

**Improving Outcomes for Younger Breast Cancer Survivors: A Phase III
Randomized Trial Targeting Behavioral Symptoms in Younger Breast Cancer
Survivors**

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The Pathways to Wellness (PTW) Study

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Improving Outcomes for Younger Breast Cancer Survivors: A Phase III Randomized Trial Targeting Behavioral Symptoms in Younger Breast Cancer Survivors - Protocol Revision Record -

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Minor technical changes in procedures, instruments, December 19, 2016 and January 23, 2017 before activation/enrollment

Minor eligibility modification and technical changes, before enrollment, June 15, 2017

Change in age eligibility based on DSMB meeting, February 2, 2018

Sample size re-estimation and change in PHQ-8 eligibility, May 2019 in consultation with NCI

Modifications due to the COVID-19 pandemic, April 10, 2020 and June 22, 2020

TABLE OF REVISIONS AND MODIFICATIONS

DATE	NATURE OF CHANGE	SECTION
December 19, 2016	Intervention training information removed from protocol and placed in Appendix B	6.1
	Change in some secondary outcome measures to reduce respondent burden and measure relevant concepts omitted	9.2, 9.3, 9.4, Table Summary of Questionnaire Measures
	Change in gene expression measurement platform	10.3.1
	Shipping of specimens to UCLA periodically during study	11
	New Appendix B describing training for instructors in both intervention conditions	Old appendix B now labeled C, and Old appendix C now labeled D
	Omit section on survivor education group formation and organization; now in training manual	Appendix D deleted pages 50, 51
January 23, 2017	Change from 3 to 2 booster sessions for mindfulness intervention	6.2.4
	Added the Social Provisions Attachment Scale	9.2
	Further refinement training plan for intervention instructors	Appendix B
June 15, 2017	Added current pregnancy as a study exclusion	4.2.5
	Modification to duration of booster sessions for mindfulness intervention	6.2.4
	Modification to educator training	Appendix B
February 2, 2018	Change in eligibility age at diagnosis from <45 years to 50 years or younger at diagnosis	Modifications in Sections 1.0, 3.5, 4.1.1, 7.1.
May 6, 2019	Change in PHQ-8 screening eligibility to include 3 or greater Revision of sample size estimation Updated details on specimen shipping	Modifications in Sections 4.1.4, 7.2, 7.3, 11.0, 18.1.2, 18.2, 18.3, 18.4
May 21, 2019	Minor accrual clarification	Modification in Section 18.2
April 10, 2020	Changes in collection of T4 data due to COVID-19 pandemic Minor corrections to questionnaire data collection	Modification in Section 8.4 Modification section 9.4
June 22, 2020	Control group sessions converted to remote delivery due to the pandemic	Modification in Section 8.4

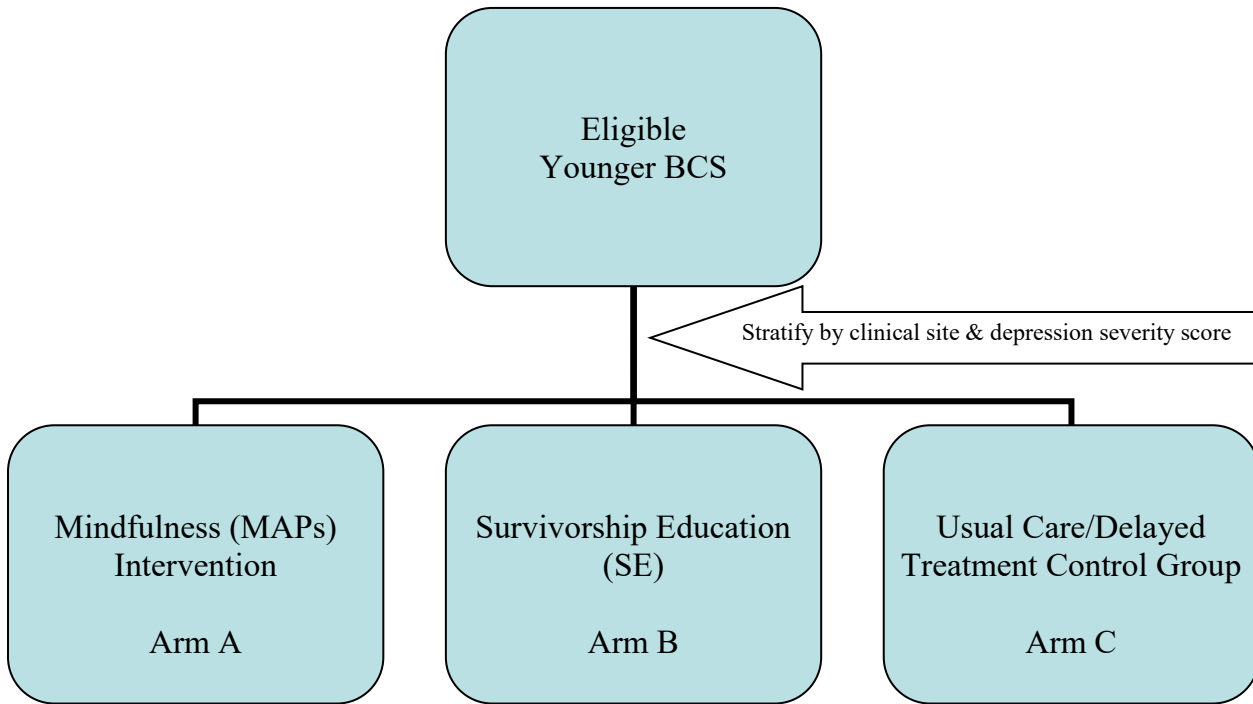
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Note: some protocol errors noted in November 2020 (e.g., modified or missing questionnaires) were corrected in the protocol document.

