of chronic pain is reported in 25% to 60% of women, and chronic fatigue is reported in 30% to 60% of survivors.[8 9] Pain and fatigue along with depressive symptoms affect quality of life and well-being and are very difficult to treat.[5] Cancer survivorship is defined as living with the challenges that occur as the result of a cancer diagnosis and treatment.[8] Thus, in this protocol patient and survivor are used interchangeably.

The objective of this protocol is to examine two mechanisms through which art therapy

has a salutary effect on symptom reduction for BC survivors: (1) emotional processing and (2) cholinergic anti-inflammatory processes. Second, examine differences in the effect of art therapy in women from different ethnocultural backgrounds.

We define emotional processing as the process of becoming aware of, expressing and having a non-judgemental and accepting attitude toward emotions as they arise and are experienced. Thus, emotional processing in this study is formalised to be comprised of (1) emotional awareness: when knowledge is transferred from sensorimotor or bodily information to patterns of explicit thought that include conscious processing through language or other symbolic formations, such as visual art,[10–12] (2) expression: the extent to which feelings are intentionally[13] (mainly verbally) and non-intentionally[14] (eg, body language, facial expressions) conveyed to others and (3) acceptance is an emotion regulation strategy in which individuals embrace an attitude of being accepting, friendly and nurturing toward their feelings.[15 16] Emotional processing has been formulated in this manner in several studies with breast cancer survivors and has been shown to be associated with improved physical and psychological health in BC survivors.[15–25]

Women from traditional backgrounds, in which there is an emphasis on collectivism as opposed to individualism and a reliance on religion as a major coping strategy, may respond differently to cancer diagnosis and treatment than do more modern/secular women. Women from traditional backgrounds, such as Arab women, may see cancer diagnosis as fate and fear stigma related to exposing their diagnosis[26] and these women may not express their distress openly, which leaves them at risk for loneliness and not receiving help for their symptoms.[27–29] Since expression of emotion and venting is distressing for some ethnic minorities, such as Arab women,[30 31] art-making may be less distressing and more helpful in reducing symptoms and improving quality of life.[32 33] Israel is a multicultural country with differences between the Jewish and Arab populations. Israeli Arabs of different subgroups in comparison to Israeli Jews have been found to be more conservative and hierarchical, and less autonomous.[27]

Art therapy is a form of psychotherapy that involves the use of visual art-making (drawing, painting, sculpting, collage, and so on) for expression and communication within a safe and supportive relationship, in a therapeutic setting.[34] Art therapy has been well documented in cancer settings to alleviate psychological symptoms and reduce physical complaints.[35–41] We hypothesise that increased emotional processing is a primary mechanism through which art therapy effects psychological and physical symptom reduction in patients with BC. The temporal delineation of changes that occur in emotional processing has not been studied in depth, however qualitative studies have demonstrated changes in emotional processing, following art therapy after two sessions, or after 2 weeks.[41] In a pilot study that examined the feasibility of the intervention protocol in this study, we observed large effect size changes in acceptance of emotion and emotional awareness after 8 weekly sessions.[42] Art therapy and inflammation has not been examined in previous studies, however inflammation, heart rate variability and inflammation are related to emotional processing and depression, fatigue and pain (to be discussed below). A systematic review and meta-analysis of the effect of art therapy on patients with cancer found significant reductions in depressive symptoms and fatigue as well as improved quality of life in interventions that ranged from 1 to 18 weekly sessions.[43]

Heart rate variability (HRV) is a measure of beat-to-beat temporal changes in heart rate that reflect the output of the central autonomic network. The vagus nerve carries the efferent parasympathetic signalling via cholinergic transmission of the parasympathetic branch of the peripheral autonomic system that regulates metabolic output in response to environmental stimuli and enables social engagement.[44] The neurovisceral integration model asserts that lower HRV is associated with excess pro-inflammatory cytokines (allostatic load).[45–47] High levels of pro-inflammatory cytokines and low HRV are related to depressed mood, fatigue and pain in patients with cancer;[47–50] while low HRV is associated with difficulties in emotion regulation[51–53] as well as sadness and crying in depressed individuals.[54 55] Inflammation has been shown to lead to depressed mood in hours and sickness symptoms (fatigue) 1 hour after increased inflammation.[56] Changes in the cholinergic anti-inflammatory pathway have been shown to be associated with psychological and physical symptom reduction.[17 57–61]

Objectives and hypotheses

Objective 1

To examine two mechanisms: (1) emotional processing (awareness, acceptance and expression) and (2) cholinergic anti-inflammatory processes (resting HRV and inflammatory cytokines), through which art therapy reduces depression, pain and fatigue in Jewish and Arab BC survivors.

Hypothesis 1

Participants in art therapy versus Mandala will experience greater increases in emotional processing (awareness, acceptance and expression), resting HRV and regulatory cytokine expression as well as a greater decrease in pro-inflammatory cytokine expression: which in turn will mediate the effect of art therapy on depression, pain and fatigue.

Hypothesis 2

Changes in emotional processing and cholinergic anti-inflammatory processes will have correlated as well as unique effects on depression, pain and fatigue.

Exploratory hypothesis

In addition to direct effects of art therapy on symptoms, the effects of art therapy versus Mandala will be sequentially

mediated by increased emotional processing through increased cholinergic anti-inflammatory processes (or vice versa) to reduce depression, pain and fatigue.

Objective 2

To examine ethnocultural differences in the effect of art therapy in women from a traditional collectivist ethnocultural background, in comparison to women from a more individualist western ethnocultural background.

Hypothesis 3

Individuals from a traditional collectivist ethnocultural group (Arab) will demonstrate a more prominent response to the art therapy intervention (greater increases in emotional awareness, acceptance and expression), as compared with women in the more individualist western ethnocultural group (Jewish), beyond differences in traditional values.

METHODS AND ANALYSIS

Study design

This is a randomised controlled trial designed to be able to isolate and examine emotional processing and the effect of enhancing emotional processing on HRV and inflammatory cytokines and examine how these may mediate the effect of art therapy on depressive symptoms, pain and fatigue in patient with breast cancer. Unidentified patient reported data will be collected and managed using REDCap electronic data capture tools hosted at The University of Arizona.[62] See figure 1 for a flow chart of the research procedure.