SCHEMA

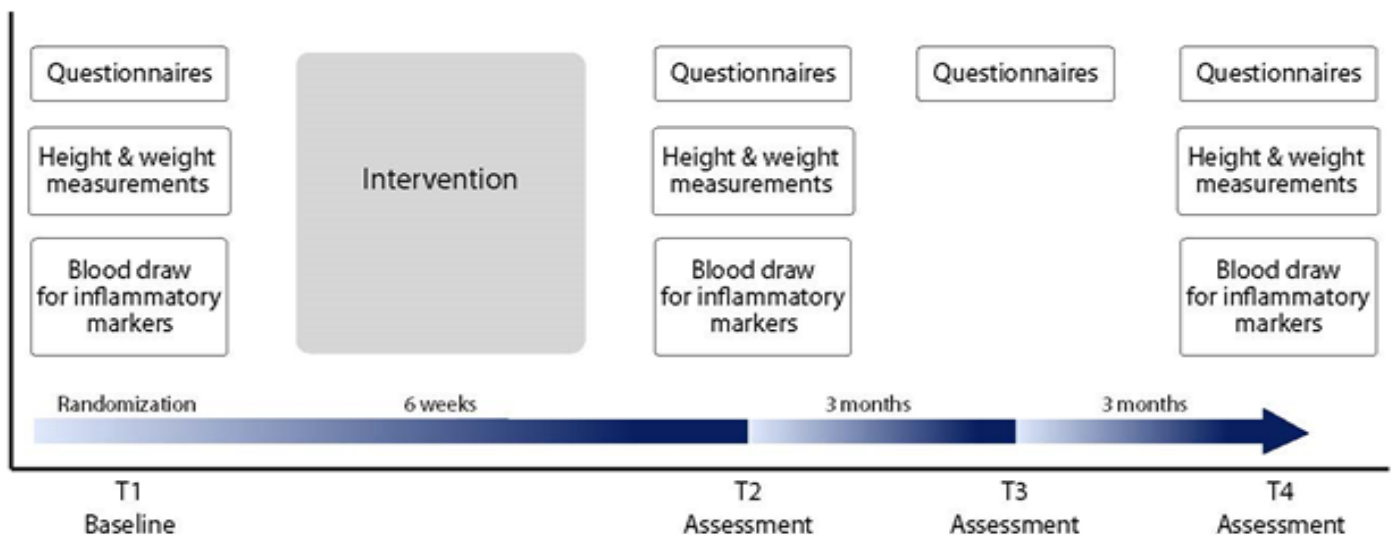


1. STUDY DESIGN/SUMMARY

This is a multi-site, randomized, three arm, Phase III trial that will evaluate the efficacy of two distinct types of group interventions that are specially designed for younger women who are more than 6 months post initial treatment for breast cancer. The first intervention is a mindfulness meditation-based intervention focused on improving psychological, behavioral, and biological function in younger breast cancer survivors that is adapted from an institutional program in place for the general public at UCLA's Semel Institute for Neuroscience and Human Behavior. The mindfulness group intervention program will be conducted once a week, for 2 hours, for 6 weeks, by a trained provider who will follow the study intervention protocol and will be trained centrally in the intervention at UCLA. The second intervention is a 6-week didactic group-based survivorship education seminar series that will review specific topics of importance to younger breast cancer survivors including: quality of life after breast cancer; medical management and quality of care post treatment; relationships and work-life balance; body image, sexuality and fertility; energy balance, nutrition, and physical activity; cancer in the family, genetics, and related issues. This curriculum has been adapted from two studies already completed by the investigators, and has a standardized slide set, and will be delivered by a health educator or advanced practice nurse at each of the participating institutions. For both interventions, the sessions will be 2 hours in length once per week, for 6 weeks. There will be a maintenance period that follows the 6-week group interventions to help sustain both mindfulness and health behaviors. The third arm of the study (Arm C) will include a usual care group with delayed intervention offered to the participants after they have completed parallel outcome assessments alongside the participants receiving the two interventions (Arm A and Arm B), but not until the end of data collection (6 months after the post-intervention assessments for the cohort).

360 breast cancer survivors* who were diagnosed with breast cancer at 50 years of age or younger, between 6 months and 5 years since diagnosis, and who have completed their primary cancer treatment (i.e., surgery, radiation, and/or chemotherapy) will be enrolled and randomized 1:1:1 to one of the two intervention groups or the control group. Participants will complete questionnaires and blood collection before and after the 6-week intervention, as well as 6 months after the end of the intervention. An interim questionnaire will be administered 3 months after the post-intervention visit. The figure below provides an overview of the study procedures.

*Note: Sample size protocol modification in 2019 (see section 18.2) to n=210



2. OBJECTIVES

2.1 Primary Objective

To evaluate the efficacy of two different types of group interventions (mindfulness and survivorship education), specifically tailored to the needs of younger female breast cancer survivors, in reducing depressive symptoms, compared to a usual care control group.

2.2 Secondary Objectives

- 2.2.1 To compare the efficacy of the two interventions relative to a usual care control group on fatigue, sleep disturbance, and vasomotor symptoms.
- 2.2.2 To examine the efficacy of the two interventions relative to a usual care control group on circulating and genomic markers of inflammation.
- 2.2.3 To explore potential moderators and mediators of intervention efficacy in the two intervention groups.

3. BACKGROUND

3.1 Younger Breast Cancer Survivors are a Vulnerable Population

Breast cancer is the most common cancer in younger women (< 50 years), with 1 in 53 women in this age group developing breast cancer. Breast cancer is also the most common cause of cancer death for younger women.¹ However, with advances in detection and treatment, the number of women who survive breast cancer has increased significantly, with five-year survival rates approaching 90%, resulting in an estimated 3 million North American women surviving long-term.² As survival times increase, addressing the impact of breast cancer and its treatments on long-term outcomes has become increasingly important, especially for younger women who make up approximately 25% of breast cancer cases. These young women can expect several decades of survival after breast cancer treatment ends; however, they are at high risk for adverse psychological and physical problems that can negatively impact the quality and potentially, the length of their survivorship. Indeed, younger women are at elevated risk for breast cancer recurrence and cancer-specific mortality, as well as secondary cancers, premature menopause, osteoporosis, and cognitive declines.

Studies have consistently shown that younger women have greater psychological morbidity after breast cancer than older women and age-matched women with no cancer history, including elevated levels of depressive symptoms, anxiety, and perceived stress.^{3,4} Younger breast cancer survivors experience greater impact from cancer, perceive cancer as more threatening⁵ and report greater fear of recurrence. They also report feeling more isolated and less satisfied with support groups due to their age.⁶ In addition to psychological disturbances, younger women are at increased risk for physical and behavioral side effects of cancer treatment, including fatigue, sleep disturbance, and ongoing vasomotor symptoms associated with long-term endocrine therapy and premature menopause.^{3,7-9} Impairments in emotional and physical functioning have been documented up to 10 years after diagnosis, suggesting that effects may not remediate even over time without intervention.¹⁰ Thus, younger breast cancer survivors (BCS) are at risk for negative emotional and physical sequelae that may persist for years after diagnosis and treatment, making them a particularly vulnerable population.

3.2 Potential Interventions to address Behavioral Symptoms in Younger Breast Cancer Survivors

Despite the increased behavioral symptoms reported by younger BCS, few psychosocial interventions have specifically targeted this vulnerable age group.¹¹⁻¹³ In a focus group study with 36 younger BCS conducted by Partridge's group,¹⁴ participating women reported feeling different from older women, especially with regard to relationships, fertility, menopausal symptoms, treatment side effects, and work/financial issues. They also reported facing unique challenges (e.g. partner relationships, dating, infertility, concerns about their young children, work and finances), and noted substantial difficulties transitioning into the survivorship phase of care. Finally, younger BCS reported desiring assistance, including connecting with other young patients, help navigating the healthcare system, tailored educational materials, and referrals to appropriate counselors.¹⁴ These findings document the desire for intervention among younger women and provide some direction with regard to how to address the emotional and physical needs of this group.

In a 2012 systematic review,³ we identified only three published randomized controlled trials (RCTs) that specifically targeted younger women with breast cancer. The first study by Allen et al.¹¹ evaluated a problem solving intervention for young breast cancer patients undergoing chemotherapy that led to improvements in quality of life and mental health. The second study, by Scheier et al.¹² was a three group RCT that recruited younger women after chemotherapy completion, and assigned them to a nutrition education or a health education group delivered over 4 monthly sessions and compared them to a concurrent control group. Women in both education groups had significant improvements in physical function and depressive symptoms compared to the control group in the follow-up year. A third study targeted younger survivors who were 5 years post-diagnosis and provided education-based workshops delivered in 3 monthly sessions.¹⁵ This intervention led to improvements in breast-cancer related knowledge and physical activity, though effects on quality of life and symptoms were not assessed. In the broader literature, psychoeducational interventions have been recommended for addressing depressive symptoms and fatigue in cancer patients and survivors.^{16,17} These studies provide preliminary evidence that psychoeducational approaches may be helpful to younger BCS during treatment and into the survivorship period. **However, these promising findings have not been translated into the clinical care setting, nor have such interventions been implemented in the post-treatment period, despite considerable need and potential benefit.**

Recently, mindfulness meditation has emerged as a promising intervention for general and cancer populations¹⁸⁻²⁰ and may be a particularly good option for younger BCS, given their considerable interest in mind-body treatments.²¹ Mindfulness involves bringing attention to one's present moment experiences, including thoughts, feelings, and physical sensations, with openness, curiosity, and absence of judgment.²² Interventions have been developed to cultivate mindfulness through formal meditation and informal practice, and RCTs have documented benefits of mindfulness-based interventions among BCS, including improvements in depressive symptoms, stress, and fatigue.²³⁻²⁶ We have recently completed a phase II RCT of a 6-week Mindful Awareness Practices (MAPs) group intervention program in younger BCS and have demonstrated its benefit on reduction behavioral symptoms at the immediate post-treatment assessment,¹³ suggesting the feasibility and preliminary efficacy of this intervention in the target population of younger BCS (see preliminary data below). Further, we also saw reductions in inflammatory signaling in this trial, which may be due to decreases in physiological arousal. Although trials by our group and others are promising, almost all have been conducted at single institutions and have focused on the short-term effects of mindfulness practice, limiting their translation and potential impact on longer-term health. In the proposed study, we will implement strategies to encourage maintenance of practice beyond the 6-week group intervention, as we hypothesize that this will be important for sustained reduction in behavioral symptoms in this vulnerable population.

3.3 Preliminary Data

3.3.1 Mindfulness Intervention Program (MAPs)

We have recently completed a phase II randomized trial at UCLA evaluating the efficacy of a mindfulness meditation intervention in younger women who had been diagnosed and treated for premenopausal breast cancer. They were randomly assigned to a 6-week mindfulness meditation intervention designed for breast cancer survivors (n=39) or to a wait-list control group (n=32). At pre- and post-intervention, participants completed questionnaires and provided blood samples for genome-wide transcriptional profiling and bioinformatic analyses as well as circulating inflammatory markers. The primary outcomes of interest were perceived stress and general depressive symptoms, which are commonly reported by younger BCS and are specifically targeted by this treatment. We also examined effects on cancer-specific measures of distress, including intrusive thoughts about cancer and fear of cancer recurrence, and cancer-related physical symptoms, including fatigue and sleep disturbance, as well as vasomotor symptoms. Finally, effects on positive psychological outcomes were assessed. The full study was recently reported.¹³

3.3.2 Assessments

Eligible participants were scheduled for a pre-treatment baseline assessment at UCLA, which was conducted 1-2 weeks before receipt of the intervention program or assignment to the delayed treatment control group. This assessment included completion of self-report questionnaires as well as collection of fasting blood samples and an evaluation of cardiovascular status and autonomic activity. A post-treatment assessment was conducted 1-2 weeks after treatment completion at UCLA to determine acute effects of the intervention. This assessment included completion of self-report questionnaires, collection of fasting blood samples, and an evaluation of cardiovascular and autonomic activity. At three months post-intervention, a follow-up questionnaire packet was mailed to study participants to assess maintenance of treatment effects.

3.3.3 Intervention

The mindfulness meditation-based intervention was based on the Mindful Awareness Practices (MAPs) for Daily Living, a 6-week program developed by Diana Winston and colleagues at the Mindfulness Awareness Research Center (MARC) at UCLA. We tailored the MAPs program for younger breast cancer survivors by including information about enhancing health and preventing breast cancer recurrence. Participants met for 6 weekly, 2 hour, group sessions conducted by an experienced mindfulness instructor that included presentation of information on mindfulness, relaxation, and the mind-body connection; experiential practice of meditation and gentle movement exercises; and a psycho-educational component for cancer survivors. Lecture, discussion, and group process focused on solving problems concerning impediments to effective practice, working with difficult thoughts and emotions, managing pain, and the cultivation of loving kindness. Home practice is a key component of MAP, and participants were instructed to practice mindfulness techniques on a daily basis.

The wait-list condition controlled for naturally occurring changes in stress and other outcomes over the six-week intervention period. After the post-treatment assessments were completed, those assigned to the wait-list control group were offered participation in the MAPs classes.

3.3.4 Outcome Measures

The primary outcomes of interest were depressive symptoms and perceived stress. Depressive symptoms were assessed with the *Center for Epidemiologic Studies-Depression* scale (CES-D), a reliable and valid 20-item measure that assesses depressive symptomatology in the last week.²⁷ Stress was assessed with the *Perceived Stress Scale (PSS)*, a 10-item scale that measures the degree to which

an individual's life situations are appraised as stressful.²⁸ A number of secondary outcomes were also assessed. To determine whether intervention effects extended to cancer-specific distress, cancer-related intrusive thoughts and fear of cancer recurrence were assessed. Intrusive thoughts about cancer were assessed with the 7-item subscale of the *Impact of Events Scale*;²⁹ this subscale was of interest because it predicts poor quality of life in cancer survivors.³⁰ *Fear of recurrence* was assessed with a 4-item subscale of the *Quality of Life in Adult Cancer Survivors (QLACS)* questionnaire that assesses concerns about cancer recurrence.³¹

To determine whether the intervention would influence physical symptoms that are common among younger BCS, we assessed fatigue, sleep disturbance, and other physical side effects of cancer treatment. Fatigue was assessed with the *Fatigue Symptom Inventory (FSI)*, a 13-item measure that assesses fatigue intensity, duration, and interference with daily functioning.^{32,33} Subjective sleep quality was assessed with the *Pittsburgh Sleep Quality Index (PSQI)*, a 19-item scale that assesses sleep quality and disturbances.³⁴ Side effects of cancer treatment were assessed with 20 items from the *BCPT symptom scales*, which include a variety of physical symptoms relevant to cancer survivors.³⁵ Effects on positive psychological outcomes were also examined. Meaning and purpose in life were assessed with the 8-item subscale of the *Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being*.³⁶ Self-reported demographic and disease-related variables were assessed at baseline, and homework was assessed using questionnaires completed each week during the intervention. Participants in the mindfulness group reported on the number of minutes they engaged in formal mindfulness practice each week.

3.3.5 Results

The study took place at the UCLA Medical Center, Los Angeles, CA between March 2011 and October 2012. We screened 151 women for eligibility; 11 (7%) were not eligible, and 69 (46%) were not interested in participating. The primary reasons for ineligibility were breast cancer recurrence or metastasis, or another cancer. We randomized 71 women to either the 6-week MAPs intervention (n = 39) or to a wait-list control condition (n = 32). Thirty-eight women received the allocated intervention, which we defined as attending at least two of the six classes, and complete follow-up data were obtained on 59 participants (83%).

In the MAPs group, the mean number of classes attended was 5.1 (85%) and the median was 5 (83%). The mean number of minutes of mindfulness practice each week, including time spent in the mindfulness classes was 180. At the 3-month post-intervention follow-up, 23 of the 31 women (75%) who attended the mindfulness classes and who completed the 3-month follow-up questionnaire were continuing to use techniques learned in class at least once a week.

The demographic and clinical characteristics of the participants are shown in Table 1 on the next page.

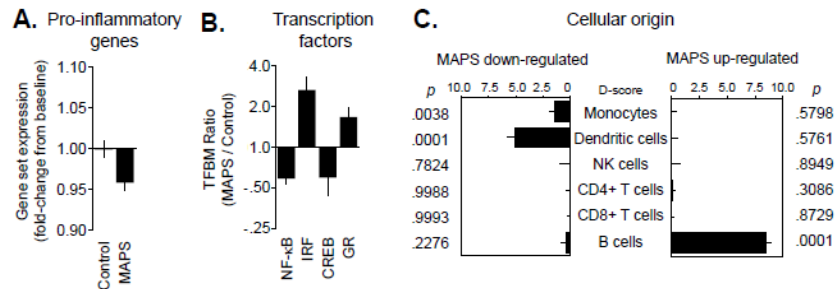
TABLE 1. Demographic and Clinical Characteristics of Study Participants

Characteristic	MAPS Group, n = 39	Control Group, n = 32
Age: Mean (range), y	46.1 (28.4-60)	47.7 (31.1-59.6)
Time since diagnosis: Mean \pm SD, y	4.0 \pm 2.4	4.1 \pm 2.3
Ethnicity, no. of patients		
White	29	25
African American	1	1
Asian	3	5
Other	6	1
Married, % ^a	56	75
Education, %		
<College	13	22
College graduate	23	25
>College	64	53
Employed full- or part-time, %	80	63
Income >\$100K, %	62	58
Received chemotherapy, %	77	69
Received herceptin, %	21	31
Received radiation, % ^a	77	56
Currently on endocrine therapy, %	62	66
Smoking history, %		
Ever smoked ^a	28	53
Currently smoke	5	13

Abbreviations: MAPS, Mindful Awareness Practices; SD, standard deviation.
^a For this variable, there was a chance imbalance between groups, as indicated by $P < .10$ (chi-square test or 2-sample t test).