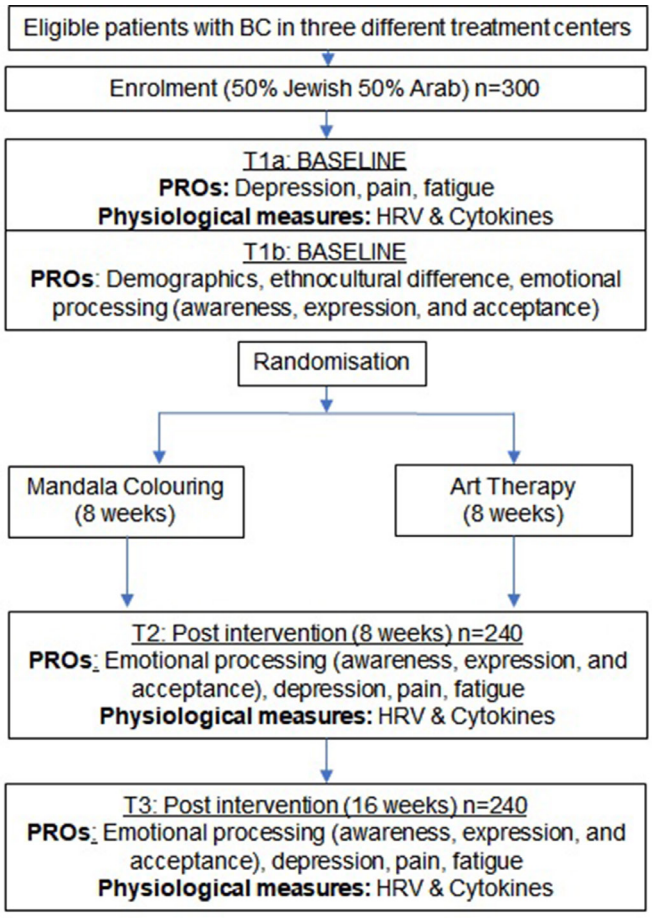

Figure 1 Flow chart.

Patient and public involvement

The study was supported by a patient advocate who provided input to the programme of research. This patient advocate will meet with the primary investigator (PI) for the duration of the study and is available for consult. So far, the patient advocate has partnered with us for the design of the study and the burden of the intervention from the patient's perspective. At the end of the study, the patient advocate will comment on the findings and contribute to the dissemination plan.

Participants

We will accomplish the objectives by recruiting 240 Jewish and Arab women (>18 years) who have been diagnosed with breast cancer and have completed chemotherapy, surgery and/or radiation therapy at least 3 months and no longer than 18 months before the intervention begins. We plan to recruit 50% Jewish women along with 50% Arab women (30% more than represented both in general society and in the cancer population), for comparison. Study criteria were chosen to enable participation of a representative sample of most post treatment breast cancer survivors and support the generalisability of the results. We will inquire about and document any illness in the previous week with infection or acute viral disease as well as having dental work[63] to account for these in our analyses as they may influence physiological measurements.

Inclusion criteria

(1) Adult (>18) women with initial, first recurrence BC or second primary BC; (2) study entry within 24 months of diagnosis and at least 3 months after adjuvant cancer care (chemotherapy and radiotherapy) or reconstructive surgery; any additional or replacement standard medical treatment for cancer is allowed (ie, surgery, chemotherapy, radiotherapy, neoadjuvant chemotherapy, endocrine therapy); (3) additional medication is allowed, excluding what is described in exclusion criteria, and will be assessed for potential inclusion as a covariate; (4) can complete assessments in Arabic or Hebrew; (5) provides informed consent; (6) able to appropriately be part of a group.

Exclusion criteria

(1) Men; (2) lifetime history of bipolar disorder, schizophrenia, schizoaffective disorder or with a pre-cancer diagnosis of fibromyalgia or chronic fatigue syndrome; (3) active suicidal plan (will ensure immediate intervention); (4) dementia/other disorder that would preclude informed consent or comprehension of assessments; (5) individuals taking anticholinergic medications, and post myocardial infarction (6 months before recruitment)

Figure 2 Example of Mandala.

or with a pacemaker, which would render the metric of HRV invalid; (6) flare-up in systemic autoimmune disease (such as arthritis, lupus or multiple sclerosis), thyroid dysfunction that requires increases in medication because these would mask the changes in cytokines associated to the intervention.

Sample size

A power analysis was conducted via Monte Carlo simulation in Mplus (Muthen & Muthen: Los Angeles, California) showed that a sample size of 240 (120 per condition), provides: (1) >90% power to detect a moderate effect size (Cohen's d=0.50) of treatment on mechanisms, (2) >90% power to detect a moderate association (r=0.30) between mechanisms and symptoms and (3) >90% power to detect an indirect effect from treatment to symptoms via mechanisms. The sample size will also provide >80% power to detect a moderate effect size for the condition by ethnocultural group interaction. We expect a 15% attrition rate, thus recruiting 300 participants across sites should guarantee a sample size of 240.

Consenting procedure

The research nurse, oncologist or their designee, will obtain verbal consent from the patient agreeing to participate in the screening session. During the screening session, there will be a single informed consent form (online supplemental file) that describes both the screening and study procedures. Once eligibility is established, Subject's Consent Form and Health Information Privacy Protection Act (HIPAA) information will be reviewed and, if consenting, participants will sign. Each site will review documents related to medical and symptom-based eligibility criteria. After consent is obtained, potential subjects will be screened by study personnel to determine that the subject meets all inclusion and exclusion criteria for study participation.

Randomisation

Randomisation will occur immediately following the baseline visit which will occur within 14 days of the screening visit and 1 week before the intervention begins. Consented participants will be randomised into the art therapy or Mandala using block randomisation stratified by site, ethnicity and traditionalism to ensure equal sample sizes between groups over time in each site and in each ethnicity. Permutations of group assignment will be generated in random blocks of four, six and eight so that staff cannot guess the condition of the final participant as the block size varies.

Blinding

Participants will be blinded to their randomisation as will the research nurses and research coordinators. Participants will be told they are participating in an 'art-making' study where they will be assigned to an art-making group. Participants will not be told which is expected to be superior. PhD students will have randomised lists, to schedule sessions and make weekly calls to encourage attendance, therefore both will be unblinded to study assignment. The research nurse will collect and enter data, collect bio specimens and manage the database, and thus will be unblinded after randomisation. The research assistant will remain blinded throughout the study, and will receive lists of participants to call, without knowing which group they are assigned to.

Interventions, administration and duration

The interventions

The interventions will be administered by an experienced art therapist who will be trained in this specific protocol. The intervention is designed to follow the Bodymind model of art therapy.[64] Each session will start with a 10 min rapport building and touching base and continue with 50 min of art-making in a calm and supportive environment. Art materials are on the table and after the art therapist provides a brief explanation of the use of the materials; participants are encouraged to explore and experience as they wish. The art therapist is present to guide and assist. Participants are encouraged to minimise conversation; instrumental music is played to encourage introspective experiences. The session ends with 30 min of processing and discussion in which each participant shares and briefly presents their work and group participants can respond and/or provide support. The art therapy treatment protocol derives its theoretical framework from the Bodymind model of art therapy[64] and from the application of Focussing to art therapy[65 66] for the purpose of body awareness and developing a focussing ('being friendly, accepting, non-judgemental and welcoming to one's inner felt sense').[65] The art therapist creates an atmosphere that is calm and by remaining tuned into the verbalisations and body language of participants.

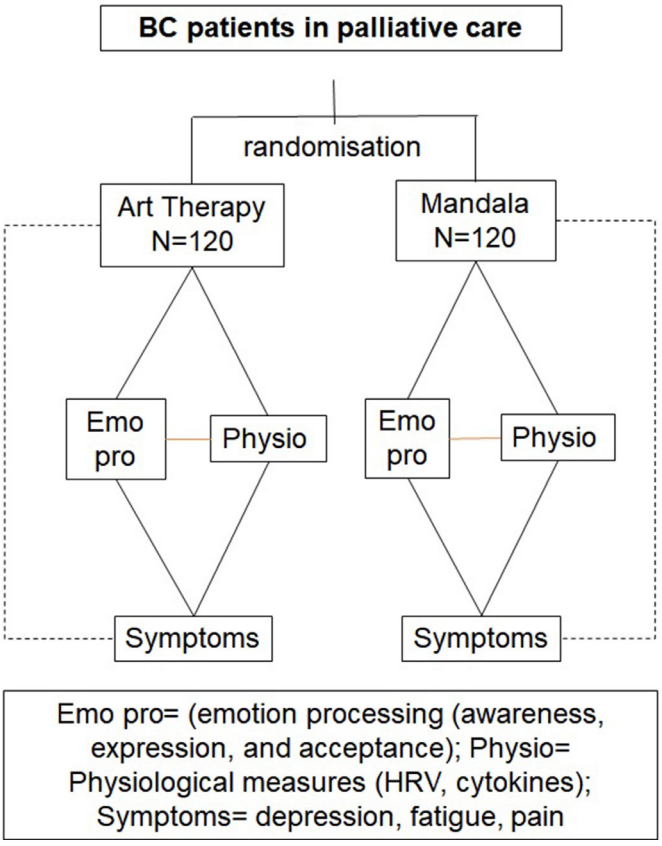

Figure 3 Hypotheses 1 and 2.

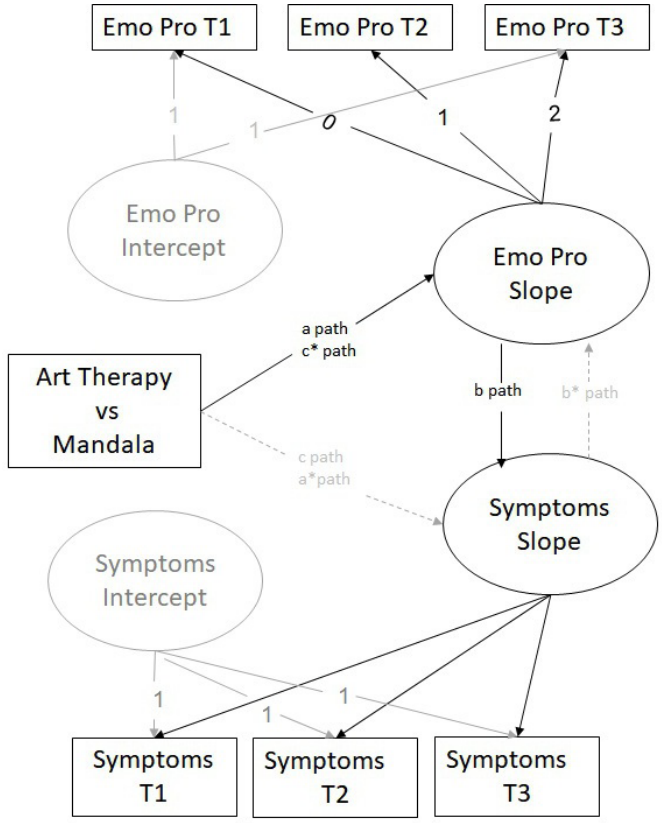

Figure 4 Hypothesis 3. EmoPro

If needed she can provide individual attention that is geared toward neutralising concerns regarding performance during the art-making. This approach is defined as providing a 'Third-hand'[67]: assisting in problem solving and dilemmas related to the art-making process. The art therapist encourages participants to refrain from conversation and instrumental music is played to encourage introspective experiences. The session ends with 30 min of processing and discussion in which the art therapist requests each participant to share and briefly presents their work and group participants can respond and/or provide support. The art therapist will remind group members to be respectful and non-judgemental toward other participants and themselves.

The comparison group has been tailored to include many elements of the intervention group, including engagement with art materials and being in a group setting. However, it does not include encouragement to use self-exploration and expression, and thus serves as a control for the non-mechanistic components of our proposed intervention, allowing us to test the hypothesised mechanisms of the art-therapy. The interventionist will encourage the participants to colour prefabricated shapes for 40 min. The same art materials as in the intervention group will be on the table as will the same instrumental music. We will not be controlling for the whole 90 min of the intervention group as are concerned that comparison group participants will become bored and this will defeat the purpose of the comparison group. These sessions will not have a rapport building component and will include 40 min of colouring prefabricated shapes (Mandalas - see figure 2) in a calm environment and 20 min of self-care instruction. Colouring Mandalas has been demonstrated to reduce anxiety.[68–70] Participants are encouraged to minimise conversation; instrumental music is played to encourage introspective experiences.

Both interventions will be administered in a group format by a trained individual. Each session will be 1.5 hours (intervention) and 1 hour (comparison) once a week for 8 weeks. The interventionists of both groups will keep scores that will be rated by the PI against the treatment manual to ensure fidelity.

Measures

Baseline assessments

We will be collecting baseline demographic data (age, marital status, children (if yes, and how many), religion, religiosity, education, employment, nutrition, exercise and alcohol consumption habits and previous and current experience with art-making. Disease parameters, stage, type of disease, date of diagnosis and current medications will be collected through chart review.

Collectivism

We will measure ethnocultural differences using the Portrait Values Questionnaire (PVQ-RR), which is a 57-item scale consisting of items designed to measure 19 cultural values.[71 72] The scale has been validated in Israel.

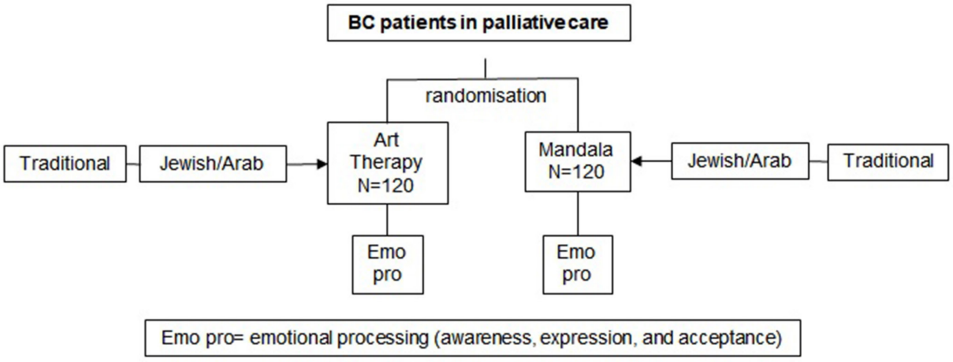

Figure 5 Alternative hypotheses.

The mean Cronbach's α for the tradition values (which we will use as a covariate to enrich the ethnocultural differences between Jews and Arabs), was 0.83.

Primary outcome measures

Depression

The Center for Epidemiologic Studies-Depression (CES-D) scale[73] - 10-item scale to assess depressive symptoms. Considering symptom overlap of depression with cancer and its treatments[74] we chose the CES-D because it has strong psychometric properties. This scale had a Cronbach's α=0.89 and a test–retest reliability r=0.57.[75] The CES-D has been translated and validated in Hebrew and Arabic.

Fatigue

The Fatigue Symptom Inventory (FSI).[76] The 13-item self-report FSI has been developed and validated specifically among patients with BC/survivors and demonstrates high internal consistency, α>0.90. The FSI has been translated and validated in Hebrew and Arabic.