Scores on the PSS, PSQI, CES-D, and FSI in this group of younger women, who were not screened for evidence of distress, indicate very high levels of stress, depressive symptoms, fatigue, and sleep disturbance, demonstrating the need for clinical intervention.

The main analysis outcomes were post-treatment assessment of **perceived stress (p=0.004)** and **depressive symptoms (p=.09)**, which were both lower in the intervention group. We also found that women in the intervention group had higher levels of positive affect (p=.033), meaning & peace (p=.001), and self-compassion (p=.004) at the post-treatment assessment, as well as lower fatigue severity (p=.007), better sleep quality (p=.015), and less severe vasomotor symptoms (p=.015). Although there was no difference between groups in the change in cancer-related distress or fear of recurrence from baseline to post-treatment, there was a significant difference between groups from baseline to the three month follow up time point for both cancer-related distress (p=.049) and fear of recurrence (p=.002), suggesting longer term effects of the intervention on these outcomes. (See Bower et al¹³ publication and Appendix A for table with full results of all time points and with all measures.) Further, the intervention group also showed significant down-regulation of pro-inflammatory genes, with accompanying bioinformatic indications of reduced NF- κ B and increased glucocorticoid receptor (GR) signaling (all ps < .05); see Figure Panels A and B next page. Transcript origin analysis indicated that these changes were primarily driven by changes in monocytes and dendritic cells (panel C). Unfortunately, by the 3-month post-intervention assessment, both depressive symptoms and perceived stress had returned to the baseline level of severity, suggesting the need for additional support to maintenance of mindfulness practice. There were no significant group effects on plasma inflammatory markers, although post hoc within-group analyses indicated that more minutes of mindfulness practice per week were associated with reductions in the proinflammatory cytokine IL-6 in the intervention group (p = .003). Thus, for the current study, we are also planning to examine the impact of the intervention on inflammatory biology as a secondary aim.



In summary, the results from this phase II randomized pilot study support the short term effects of mindfulness meditation in younger breast cancer survivors on reduction of perceived stress and depressive symptoms, with the suggestion that this intervention may also have beneficial effects on inflammatory processes, with potential relevance for behavioral and disease-related outcomes. In addition, there were favorable effects on common behavioral symptoms, including fatigue, perceived sleep quality, and vasomotor symptoms. Thus this intervention appears quite promising. In addition, women who received the mindfulness intervention had sustained improvement in intrusive thoughts and reduced fear of recurrence as measured at 3 months post-intervention,

3.4 Survivorship Education (SE) Intervention Program

For the survivorship education intervention, we have adapted materials from several other studies that have provided survivorship education to women with breast cancer including a study of younger women with breast cancer³⁷ as well as those used in a previous evaluation of women with post-treatment fatigue, who received this intervention in comparison to an Iyengar yoga intervention, which was found to improve depressive symptoms.³⁸ Similarly, the intervention education programs used in the Scheier study described in the background section¹² and in the Moving Beyond Cancer study³⁹ demonstrated benefit to women enrolled in those trials. The Johns Hopkins team also has considerable experience in the delivery of survivorship education to this target population. The expertise of the three clinical sites has been used to refine the survivorship education curriculum and slide set so it can be delivered systematically by each of the participating research sites. The full lecture series has been developed and is ready for pilot-testing prior to implementation across the three sites.

3.5 Rationale and Significance of the Planned Study

Younger women with breast cancer account for one quarter of the newly-diagnosed breast cancer cases each year, and close to one million of the 3 million breast cancer survivors. The largest gains in survival from multi-modal treatments have occurred in this age group. Although younger women with breast cancer can expect long survival times after diagnosis and treatment, they also face an extended period of time living with the risk for breast cancer recurrence, as well as long term and late effects of cancer treatments. Research has documented higher levels of depression, anxiety, stress and other symptoms in these younger women. Many are also in a stressful period in their lives, completing their education, establishing intimate partnerships, having children or raising a family, as well as working and caring for elderly parents. Finding effective behavioral or educational strategies to help younger breast cancer patients heal and maintain good physical and mental health during the post-treatment period is a high priority for post-treatment survivorship care. The development and evaluation of interventions that hold promise for this population of breast cancer patients is a cancer control priority given their unique needs and long life expectancy. In this study we will focus on breast cancer survivors who were diagnosed at 50 years of age or younger, because they are particularly at risk for greater depressive symptoms, as supported in the literature. In addition, eligibility

inclusion will focus on younger women who are manifesting evidence of increased depressive symptoms, so that we are targeting those most likely to benefit from the interventions being tested.

The interventions that will be tested in this research have face and content validity, a history of use in other populations, and preliminary efficacy in younger breast cancer survivors with psychological and physical symptoms. The intervention programs are already developed with proven preliminary efficacy in related populations and the clinical coordinating center and selected research sites have a track record conducting studies similar to these. The testing of these two interventions in a phase III RCT setting in multiple sites will establish the feasibility of the intervention delivery in settings that have not used them before, determine the short term efficacy of the two interventions compared to the control condition, and the correlative science study will enhance our understanding of potential mechanisms for the efficacy of the intervention(s) if one or both are deemed effective.

4. PARTICIPANT SELECTION

4.1 Inclusion Criteria

- 4.1.1 Women diagnosed with early stage, resectable breast cancer (Stage 0, I, II, or III) at 50 years or younger, and are within 5 years of diagnosis
- 4.1.2 Have completed all surgery, radiation, and/or chemotherapy treatments at least 6 months previously. May still be receiving trastuzumab or endocrine adjuvant therapy.
- 4.1.3 Ability to complete evaluation surveys in English.
- 4.1.4 Have evidence of at least mild clinical depression on a standardized screening questionnaire (i.e., score of 5 or greater, later revised to score of 3 or greater, on PHQ-8; implemented May 6, 2019 for cohort 5).

4.2 Exclusion Criteria

- 4.2.1 Has a breast cancer recurrence, metastasis, or another interval cancer diagnosis following the breast cancer (excluding non-melanoma skin cancer);
- 4.2.2 Unable to commit to intervention schedule (6 weekly group meetings)
- 4.2.3 Actively practicing mindfulness meditation
- 4.2.4 Has another serious or chronic medical or psychiatric condition that contributes to substantial physical or emotional disability that would detract from participating in either of the intervention programs or from the measurement of intervention outcomes.
- 4.2.5 Is currently pregnant

4.3 Inclusion of Underrepresented Populations

Individuals of all races and ethnic groups are eligible for this trial. There is no bias towards race in the clinical trial outlined, and special efforts will be made to encourage participation of women of diverse racial/ethnic groups. This trial is open to the accrual of women only because there are so few men who develop breast cancer at a young age, and for scientific reasons this study is focused on younger women.

5. REGISTRATION PROCEDURES

5.1 Guidelines for All Participating Institutions

Eligible participants will be entered on study through the RedCAP database that will allow entry and review of study eligibility, followed by random assignment if all eligibility criteria are met. Participants will only be randomized after all of the components of the enrollment visit are completed.

6. Intervention Groups

6.1 Pre-Intervention Preparation

Potential instructors for the mindfulness intervention will be screened by Ms. Winston from the Mindful Awareness Research Center (MARC) at UCLA to ensure that they have had adequate training to deliver this particular intervention. Potential instructors for the survivor education intervention will be identified by site PIs and evaluated for experience in survivorship education, nursing, and oncology. The details of the selection and training of both groups of instructors are found in Appendix B.