Pain

The PROMIS (Patient-Reported Outcomes Measurement Information System) Pain Intensity (3-item short-form a) measures how much pain was intense in the past week and currently and the PROMIS Pain Interference (6-item short-form a)[77] which measures how much pain interfered with different aspects of life in the past week on a 1 to 5 Likert scale with high internal consistency, α>.90.[77] Both measures have been translated and validated in Hebrew and Arabic.

Mechanism measures

Emotional awareness

The Levels of Emotional Awareness Scale is a written performance index of variation in the differentiation and complexity of emotional words used to answer the question 'how would you feel and how would the other person feel' when presented with 10 evocative scenarios.[78] Responses are scored according to the degree of specificity in the terms used and the range of emotions described. Cronbach's α=0.84; 2-month test–retest reliability=0.75.[10] We have translated and back translated from English to Hebrew and Arabic and then back to English as well as completed a validation study of the scale in Hebrew and in Arabic with n=130, respectively.

Emotional expression

Emotional Approach Coping scales (eg, emotional processing, emotional expression)[79] and COPE avoidance-oriented coping subscales (eg, denial, mental disengagement),[80] all completed with reference to women's experience of BC.[81] The COPE scales have been validated in Hebrew[82] and Arabic[83] and been used in patients with cancer.[84 85] The Emotional Approach Coping scales have been used in Hebrew with a Cronbach's α=0.91 for emotional expression and Cronbach's α=0.93 for emotional processing.

Acceptance of emotion

The Acceptance of Emotions Scale assesses the extent to which subjects are accepting and nurturing toward their feelings.[25] Thirteen items include statements such as 'I naturally and easily attend to my feelings'. Responses range from 0 for never/not at all to 100 for always/perfectly (Cronbach's α=0.92; 15-month test–retest reliability is 0.58).[86–88] Translation and back translation between English and Hebrew and Arabic confirm the accuracy of the scale translation.

HRV

Resting ECG data will be recorded for 20 min. The participants will be given instructions not to drink coffee or smoke for several hours before the laboratory visit as well as to sit quietly without talking or moving during the ECG recording. The participants will be instructed not to drink coffee or smoke for 3 hours before the laboratory visit as well as to sit quietly without talking or moving during the ECG recording. No instructions will be given to the participants on how to breathe. ECG will be recorded using a Zephyr BioPatch (Zephyr Technology, Annapolis, Maryland) which has been used and validated in ambulatory and clinical settings.[89] The BioPatch consists of a Bio Module and holder. Data are stored in the module and transmitted to smartphones using Bluetooth technology to synchronise time and ensure recording. The offline analysis of the raw digitised (1024 Hz) ECG signal will be performed by extracting interbeat interval (IBI)

series from the raw ECG recording by using QRSTool Software.[90] Since even a single artefact can distort an index of respiratory sinus arrhythmia (RSA)[91] each extracted interbeat series will be hand-corrected for artefacts. According to the guidelines of the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology[92] for the quantification of HRV, the high frequency (HF) band of the heart rate spectrum is assumed to represent vagal influences. HRV in the HF band (0.12 to 0.4 Hz), which is assumed to be related to respiration, will be derived with CMetX Cardiac Metric Software[90] and used to calculate an estimate of RSA. The CMetX programme converts IBI series to a time series sampled at 10 Hz with linear interpolation. A 241-point optimal finite impulse response digital filter designed using FWTGEN V3.8[93] with half-amplitude frequencies of a 0.12 to 0.40 Hz was applied to the 10 Hz time series representation of the IBI series. The natural log of the variance of the filtered waveform will be used as the estimate of RSA. All participants will be verified to be breathing within the respiratory frequency range (0.12 to 0.40 Hz), assessed by examining the dominant frequency in the power spectrum of the respiration waveform. This validation check will be performed to confirm that participants are breathing neither too slowly nor too quickly, to ensure the RSA metric adequately captures their respiratory-related variations in heart rate.

Inflammation

We will collect 10 ccs of blood in order to measure immune dysregulation (pro-inflammatory cytokines interleukin (IL)-6, IL-8, IL-1β, tumournecrosis factor alpha), anti-inflammatory (IL-4, IL-10) and regulatory cytokine (transforming growth factor β (TGF-β)). Blood will be collected in vials with sodium citrate or heparin, placed on ice and transferred to tubes (BD, Plymouth, UK) for separation and then frozen in aliquots in –80°C (Nunc Brand Products, Denmark). Quantitative detection of cytokines in serum: we will be using Luminex High Performance Assays which use color-coded polystyrene or superparamagnetic beads coated with analyte-specific antibodies. Beads recognising different target analytes are mixed together and incubated with the sample. Captured analytes are subsequently detected using a cocktail of biotinylated detection antibodies and a streptavidin-phycoerythrin conjugate. For analysis, we will use the MAGPIX (R&D Systems) which is Luminex's xMAP's multiple analyte detection system based on fluorescent bead immunoassay. Since TGF-β1 requires acidification in order to be separated from its latency associated proteins and recognised in analysis, it cannot be measured at the same time as the other cytokines. Therefore, we will use a separate kit for analysis.[94]

Data analysis

Prior to testing hypotheses, we will produce a thorough descriptive profile of the sample and examine the distributions of key variables involved in the hypotheses. We will also examine levels of non-response and missing data. Prior experience indicates attrition will be low; although, some missing data are expected due to missed assessments and dropout, which will be addressed using full information maximum likelihood.

The first part of Hypothesis 1: women in the art therapy group experience greater increases in emotional processing, HRV and regulatory cytokine levels and greater decreases in pro-inflammatory cytokines than women randomised to the Mandala condition will be tested using linear mixed models.[95] Models will include a Time x Condition interaction to test whether the change over time in emotional processing and cholinergic anti-inflammatory processes is significantly different between treatment groups and simple slope tests to characterise the degree of change in the art therapy and Mandala conditions.

The second part of Hypothesis 1: emotional processing and cholinergic anti-inflammatory processes mediate the effects of art therapy on symptoms (depression, pain, fatigue) will be tested using path analysis. Specifically, models will be tested where condition (art therapy vs Mandala) predicts the change in emotional processing or physiological correlates (path a) and the change in emotion processing or physiological correlates with the change in symptoms (path b). Mediation will be tested by calculating the indirect effect as the product of coefficients (path a x path b) and using bootstrapping to calculate 95% CIs and statistical significance.[96] This approach was chosen over approaches such as autoregressive mediation[97] because we expect that mechanisms will continue changing throughout the intervention period and may unfold over hours or days whereas our assessments are across weeks. A limitation of this approach is that it does not distinguish the temporal ordering.

Hypothesis 2: changes in emotional processing and cholinergic anti-inflammatory processes will be correlated and have unique effects, will be tested by expanding the path analyses from Hypothesis 1 to simultaneously include all proposed mediators on each symptom outcome. Indirect effects with bootstrapped CIs will be calculated as before. The change in mediators will be allowed to freely correlate to examine their relations.