6.2 Intervention Programs

6.2.1 Arm A- Mindfulness Meditation (MAPs)

The specific curriculum for this 2 hour/week, 6-week program will be provided to women who are assigned to this group as part of the randomization. Each session will provide structured training and exercises in mindfulness, and women will be given tools to facilitate their practice of these techniques at home through formal meditation practice as well as through guidance in the informal use of mindfulness during daily life. During each session the instructor will assist the participants in learning this practice and will regularly assess how the participants are doing with their mindfulness practice. A general overview of the content for each session is found in Appendix C. A detailed training manual has been developed specifically for use with breast cancer survivors to be used across the clinical sites, and will be used in the instructor training. The sessions will introduce the following topics and associated practices: 1) What is mindfulness? 2) Listening, embodiment, and obstacles; 3) Working with pain; 4) Working with difficult emotions, cultivating positive emotions; 5) Working with thoughts, mindful interactions; 6) Wrap up. This standardized curriculum with delivery by trained clinical providers at each site will be necessary to evaluate the efficacy of the intervention program.

6.2.2 Arm B- Survivorship Education Intervention (SE)

The specific curriculum for this 2 hour/week, 6-week program will be provided to women who are assigned to this group as part of the randomization. The SE intervention is a series of didactic sessions designed specifically for younger breast cancer survivors and to be delivered in a small group format. The seminar series focuses on cancer survivorship issues, but also allows group discussion and support. Lecture topics were selected to address a range of issues that are of high importance to younger breast cancer survivors based on a review of the literature, discussions with younger breast cancer survivors, and input from other experts in breast cancer survivorship. The seminars will be led by an oncology clinician, e.g., nurse, advance practice provider or physician at the clinical site who has expertise in breast cancer survivorship.

The SE sessions will follow a didactic format, with lectures followed by group discussion, as part of a psychoeducational approach. The material presented is based on the empirical literature and on clinical experience with this patient population. The sessions are designed to provide information and include

recommendations for “healthy” behaviors in particular areas (e.g., American Cancer Society recommendations for healthy diet and exercise). The overarching goal is to provide current, comprehensive, and engaging coverage of health-related topics that are of central importance to young breast cancer survivors. In addition, the instructor will facilitate group interaction and social support, which has been identified as a key need by young breast cancer survivors. The planned lecture schedule and format are described in Appendix D. An intervention manual will be prepared for delivery of the SE intervention program, along with a slide set for each lecture, power point notes, and information about local community resources that may be helpful to the young survivors to address the health and behavior issues covered in the seminar series.

6.2.3 Arm C- Usual Care/Delayed Treatment Control Group

The participants assigned to this group after randomization will not receive any specific intervention until they have completed their T4 research assessment (6 months after the post-intervention assessments at T2). We will offer the Arm A and Arm B interventions to this group of participants after they have completed their assessments. The Arm C participants will be able to select which program they would like to attend.

6.2.4 Arm A and B Maintenance Activities

To enhance maintenance of treatment effects in both intervention arms, we have developed activities and materials designed to sustain key components of each intervention. For women assigned to the MAPs arm, we will conduct monthly, in person booster sessions led by the mindfulness instructor and attended by other group members for 2 months after the 6-week group intervention (2 booster sessions). These 60 minute sessions will include guided meditation, questions, and discussion of how to maintain a mindfulness practice. Women in the SE arm will receive monthly, electronic newsletters with tailored information about topics of interest to younger survivors, including cancer-related events in the community and tips about following through on recommendations for healthy living (2 newsletters).

6.3 Concomitant Treatments

Participants will be discouraged from engaging in any other psychosocial, educational or behavioral research programs for the duration of the study. Participation in other activities will be monitored through a questionnaire.

6.4 Duration of Therapy and Timing of Assessments

The Arm A and Arm B interventions will last 6 weeks. In-person pre (T1) and post-intervention (T2) assessments will occur, with only a survey 3 months later (T3) and a final in person visit (T4) at 6 months post intervention. These assessments will be done in all study participants.

6.5 Duration of Follow-Up

Participants will be followed through the T4 assessment. As a standard procedure we will include in the consent form an option for the participant to be re-contacted for future research. This will provide the option for longer follow-up by questionnaire or telephone if the study findings indicate a need to do so.

6.6 Criteria for Removal from Study

Participants will be removed from study when any of the criteria listed in Section 6.7 applies. All eligible patients who are randomized will be included in the overall evaluation of outcomes (intent-to-treat analysis). All reasons for discontinuation of participation will be documented in the research records.

6.7 Discontinuation of Treatment

Potential reasons for discontinuation of protocol treatment include:

- Breast cancer recurrence. The participant could potentially continue receiving the intervention (if not too disturbing to remaining participants), but outcome data collection would not continue.
- Non-attendance at Arm A or Arm B intervention sessions, e.g., failing to attend after the first session and causing disruption for group as a result of behavior or intermittent participation; the Protocol Chair will determine when non-compliance should lead to removal from study, although participant data will still be included in the intent-to-treat analysis.
- Intercurrent illness or condition that would, in the judgment of the treating investigator, affect assessment of study outcomes to a significant degree or require discontinuation of study treatment. At participant's own request. Note: The reason for discontinuation from the study must be documented. The participant will be included in the overall evaluation of outcomes (intent-to-treat analysis) if any protocol therapy was administered prior to withdrawal.
- Study is closed for any reason (e.g. new information shows that the trial should be stopped or that administrative factors prevent continuation of the study)
- General or specific changes in the participant's condition render the participant unacceptable for further study involvement in the opinion of the treating investigator.

6.8 Withdrawal from Study

6.8.1 The reasons for withdrawal from the study include:

- Participant withdraws consent.
- Participant is lost to follow-up.
- Study is terminated for any reason.

6.9 Additional Information

Participants will have their parking paid for at the evaluation visits, as well as to attend all of the assigned sessions for Arm A and Arm B. Participants assigned to Arm C will receive the same parking coverage when they receive their chosen intervention after completion of the study.

7. PARTICIPANT RECRUITMENT, ELIGIBILITY SCREENING, AND ENROLLMENT

7.1 Recruitment of Younger Breast Cancer Survivors

Each site will develop local strategies for identification of potentially eligible younger female breast cancer survivors (age 50 years or younger at diagnosis). Institutional tumor registries and clinic lists are excellent initial places to identify potential participants, and with IRB approval they may be invited to participate in the study with an invitation letter and response form (sample letters and response forms will be provided by the UCLA Coordinating Center). Flyers and other announcements should be disseminated to community based support groups, clinical affiliate practices, as well as posted on social media sites (e.g., Young Survival Coalition, Stupid Cancer, Facebook posting/advertisement). We will also do a centralized posting of the study to the Army of Women to recruit breast cancer survivors who live in the geographic areas served by the participating sites. Clinical sites may also choose to do local news or press releases if appropriate for their institution and community. Extra efforts will focus on recruitment of underserved and ethnic minority women to ensure that all members of community are represented in the study sample. Each of the institutions has established community collaborators that will facilitate these outreach activities. Casting a wide net is very important, as each site will likely have to screen twice the number of individuals needed for the site specific enrollment based on recent experience with the mindfulness meditation study.¹³

7.2 Screening for Eligibility

Potentially interested and eligible participants must complete a screening telephone call with the study coordinator at each clinical site. The screening call will review information about the woman's age at diagnosis, her disease stage, when last treatments were completed, if she is disease-free, does not have other serious medical conditions, as well as be screened for level of depressive symptoms with the PHQ-8. For the purposes of study eligibility, we will use a cut point for mild depressive symptoms on the PHQ-8 with a score of 3 or greater. Only women who meet this criterion will be eligible. If the woman is clinically eligible (review of all eligibility inclusion and exclusion criteria), the study will be described in greater detail and she will be asked if she is interested participating and would be able to attend the 6-week group intervention program. If affirmative, then the woman will be invited to attend an enrollment visit. In order to accommodate these young women's busy life schedules, and facilitate their ability to attend the 6 session group intervention programs, we will try to schedule the group interventions at the best time of day/day of week/location to maximize both recruitment and retention. Thus with at least 4 cohorts being recruited at each site, a woman who cannot attend on a week night might be able to attend on a weekend day and join a subsequent cohort. Those women who are either ineligible or not interested will be thanked for their interest and there will be no further contact.

7.3 Formation of Study Cohorts and Preparing for Enrollment

Eligible participants will be enrolled and randomized after the study site has identified up to 15-20 potential participants who will form a cohort for randomization to one of the three groups (the two active interventions and control), so that there will be approximately 6-7 women assigned to each group. Each study site will be expected to enroll 4-6 study cohorts during the course of the trial, with a total target of 70 women randomly assigned to one of the three arms.

Across the three clinical sites, we anticipate achieving the target sample size of 210 randomized participants within a 36-month period of time. Enrollment will be monitored closely to ensure that the target enrollment is achieved in a timely fashion.

7.4 Enrollment Visit

To accomplish the cohort formation, the project coordinator will have to screen a sufficient number of women to form a cohort of women who are willing and able to attend either one of the two intervention groups or be in the usual care/delayed intervention group. If a woman is not able to commit the time to come to a 6-week group intervention during the assembling of cohort 1, then she can be considered for cohort 2 when it is formed. All women who are considered eligible for the study and enrollment as part of a specific cohort will be invited for their in-person baseline assessment (T1) that will occur prior to randomization. At the time of that visit, the study protocol and consent form will be reviewed and signed, and the study questionnaire will be completed. Height and weight will be measured and blood specimens will be drawn. At the end of the visit the results of the random assignment will be revealed to the participant and the research team.

8. OUTCOME ASSESSMENTS

8.1 Baseline visit (T1)-In Person

This is the pre-randomization visit at which all data collection will occur after the participant has consented to participate. This visit should take approximately 60-90 minutes and should be done in the morning between 8-11 AM (fasting is not necessary). After the completion of all procedures the results of the randomization assignment will be revealed and the participant will be informed of her assigned group and given information about when it is scheduled. These visits will occur within 3 weeks of the initial Arm A and Arm B intervention scheduled start times.

8.2 Immediate Post-Intervention Visit (T2)-In Person

This visit will be scheduled to occur within the first 2 weeks after the conclusion of the Arm A and Arm B intervention programs. The Arm C participants from the same cohort can be brought in at any time within this window of time. Sites will have to work carefully to schedule these visits in a timely fashion within the time window. The same procedures conducted at baseline (T1) will be repeated at this visit, and will be conducted between 8-11 AM. Participants should be scheduled for their anticipated T4 follow-up visit at the conclusion of this visit.

8.3 Interval Follow-up Questionnaire (T3)

All study participants within a cohort will receive an electronic mailing or mailed paper questionnaire (depending on what format has been used in the prior visits) asking them to complete the study questionnaire, with electronic reminders to facilitate completion. This assessment will occur three months after the post-intervention (T2) visit.

8.4 Final Follow-up Visit (T4)-In Person

This visit is planned for approximately 6 months after the conclusions of the Arm A and Arm B intervention programs. At this visit, the same procedures as in the other visits will be performed, and will be conducted between 8-11AM. Participants will be thanked for their role in the study. Those women who were assigned to Arm C will be offered the opportunity to participate in either of the two intervention programs.

Amendments 4/10/20 and 6/22/20: due to the COVID-19 pandemic, the T4 data collection for the final study cohort was done electronically, in same format as the T3 data collection, and in-person assessments and blood collection were not performed. The wait-list control participants who had not yet participated in either MAPS or SE at all three sites were invited to participate in Zoom led classes at two different sessions. These classes were led by one of the UCLA site instructors.

9. OUTCOME MEASUREMENTS: QUESTIONNAIRES AND ANTHROPOMETRIC MEASURES

We will examine intervention effects on psychological, behavioral, and biological measures. The questionnaires to be used all have good psychometric properties, and many were specifically designed for cancer survivors. The questionnaires will be administered electronically or by paper (consistent method across time points), as preferred by the participant, and will take about 45 minutes to complete at T1 and 30 minutes at T2, T3 and T4.

9.1 Background Variables and Potential Confounds

Demographic information (e.g., age, race, ethnicity, education, relationship status) will be collected via self-report using a standardized form. Clinical information (e.g., data of breast cancer diagnosis, disease stage, previous forms of cancer treatment, dates of previous treatments, endocrine therapy type and duration) will be collected via self-report at baseline, along with concomitant medications. Self-report of this medical information has been found to be reliable in breast cancer patients.⁴⁰ Alcohol and tobacco use will be obtained from standardized epidemiologic measures and physical activity using the Godin Leisure-Time Exercise Questionnaire.⁴¹ Height and weight will be measured using standardized anthropometric methods. Comorbid medical conditions will be assessed using a validated self-report instrument developed by Katz and colleagues.^{42,43} We will also collect information on concurrent medications at each visit, as well as use of psychosocial support services for cancer-related concerns, both using measures from previous studies with this patient population. Data on current and past use of integrative medicine services will be collected at T1 only. We will also administer the Patient Health Questionnaire-9 (PHQ-9)⁴⁴ to evaluate clinically-significant depression at baseline only. Screening PHQ-8 data will be used for stratification purposes in the randomization process, but will not be included as part of this database.

9.2 Self-reported Outcome Variables

The primary trial outcome is depressive symptoms, which will be assessed with the *Center for Epidemiologic Studies-Depression* scale (CES-D), a 20-item self-report scale developed for the general population to assess depressive symptomatology in the last week.²⁷ Secondary outcomes include cancer-related behavioral symptoms, including fatigue, sleep disturbance, and vasomotor symptoms. Fatigue will be assessed with the *Fatigue Symptom Inventory* (FSI), a 13-item measure that assesses fatigue intensity, duration, and interference with daily functioning.³³ We focus on fatigue severity (assessed with 4 items that capture most fatigue, least fatigue, average fatigue, and current fatigue) and fatigue duration (assessed with 1 item). Subjective sleep quality will be assessed with the *Insomnia Severity Index* (ISI).⁴⁵ Side effects of cancer treatment will be assessed with 20 items from the *BCPT Symptom Scale*, which include a variety of physical symptom scales relevant to cancer survivors.³⁵ In particular, we will focus on the vasomotor symptom scale. The *SF-12 health survey*⁴⁶ will be used to capture the broad domains of physical and mental health functioning at each assessment.