The Exploratory Hypothesis posits 2, sequential mediators: treatment (art therapy vs Mandala) to emotional processing (path a) to cholinergic anti-inflammatory processes (path b) and finally to symptoms (path c). To help establish temporal precedence, change in emotional processing from baseline to intervention end and change in cholinergic anti-inflammatory processes from intervention end to follow-up and change in symptoms from baseline to follow-up will be used. Indirect effects will be calculated as the product of three coefficients (path a x path b x path c) capturing the hypothesised sequentially

mediated effect. Bootstrapped CIs and significance tests will be calculated. To test the reverse ordering, the same process will be used exchanging the time points and order of emotional processing and cholinergic anti-inflammatory processes. See figure 3 for the model for Hypotheses 1 and 2. This approach will help to untangle temporal ordering although with two hypothesised mediators and only two assessments after the start of intervention, the change in anti-inflammatory processes and symptoms will both use the follow-up time point, which is a limitation.

Hypothesis 3: the effect of art therapy vs Mandala on emotional processing will be stronger in women from an ethnocultural minority group will be tested by expanding the linear mixed models from Hypothesis 1 by including measures of traditional values as a covariate and a Time x Condition x Ethnocultural Group (Jewish vs Arab) interaction to test whether ethnocultural group moderates the Time x Condition interaction from Hypothesis 1. If the three-way interaction is significant, simple slopes will be calculated and graphed to characterise the change in emotional processing by treatment condition and ethnocultural group. (figure 4)

As for Hypothesis 1, a competing hypothesis that all symptoms have correlated but unique effects on our proposed mechanisms will be tested by reversing mechanisms and symptoms role in the models. Standardised indirect effects will be evaluated to compare the relative magnitude of evidence for each hypothesis. An example diagram is shown in figure 5 for competing hypotheses. The hypothesised direction is shown in solid lines. A competing hypothesis, that change in symptoms mediates the effect of art therapy versus Mandala on emotional processing is shown in dotted lines (a* path x b* path). These competing models will be tested separately. The standardised indirect effects from the primary and competing hypothesis models will be compared with to provide information about the relative magnitude of the indirect effects in the hypothesised versus competing direction.

Study timeline

The study is designed to occur across 3 years in which the first 6 months are intended to be used to set up the study the various sites. Data collection should start following the set-up period and the interventions are planned to occur in four cohorts at three hospitals in Israel. (table 1)

Fidelity and adherence

Adherence to the study regimen will be defined as attending 80% of the group sessions, which will be monitored and recorded by the interventionist. The moderation of the effect of attending less than 80% will be assessed and dealt with during data analysis. Furthermore, fidelity of the intervention itself will be ensured by scoring the sessions against the treatment manual and observational fidelity checks by the gold standard rater (PI Czamanski-Cohen initially and then trained PhD student 20% of sessions). Fidelity below an average of 4 will indicate the need for further training of the interventionist (see table 2 below). Data will be continuously monitored, and adverse events will be documented and reported to the data monitoring and safety committee. Participants who display distress beyond what can be treated in the group setting will be referred to the hospital unit's social worker for further care. Furthermore, we will make efforts to promote participant retention and complete follow-up by conducting reminder emails and phone calls. PIs, Dr Czamanski-Cohen and Dr Weihs shall be the owner of data, analyses, reports and work product generated at the clinical sites.

ETHICS AND DISSEMINATION

The study has been approved by the Helsinki committees of all participating sites. On study completion we will be left with the task to disseminate the knowledge established and work towards the long-term goal of applying this knowledge in clinical palliative care settings. We created a website (http://repat.haifa.ac.il/en/) to help disseminate information about the study to potential participants. Changes to the trial protocol will be approved by and reported to the funding agency and trial registries.

Acknowledgements We wish to first and foremost thank our study participants. Without their willingness to come forward and contribute their time and effort, we will not be able to complete this study. We wish to thank the medical staff and our current collaborating hospitals for hosting our study and helping implement this protocol. Thank you to Richard Lane, MD PhD who provides consultancy on the Levels of Emotional Awareness scale and its validation in Hebrew and Arabic. Thank you to our co-investigators Miri Cohen, PhD who advises on Psychoneuroimmunological aspects of the study, as well as ethnocultural

Table 1 Study timeline

Months	1–6	7–12	13–18	19–24	25–30	31–36
Preparation/ training	X					
Team meetings	X4	X4	X2	X1	X2	X6
Intervention		Cohort1	Cohort 2	Cohort 3	Cohort 4	
Data check*		X		X		
Analysis				X (preliminary)		X

Final cohort begins at month 25 and allows final data at month 31.
*Data check/quality. Balance across arms on factors used in minimisation technique will be monitored and adjusted.

Table 2 Fidelity assessment

	1 - not at all	2 - a little bit	3 - neither yes or no	4 - quite a bit	5 - very much so	Not applicable
(1) Was there a sense of calm in the room?	1	2	3	4	5	N/A
(2) Did you feel like you were able to support the participants?	1	2	3	4	5	N/A
(3) Were the participants deeply engaged in art-making?	1	2	3	4	5	N/A
(4) Was the session divided in to 10 min introduction, 60 min art-making and 20 min discussion?	1	2	3	4	5	N/A
(5) Was the art-making done with minimal conversations?	1	2	3	4	5	N/A
(6) Was the group discussion respectful and safe?	1	2	3	4	5	N/A

differences, and Faisal Azaiza, PhD who we consult on ethnocultural differences and needs of Arab breast cancer patients.