Secondary psychological outcomes are as follows: Meaning/purpose in life will be assessed with the *Functional Assessment of Chronic Illness Therapy-Spiritual Well-Being* subscale (FACIT-SP-12), a 12-item scale that measures feelings of meaning/purpose in life and feelings of faith.³⁶ For this study, we will use 8 items from the meaning/purpose in life subscale. In addition, clinically-significant anxiety will be assessed using the *Generalized Anxiety Disorder-7* questionnaire, a 7-item scale that assesses anxiety symptoms in the past two weeks.⁴⁷ Stress will be assessed with the *Perceived Stress Scale* (PSS), a 10-item scale that measures the degree to which an individual's life situations are appraised as stressful.²⁸ Positive affect will be assessed with the 10-item positive affect subscale of the *Positive and Negative Affect Scale* (PANAS), as well as the Joviality and Serenity subscales of the PANAS-X.⁴⁸ Various aspects of the impact of cancer will be measured with three scales (worry, life interference, altruism/empathy scales) from the *Impact of Cancer Version 2* (IOC v.2),⁴⁹ and cancer-related distress with the intrusions subscale of the *Impact of*

Events Scale (IES),²⁹ focused on cancer. Social support will be assessed with the 12-item emotional support subscales of the *2-way Social Support Questionnaire*⁵⁰ as well as the 4-item attachment subscale of the *Social Provisions Scale*.⁵¹ Effects of cancer on work and other activities will be assessed with the *6-item Work Productivity and Activity Impairment Questionnaire* (WPAI-GH).⁵²

9.3 Potential Moderators of Intervention Efficacy

We will examine several hypothesized moderators of intervention effects, drawing from the empirical literature and our conceptual model. Previous trials have shown that *preparedness for survivorship* and *intervention preference*⁵³ moderates effects of psychosocial interventions for cancer patients⁵⁴ and are conceptually related to our proposed interventions; thus, we will assess this constructs using validated measures. In addition, a growing body of evidence indicates that childhood adversity moderates effects of mindfulness intervention;⁵⁵ thus, we will administer the *Risky Families Questionnaire* at baseline to assess this construct.⁵⁶

9.4 Potential Mediators of Intervention Efficacy

Previous research has shown that self-efficacy is a non-specific mediator of behavioral interventions. Thus, we will include a measure to assess *self-efficacy to cope with survivorship* at each assessment.⁵⁷ In addition, the following constructs have been found to mediate effects of mindfulness-based interventions: mindfulness, self-kindness, and rumination. These constructs will be assessed at each assessment point with the following measures: the *Mindful Awareness Attention Scale*,^{58,59} the self-kindness subscale of the *Self-Compassion Questionnaire*,⁶⁰ and the rumination subscale of the *Rumination and Reflection Questionnaire*.⁶¹ Note that these constructs are also relevant to the content of the Health Education program.

Amendment notation 4/10/20: we became aware that the self-efficacy questions were inadvertently omitted from the follow-up questionnaires at T2, T3 and T4. Table of instruments was modified

9.5 Process Related Variables

Shortly after introduction of the assigned intervention, intervention coordinators will administer to all participants a measure of intervention credibility we have used in prior intervention research.^{38*} As part of intervention delivery, we will track attendance at intervention group meetings. Participants in the MAPs condition will be asked to record practice of meditation between classes and after the 6-week intervention period. All participants will be asked to report on use of prescription and nonprescription medications, vitamins, supplements, support services (e.g., professional counseling), and mind-body interventions over the course of their participation.

*Note: we became aware that the intervention credibility scale was inadvertently omitted from the baseline assessment in November 2020.

On the next page we provide a summary table of the questionnaires and the timing of their administration.

9.6 Summary of Questionnaire Measures

Table of Measures	T1	T2	T3	T4
Background characteristics and potential confounds				
Demographic and clinical characteristics	x			
Comorbid conditions	x			
Height and weight	x	x		x
Biobehavioral factors (tobacco and alcohol use, physical activity)	x	x	x	x
Use of integrative therapies	x	x	x	x
Use of psychosocial counseling and support services	x	x	x	x
Medications	x	x	x	x
Depression (Patient Health Questionnaire-9 [PHQ-9])	x			
Outcomes				
Depressive symptoms (Center for Epidemiologic Studies – Depression [CES-D])	x	x	x	x
Fatigue (Fatigue Symptom Inventory [FSI])	x	x	x	x
Insomnia (Insomnia Severity Index [ISI])	x	x	x	x
Menopausal symptoms (BCPT Symptom Checklist)	x	x	x	x
Perceived stress (Perceived Stress Scale [PSS])	x	x	x	x
Anxiety (Generalized Anxiety Disorder-7)	x	x	x	x
Peace and meaning (FACIT- spirituality subscale)	x	x	x	x
IOC v.2 scales (worry, life interference, altruism/empathy)	x	x	x	x
Cancer-related distress (Impact of Events Scale [IES] – intrusions subscale)	x	x	x	x
Positive affect (Positive and Negative Affect Scale [PANAS]- positive affect subscale + items for joviality and serenity subscales)	x	x	x	x
Social support (2-way Social Support Questionnaire – emotional support subscales; Social Provisions Scale – attachment subscale)	x	x	x	x
Work productivity and activity impairment (WPAI-GH)	x	x	x	x
Health Status (SF-12)	x	x	x	x
Inflammatory markers	x	x		x
Moderators				
Preparedness for cancer survivorship	x			
Intervention preference	x			
Childhood adversity (Risky Families Questionnaire)	x			
Mediators				
Cancer coping self-efficacy	x			
Self-kindness (subscale of Self-Compassion Scale [SCS])	x	x	x	x
Mindfulness (Mindful Attention Awareness Scale [MAAS])	x	x	x	x
Rumination (subscale of Rumination and Reflection Questionnaire [RRQ])	x	x	x	x

10. OUTCOME MEASURES: BIOLOGICAL

10.1 Assessing the Effects of Interventions on Inflammatory Biology: Rationale and study design

Mindfulness has been shown to have beneficial effects on mental health outcomes, including reductions in stress and depressive symptoms. There is growing interest in the effect of mindfulness on physiological processes, particularly inflammation. Inflammation plays a key role in the onset and progression of a number of physical conditions, including cancer and cardiovascular disease,^{62,63} and is also linked to depression, pain, fatigue, and other behavioral disturbances.⁶⁴

A handful of randomized trials have examined the effect of mindfulness interventions on inflammatory outcomes. A trial conducted with individuals at risk for cardiovascular disease showed a marginally significant decrease in C-reactive protein (CRP) levels in the mindfulness group relative to an active control condition receiving a lifestyle education program.⁶⁵ Another recent trial found significant reductions in inflammatory signaling through the pro-inflammatory NF- κ B control pathway among older individuals randomized to mindfulness relative to wait-list controls.⁶⁶ In a phase II randomized trial of mindfulness conducted by our group with younger breast cancer survivors described earlier, we also found a significant intervention effect in down-regulating expression of pro-inflammatory genes, with accompanying indications of reduced NF- κ B and increased glucocorticoid receptor (GR) signaling.¹³ Although there was no intervention effect on circulating inflammatory markers, participants who practiced mindfulness techniques more frequently during the intervention period showed corresponding reductions in IL-6.

Based on preliminary work suggesting beneficial effects of mindfulness on inflammation, including our pilot trial with breast cancer survivors, we hypothesize that women randomly assigned to the 6-week mindfulness intervention will show decreases in markers of inflammatory activity relative to survivorship education and control group. We are particularly interested in the NF- κ B signaling pathway, given its central role as a regulator of pro-inflammatory gene expression.⁶⁷

10.2 Hypotheses

Specifically, we hypothesize that mindfulness will lead to reductions in NF- κ B signaling and increased activity in the anti-inflammatory glucocorticoid receptor in comparison to the two other groups. Secondly, we will explore whether the mindfulness intervention will lead to reductions in circulating markers of inflammation in comparison to the two other groups.

10.3 Methods and approach

RNA and DNA will be collected to look at expression of immune related genes and genetic/epigenetic features. In addition, we will examine a panel of pro-inflammatory biomarkers that are linked to stress, cancer recurrence and mortality, including IL-6 and C reactive protein (CRP), as well as an anti-inflammatory cytokine, IL-10.

Participants will provide blood samples at baseline (T1), immediately post-intervention (T2), and 6 months (T4) post-intervention for immune assessment. Blood draws will be conducted before noon to control for diurnal influences on immune parameters. At each assessment point, blood samples will be obtained by venipuncture into EDTA tubes (for circulating markers and DNA) and PAXgene tubes (for RNA). Blood samples will be processed and stored frozen at each site until all sample collection is complete. Completed sample sets will be shipped frozen to the UCLA Inflammatory Biology Core (IBC) Lab where the specimens will be analyzed.