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REFERENCES

1 DeSantis CE, Lin CC, Mariotto AB, *et al*. Cancer treatment and survivorship statistics, 2014. *CA Cancer J Clin* 2014;64:252–71.
2 Mitchell AJ, Chan M, Bhatti H, *et al*. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 Interview-Based studies. *Lancet Oncol* 2011;12:160–74.
3 Stanton AL, Wiley JF, Krull JL, *et al*. Depressive episodes, symptoms, and trajectories in women recently diagnosed with breast cancer. *Breast Cancer Res Treat* 2015;154:105–15.
4 Steiner JF, Cavender TA, Nowels CT, *et al*. The impact of physical and psychosocial factors on work characteristics after cancer. *Psychooncology* 2008;17:138–47.
5 Wu H-S, Harden JK. Symptom burden and quality of life in survivorship: a review of the literature. *Cancer Nurs* 2015;38:E29–54.
6 Cuijpers P, Vogelzangs N, Twisk J, *et al*. Comprehensive meta-analysis of excess mortality in depression in the general community versus patients with specific illnesses. *Am J Psychiatry* 2014;171:453–62.
7 Hasegawa T, Okuyama T, Uchida M, *et al*. Depressive symptoms during the first month of chemotherapy and survival in patients with hematological malignancies: a prospective cohort study. *Psychooncology* 2019;28:1687–94.
8 Gage EA, Pailler M, Zevon MA, *et al*. Structuring survivorship care: discipline-specific clinician perspectives. *J Cancer Surviv* 2011;5:217–25.
9 Bower JE, Ganz PA, Desmond KA, *et al*. Fatigue in long-term breast carcinoma survivors. *Cancer* 2006;106:751–8.
10 Lane RD, Schwartz GE. Levels of emotional awareness: a cognitive-developmental theory and its application to psychopathology. *Am J Psychiatry* 1987;144:133–43.
11 Lane RD. *Theory of emotional awareness and brain processing of emotion*. . International Congress Series, 2006: 1287. 116–21.
12 Lane RD, Weihs KL, Herring A, *et al*. Affective agnosia: expansion of the alexithymia construct and a new opportunity to integrate and extend Freud's legacy. *Neurosci Biobehav Rev* 2015;55:594–611.
13 Kring AM, Smith DA, Neale JM. Individual differences in dispositional expressiveness: development and validation of the emotional expressivity scale. *J Pers Soc Psychol* 1994;66:934–49.
14 Collier G. *Emotional expression*. Psychology Press, 2014.
15 Weihs KL, Enright TM, Simmens SJ. Close relationships and emotional processing predict decreased mortality in women with breast cancer: preliminary evidence. *Psychosom Med* 2008;70:117–24.
16 Politi MC, Enright TM, Weihs KL. The effects of age and emotional acceptance on distress among breast cancer patients. *Support Care Cancer* 2007;15:73–9.
17 Subic-Wrana C, Beutel ME, Knebel A, *et al*. Theory of mind and emotional awareness deficits in patients with somatoform disorders. *Psychosom Med* 2010;72:404–11.
18 Bardeen JR, Fergus TA, Orcutt HK. Experiential avoidance as a moderator of the relationship between anxiety sensitivity and perceived stress. *Behav Ther* 2013;44:459–69.
19 Giorgio JM, Sanflippo J, Kleiman E, *et al*. An experiential avoidance conceptualization of depressive rumination: three tests of the model. *Behav Res Ther* 2010;48:1021–31.
20 Stanton AL, Danoff-Burg S, Huggins ME. The first year after breast cancer diagnosis: hope and coping strategies as predictors of adjustment. *Psychooncology* 2002;11:93–102.
21 Hoyt MA, Austenfeld J, Stanton AL. Processing coping methods in expressive essays about stressful experiences: predictors of health benefit. *J Health Psychol* 2016;21:1359105314550347.
22 Rost AD, Wilson K, Buchanan E, *et al*. Improving psychological adjustment among late-stage ovarian cancer patients: examining the role of avoidance in treatment. *Cogn Behav Pract* 2012;19:508–17.
23 Low CA, Stanton AL, Danoff-Burg S. Expressive disclosure and benefit finding among breast cancer patients: mechanisms for positive health effects. *Health Psychol* 2006;25:181–9.
24 Stanton AL, Danoff-Burg S, Cameron CL, *et al*. Emotionally expressive coping predicts psychological and physical adjustment to breast cancer. *J Consult Clin Psychol* 2000;68:875–82.
25 Reed RG, Weihs KL, Sbarra DA, *et al*. Emotional acceptance, inflammation, and sickness symptoms across the first two years following breast cancer diagnosis. *Brain Behav Immun* 2016;56:165–74.

26 Azaiza F, Cohen M. Health beliefs and rates of breast cancer screening among Arab women. *J Womens Health* 2006;15:520–30.
27 Azaiza F, Cohen M. Between traditional and modern perceptions of breast and cervical cancer screenings: a qualitative study of Arab women in Israel. *Psychooncology* 2008;17:34–41.
28 Miller AM, Ashing KT, Modeste NN, *et al*. Contextual factors influencing health-related quality of life in African American and Latina breast cancer survivors. *J Cancer Surviv* 2015;9:441–9.
29 Goldblatt H, Cohen M, Azaiza F. Expression of emotions related to the experience of cancer in younger and older Arab breast cancer survivors. *Ethn Health* 2016;21:564–77.
30 Goldblatt H, Cohen M, Azaiza F, *et al*. Being within or being between? the cultural context of Arab women's experience of coping with breast cancer in Israel. *Psychooncology* 2013;22:869–75.
31 Culver JL, Arena PL, Wimberly SR, *et al*. Coping among African-American, Hispanic, and non-Hispanic white women recently treated for early stage breast cancer. *Psychol Health* 2004;19:157–66.
32 Dwairy M. A biopsychosocial model of metaphor therapy with holistic cultures. *Clin Psychol Rev* 1997;17:719–32.
33 Dwairy M. Culture analysis and metaphor psychotherapy with Arab-Muslim clients. *J Clin Psychol* 2009;65:199–209.
34 Uttley L, Scope A, Stevenson M, *et al*. Systematic review and economic modelling of the clinical effectiveness and cost-effectiveness of art therapy among people with non-psychotic mental health disorders. *Health Technol Assess*
35 Archer S, Buxton S, Sheffield D. The effect of creative psychological interventions on psychological outcomes for adult cancer patients: a systematic review of randomised controlled trials. *Psychooncology* 2015;24:1–10.
36 Slayton SC, D'Archer J, Kaplan F. Outcome studies on the efficacy of art therapy: a review of findings. *Art Therapy* 2010;27:108–18.
37 Monti DA, Peterson C, Kunkel EJS, *et al*. A randomized, controlled trial of mindfulness-based art therapy (MBAT) for women with cancer. *Psychooncology* 2006;15:363–73.
38 Nainis N, Paice JA, Ratner J, *et al*. Relieving symptoms in cancer: innovative use of art therapy. *J Pain Symptom Manage* 2006;31:162–9.
39 Öster I, Svensk A-C, Magnusson E, *et al*. Art therapy improves coping resources: a randomized, controlled study among women with breast cancer. *Palliat Support Care* 2006;4:57–64.
40 Svensk A-C, Oster I, Thyme KE, *et al*. Art therapy improves experienced quality of life among women undergoing treatment for breast cancer: a randomized controlled study. *Eur J Cancer Care* 2009;18:69–77.
41 Collie K, Bottorff JL, Long BC. A narrative view of art therapy and art making by women with breast cancer. *J Health Psychol* 2006;11:761–75.
42 Czamanski-Cohen J, Wiley JF, Sela N, *et al*. The role of emotional processing in art therapy (REPAT) for breast cancer patients. *J Psychosoc Oncol* 2019;37:586–98.
43 Jiang X-H, Chen X-J, Xie Q-Q, *et al*. Effects of art therapy in cancer care: a systematic review and meta-analysis. *Eur J Cancer Care* 2020:e13277.
44 Porges SW. The polyvagal perspective. *Biol Psychol* 2007;74:116–43.
45 Thayer JF, Sternberg E. Beyond heart rate variability: vagal regulation of allostatic systems. *Ann N Y Acad Sci* 2006;1088:361–72.
46 Thayer JF, Lane RD. A model of neurovisceral integration in emotion regulation and dysregulation. *J Affect Disord* 2000;61:201–16.
47 Bower JE, Ganz PA, Irwin MR, *et al*. Inflammation and behavioral symptoms after breast cancer treatment: do fatigue, depression, and sleep disturbance share a common underlying mechanism? *J Clin Oncol* 2011;29:3517–22.
48 Miller AH, Ancoli-Israel S, Bower JE, *et al*. Neuroendocrine-Immune mechanisms of behavioral comorbidities in patients with cancer. *J Clin Oncol* 2008;26:971–82.
49 Kruse JL, Strouse TB. Sick and Tired: mood, fatigue, and inflammation in cancer. *Curr Psychiatry Rep* 2015;17:1–11.
50 Crosswell AD, Lockwood KG, Ganz PA, *et al*. Low heart rate variability and cancer-related fatigue in breast cancer survivors. *Psychoneuroendocrinology* 2014;45:58–66.
51 Geisler FCM, Vennewald N, Kubiak T, *et al*. The impact of heart rate variability on subjective well-being is mediated by emotion regulation. *Pers Individ Dif* 2010;49:723–8.
52 Geisler FCM, Kubiak T, Siewert K, *et al*. Cardiac vagal tone is associated with social engagement and self-regulation. *Biol Psychol* 2013;93:279–86.
53 Williams DP, Cash C, Rankin C, *et al*. Resting heart rate variability predicts self-reported difficulties in emotion regulation: a focus on different facets of emotion regulation. *Front Psychol* 2015;6:261.
54 Rottenberg J. Cardiac vagal control in depression: a critical analysis. *Biol Psychol* 2007;74:200–11.
55 Rottenberg J, Chambers AS, Allen JJB, *et al*. Cardiac vagal control in the severity and course of depression: the importance of symptomatic heterogeneity. *J Affect Disord* 2007;103:173–9.
56 Eisenberger NI, Inagaki TK, Mashal NM, *et al*. Inflammation and social experience: an inflammatory challenge induces feelings of social disconnection in addition to depressed mood. *Brain Behav Immun* 2010;24:558–63.
57 Chuang C-Y, Han W-R, Li P-C, *et al*. Effect of long-term music therapy intervention on autonomic function in anthracycline-treated breast cancer patients. *Integr Cancer Ther* 2011;10:312–6.
58 Kok BE, Coffey KA, Cohn MA, *et al*. How positive emotions build physical health: perceived positive social connections account for the upward spiral between positive emotions and vagal tone. *Psychol Sci* 2013;24:1123–32.
59 Lü W, Wang Z, Liu Y. A pilot study on changes of cardiac vagal tone in individuals with low trait positive affect: the effect of positive psychotherapy. *Int J Psychophysiol* 2013;88:213–7.
60 Svendsen JL, Osnes B, Binder P-E, *et al*. Trait Self-Compassion reflects emotional flexibility through an association with high vagally mediated heart rate variability. *Mindfulness* 2016;7:1103–13.
61 Wang S-M, Lee H-K, Kweon Y-S, *et al*. Effect of emotion regulation training in patients with panic disorder: evidenced by heart rate variability measures. *Gen Hosp Psychiatry* 2016;40:68–73.
62 Harris PA, Taylor R, Minor BL, *et al*. The REDCap Consortium: building an international community of software platform partners. *J Biomed Inform* 2019;95:103208.
63 O'Connor M-F, Bower JE, Cho HJ, *et al*. To assess, to control, to exclude: effects of biobehavioral factors on circulating inflammatory markers. *Brain Behav Immun* 2009;23:887–97.
64 Czamanski-Cohen J, Weihs K. The Bodymind model: a platform for the conduct of the mechanistic study of art therapy. *Arts Psychother*;51:63–71.
65 Gendlin ET. *Experiencing and the creation of meaning*. New York: Free press of Glencoe, 1962.
66 Fritsche J. Mind-Body awareness in art therapy with chronic pain syndrome. In: Rappaport L, ed. *Mindfulness and the arts therapies*. London: Jessica Kingsley Publishers, 2014: 81–94.
67 Kramer E. *Art as therapy: collected papers*. Jessica Kingsley Publishers, 2001.
68 van der Vennet R, Serice S. Can coloring Mandalas reduce anxiety? a replication study. *Art Therapy* 2012;29:87–92.
69 Curry NA, Kasser T. Can coloring Mandalas reduce anxiety? *Art Therapy* 2005;22:81–5.
70 Fincher SF. *Creating Mandalas: for insight, healing and Self-Expression*. Boston: Shambhala, 1991.
71 Sandy CJ, Gosling SD, Schwartz SH, *et al*. The development and validation of brief and ultrabrief measures of values. *J Pers Assess* 2017;99:1–11.
72 Shwartz S, Cieciuch J, Vecchione M, *et al*. Value tradeoffs and behavior in five countries: validating 19 refined values. *Eur J Soc Psychol* 2016.
73 Radloff LS. The CES-D scale: a self-report depression scale for research in the general population. *Applied Psychological Measurement* 1977;1:385–401.
74 Simon GE, Von Korff M. Medical co-morbidity and validity of DSM-IV depression criteria. *Psychol Med* 2006;36:27–36.
75 Hann D, Winter K, Jacobsen P. Measurement of depressive symptoms in cancer patients: evaluation of the center for epidemiological studies depression scale (CES-D). *J Psychosom Res* 1999;46:437–43.
76 Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the fatigue symptom inventory. *Qual Life Res* 2000;9:847–54.
77 Cella D, Yount S, Rothrock N, *et al*. The patient-reported outcomes measurement information system (PROMIS): progress of an NIH roadmap cooperative group during its first two years. *Med Care* 2007;45:S3.
78 Lane RD, Quinlan DM, Schwartz GE, *et al*. The levels of emotional awareness scale: a cognitive-developmental measure of emotion. *J Pers Assess* 1990;55:124–34.
79 Stanton AL, Kirk SB, Cameron CL, *et al*. Coping through emotional approach: scale construction and validation. *J Pers Soc Psychol* 2000;78:1150–69.
80 Carver CS, Scheier MF, Weintraub JK. Assessing coping strategies: a theoretically based approach. *J Pers Soc Psychol* 1989;56:267–83.
81 Gámez W, Chmielewski M, Kotov R, *et al*. The brief experiential avoidance questionnaire: development and initial validation. *Psychol Assess* 2014;26:35–45.
82 Ben-zur H, Zeidner M. Coping patterns and affective reactions under community crisis and daily routine conditions. *Anxiety, Stress & Coping* 1995;8:185–201.

83 Khawaja NG. An investigation of the factor structure and psychometric properties of the cope scale with a Muslim migrant population in Australia. *J Muslim Ment Health* 2008;3:177–91.
84 Ben-Zur H, Gilbar O, Lev S. Coping with breast cancer: patient, spouse, and dyad models. *Psychosom Med* 2001;63:32–9.
85 Hamdan-Mansour AM, Al Abeiat DD, Alzoghaibi IN, *et al*. Psychosocial and sociodemographic correlates of life satisfaction among patients diagnosed with cancer in Jordan. *J Cancer Educ* 2015;30:31–6.
86 Stanton AL, Kirk SB, Cameron CL, *et al*. Coping through emotional approach: scale construction and validation. *J Pers Soc Psychol* 2000;78:1150–69.
87 Gross JJ, John OP. Individual differences in two emotion regulation processes: implications for affect, relationships, and well-being. *J Pers Soc Psychol* 2003;85:348–62.
88 Gratz KL, Roemer L. Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation of the difficulties in emotion regulation scale. *J Psychopathol Behav Assess* 2004;26:41–54.
89 Johnstone JA, Ford PA, Hughes G, *et al*. Bioharness(™) multivariable monitoring device: part. I: validity. *J Sports Sci Med* 2012;11:400.
90 Allen JJB, Chambers AS, Towers DN. The many metrics of cardiac chronotropy: a pragmatic primer and a brief comparison of metrics. *Biol Psychol* 2007;74:243–62.
91 Berntson GG, Stowell JR. ECG artifacts and heart period variability: don't miss a beat! *Psychophysiology* 1998;35:127–32.
92 Berntson GG, Bigger JT, Eckberg DL, *et al*. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997;34:623–48.
93 Cook EW, Miller GA. Digital filtering: background and tutorial for psychophysiologists. *Psychophysiology* 1992;29:350–62.
94 Belabani C, Rajasekharan S, Poupon V, *et al*. A condensed performance-validation strategy for multiplex detection kits used in studies of human clinical samples. *J Immunol Methods* 2013;387:1–10.
95 Verbeke G, Molenberghs G. *Linear mixed models for longitudinal data*. Springer Science & Business Media, 2009.
96 Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. *Behav Res Methods* 2008;40:879–91.
97 Wang L, Zhang Q. Investigating the impact of the time interval selection on autoregressive mediation modeling: result interpretations, effect reporting, and temporal designs. *Psychol Methods* 2020;25:271–91.

INFORMED CONSENT FORM

I hereby signed below:

First name:	Last name:
Id number:	
Address:	Zip code:

1) Claim that I agree to participate in this study, as detailed in this document.

2) Claim that at the time of signing this document, I am not participating in another medical study that entails the use of a medical product, and I agree not to participate in an additional medical study during the time of the current study.

3) Claim that this study was explained to me by:

Name of the explaining researcher:

3.1) That the site primary researcher (name of MD): _____ received permission from the head of (name of the hospital), to conduct the study, in accordance with the National Health Regulations (Experiments with Humans- 1980), described below.

3.2) That the medical experiment on the topic of: **Role of Emotional Processing in Art Therapy for Breast Cancer Palliative Care Patients.**

3.3) The PI and co-I's have an affinity to the initiator of the study (name of site MD): The site PI is Dr. (name of site MD) and the co-PI's of the NIH funded study are Johanna Czamanski-Cohen (PhD) of the University of Haifa and Karen Weihs (MD) of the University of Arizona.

3.4) That I am free to choose not to participate in the study and am free to stop my participation in the study at any time, without it affecting my right to receive acceptable treatment.

3.5) That in the case of questionnaires- I am permitted not to answer all of the questions

in the questionnaire, or some of them.

3.6) That I am promised that my personal information will be kept confidential and will not be revealed to others involved in the study and will not be published, including in scientific publications.

3.7) That the medical institution is working to arrange for adequate insurance for the researchers, doctors and the medical team involved with the clinical trial, against claims filed by participants in the clinical trial and / or third-party claims related to the clinical trial either during or after the trial. This does not violate my rights under any law.

3.8) That I am guaranteed a willingness to answer questions raised by me and the possibility of consulting another party (such as a family doctor, family members, etc.), about making a decision to participate in and / or continue to participate in the study.

3.9) That in the case of any problem related to the study I can contact (name of doctor) by phone / mobile: (phone number of doctor), at all hours. I should immediately report to the doctor whose details are above, in regard to any medical problem, injury or other health event that may be related to the study. If I am injured as a result of my participation in the research, I should contact the research physician for appropriate medical treatment as well as further details of my rights in this regard. Signing this form does not violate my rights under the law.

4) State that I have been provided with detailed information about the study as detailed below:

4.1) **General Background and Importance of the Study.** Art therapy uses art making to help people express thoughts and feelings. Studies show that art-making reduces distress and pain that accompanies women who have breast cancer, during treatments and during the recovery period. Art therapy can take place in a group or alone with a therapist. In a group, women can express, listen, hear other women's experiences and learn that they are not alone in dealing with cancer. In this study we want to learn more about the role of emotions in reducing the mental and physical distress of women recovering from breast cancer from various sectors of Israeli society. The results of this study will help us design the best Art Therapy interventions for each patient. The study will also contribute an in-

depth understanding of the differences in emotional coping of women from different sectors of Israeli society.

4.2) **The purpose of the study.** 1. To examine whether changes in emotional processing after participation in an Art Therapy group for breast cancer patients reduces depression, fatigue and pain symptoms and improves quality of life. 2. To examine cultural differences in response to art therapy.

4.3) **Number of participants in the experiment.** 240 participants: 120 in the study group and 120 in the control group. Total (expected number) at (name of the hospital).

4.4) **The expected duration of participation in the experiment.** 11 weeks - 8 sessions once a week and 3 more data collection sessions.

4.5) **Methods - Description of the research product, a brief description of the different procedures during the experimental period (treatment and follow-up), with a clear distinction between the research procedures and the conventional procedures in medicine.**

After agreeing to participate in the study and filling out initial questionnaires, you will be randomly assigned to a research group or a control group. Participants in the research group and the control group will each participate in eight group sessions where a conversation and creation will take place through art materials once a week for an hour and a half. In both groups you will create art in the group, in one group will focus on the use of art for relaxation and relaxation and in the other group will focus on self-expression. Meetings will be held at the (name of hospital). Participants will be provided with a consent form before the study begins and will answer questionnaires at three time points: baseline, after the intervention, and 8 weeks after the end of the intervention. The group meetings will be led by an experienced art therapist trained by the research team.

You will be asked to connect to a mobile electrocardiogram (biopatch) to measure heart rate variability for 20 minutes at three time points during the study and to give 3 blood samples to measure inflammation (at baseline, after the intervention and at the end of the study) of 10 cc each.

4.6) **Benefits expected from participation or benefit to others as a result of the study.**

A participant who completes all the research will receive a total of $ 200 (to be paid in New Israel Shekels) at the exchange rate on the day of the intervention - session 11) for dedicating her time and travel to the study site. Participants may enjoy participation in the intervention and experience symptom reduction.

4.7) **The known risks and / or inconveniences foreseen for the study participant**

No risks are known, but if you feel distress as a result of participating in one of the groups, you will be referred to the social worker in oncology at (name of the hospital).

4.8) **The study includes the collection of samples.**
Source of samples:
Blood Sampling- A skilled professional will take 10 cc of blood (equivalent to 2 teaspoons).
Specimen Saving Mode: Encoded
If the samples are kept as identified, the participant may at any time request that the samples be destroyed.
Place of specimen storage: Dr. Czamanski-Cohen's laboratory at the University of Haifa. The research coordinator will transfer the blood in ice for initial processing (separation and freezing) to the University of Haifa.
Duration of sample storage: in accordance with the Ministry of Health requirements.
Erase the unnecessary: Participant agrees / disagrees with the use of samples taken for future research as approved by law.

_____
Participant Signature

4.9) Other relevant information (as provided by the study initiator).
Nothing

I hereby declare that I have given my consent voluntarily and that I have understood all of the foregoing. I have also received a copy of this informed consent form, bearing a date and duly signed.

5) By signing this consent form, I authorize the study initiator (through the lead investigator) to have access to medical records, as well as to the institutional Helsinki Committee, the auditor of the medical institution and the Ministry of Health, direct access to the medical files, for verification of medical trial methods and clinical data. This access to my medical information will be done while maintaining confidentiality, in accordance with confidentiality laws and procedures.

Name of study participant	Signature of study participant	Date

Statement of the researcher:

The above consent was obtained by me, after I explained to the participant in the study all of the above and I made sure that all my explanations were understood by her.

Name of the explaining researcher	Signature, stamp and license number	Date