10.3.1 Gene Expression Profiling

Total RNA will be extracted from 2.5 mL of whole blood collected in a PAXgene tube, and subjected to genome-wide transcriptional profiling using RNA sequencing through the UCLA Social Genomics Core following the manufacturer's standard protocol. We will focus on expression of a set of 19 pro-inflammatory cytokine genes that have previously been found to be up-regulated in the context of chronic stress and that were responsive to the MAPs intervention in our pilot study. In addition, to probe molecular underpinnings of alterations in gene expression, we will utilize a novel bioinformatics approach to assess proinflammatory signaling at the molecular level. This approach uses microarray-based genome-wide transcriptional profiling to identify genes that show differential expression in leukocytes from patients randomized to MAPs or SE vs. controls and applies the TELiS transcription factor search engine to identify transcription factor binding motifs that are differentially represented in the promoters of those differentially expressed genes.⁶⁸ To identify the primary cellular sources of differentially expressed genes, we will also carry out Transcript Origin Analysis as previously described.⁶⁹

10.3.2 Circulating Pro- and Anti-Inflammatory Markers

Multiplex immunoassays to assess 5 key cytokines (IL1 β , IL6, IL8, IL10, TNF- α) will be performed utilizing a Bio-Plex 200 (Luminex) instrument and a high-sensitivity multiplex immunoassay (Performance High Sensitivity Human Cytokine, R&D Systems, Minneapolis, MN) according to the manufacturer's protocol. A high sensitivity ELISA (R&D Systems Quantikine Human CRP) will be utilized to assess CRP.

10.3.3 Genetic/Epigenetic Analysis

Total genomic DNA will be extracted and used to look at individual genetic variation (single nucleotide polymorphisms, genetic sequencing, etc.) and epigenetic DNA modifications (telomere length, DNA methylation, etc.).

11. HANDLING OF SPECIMENS FOR INFLAMMATORY OUTCOMES

All blood draws will be conducted in the morning to control for diurnal variations. Patients will be asked to sit quietly for 15 minutes prior to blood collection. Approximately 15 mL (one tablespoon) of blood will be drawn. Blood samples should be obtained via venipuncture using a blood draw set (butterfly needle and tubing) in the following order:

1. Blood for cytokines and CRP will be collected into two 6 mL EDTA tubes (BD cat. no. 367863, plastic/Hemogard 13x100 mm K2 EDTA). Immediately following collection, EDTA tubes are to be well mixed and then held on wet ice or in the refrigerator until processed.
2. Blood will be collected into one PAXgene Blood RNA Tube (BD cat. no. 762165, 2.5 mL draw, 16-100 mm); tube must be at room temperature prior to blood draw. Be sure to allow sufficient time for the PAXgene tube to complete its filling—although the blood tube is the size of a traditional 10 mL blood draw tube, it will draw only 2.5 mL. After mixing by gentle inversion, PAXgene tube should be placed upright in a rack at room temperature for two hours before further processing/freezing.

Blood samples will be processed by a laboratory at each site, according to study protocols with detailed instructions in a manual that will be provided to each site. EDTA tubes will be processed the same day to plasma aliquots, and frozen at -80°C. PAXgene tubes will be frozen upright in a rack overnight at -20°C, then transferred to -80°C. All samples will be stored at sites and shipped to the UCLA laboratory at the end of the study at which time the planned analyses will be performed.

Samples will be shipped from the collaborating sites to UCLA and are to be shipped frozen via overnight delivery. Ship samples to UCLA no later than Wednesday of any given week. This allows both Thursday and Friday to locate samples if they should go astray. If necessary, samples could be shipped on Thursday, but Wednesday or earlier is preferred. Shipping address is:

UCLA - Cousins Center for PNI
 300 Medical Plaza, Room 3160
 Los Angeles, CA 90095
 Phone: 310-825-0302

The UCLA study team members should be notified by email in advance of when samples will be shipped, and again when they have been shipped; please always include a tracking number. If there are any questions, please contact via email or at the UCLA IBC Lab phone number shown above.

At the UCLA IBC Lab, all samples received will be stored at -80°C. EDTA plasma will be assayed for cytokines and CRP. PAXgene tubes will be stored at -80°C until RNA extraction for gene expression profiling.

(Note: We appreciate the initial specimen management protocol developed by Dr. Elizabeth Breen who is now retired.)

12. SPECIMEN BANKING

Any leftover study blood samples may be stored for future research studies. The subjects will consent to the future use of samples in the consent form for the study. Samples will only be released for use in future studies after approval by the Principal Investigator and other regulatory bodies, as appropriate.

13. STUDY CALENDAR

Procedure	T1 ¹	Treatment Period 6 weeks	T2	T3	T4
CLINICAL ASSESSMENTS:					
Study questionnaires	X		X	X	X
Height and Weight	X		X		X
LABORATORY TESTS:					
Blood drawn for inflammatory markers ²	X		X		X
TREATMENT:					
Arm A		X			
Arm B		X			
Arm C ³					

1. 1-2 weeks before start of 6-week group intervention for Group 1 and Group 2. 2. Drawn between 8-11AM, specimens sent to UCLA

3. Will receive Arm A or Arm B intervention after 6-month assessment

14. ADVERSE EVENT REPORTING REQUIREMENTS

14.1 General

Adverse events are rare in behavioral intervention research studies but may occur. First, some participants may become distressed when completing questionnaires that ask about their physical and emotional status. It will be important for the clinical site to have already identified collaborating clinicians or institutional resources where a participant who is severely distressed or depressed can be evaluated and referred for appropriate counseling or other services. In addition, some participants may be disappointed that they are assigned to the delayed intervention group. They should be reassured that they will have an opportunity to participate in the group of their choice at the end of the study.

14.2 Reporting Procedures

Any adverse event should be reported to the Coordinating Center and information related to the event will be disseminated to the participating sites within 5 days of review of the information by the Protocol Chair (or her designee in the event of extended absence) only in the case that the event(s) is believed to be related (i.e., possibly, probably, or definitely) to the study procedure.

All adverse events will be reported to the IRB per current institutional standards. If an adverse event requires modification of the informed consent, these modifications will be provided to the IRB with the report of the adverse event. If an adverse event requires modification to the study protocol, these modifications will be provided to the IRB as soon as is possible.

15. DATA AND SAFETY MONITORING

15.1 Data Management and Reporting

All data management and reporting will be conducted by the UCLA Coordinating Center under the auspices of the trial senior statistician and study data manager. Data from the clinical sites will be submitted via a secure web portal (both participant reported questionnaires and data submitted by the study coordinators) on a regular basis as collected, with queries and delinquency reminders being sent to the sites on a regular basis.

Regular assessment of data quality and any irregularities will be reported to the protocol chair who will discuss specific issues with the clinical site. Data will be summarized and reported to the Data Safety Monitoring Committee (DSMC) annually after protocol activation until the study is completed.

15.2 Meetings

The DSMC will include three faculty members from the UCLA Jonsson Comprehensive Cancer Center who are familiar with the design and implementation of behavioral intervention research in cancer patients. They will meet for the first time just prior to the activation of the study protocol and will have meetings every 12 months after protocol activation. Meetings will also be called should there be major changes in the study protocol that need discussion. This is a minimal risk study and thus we do not expect serious adverse events that would require DSMC attention. In addition, no interim analyses are planned so that the need for study discontinuation for futility or for substantial benefit will be unlikely.

15.3 Monitoring

No auditing is anticipated unless the data manager detects data variances that lead to concerns about reliability and validity.

16. REGULATORY CONSIDERATIONS

16.1 Protocol Review and Amendments

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center. UCLA will serve as the main institution for the study, and the other clinical sites will be collaborating institutions.

Any changes to the protocol will be made in the form of an amendment and must be approved by the IRB of each institution prior to implementation.

The Protocol Chair is responsible for the coordination and development of all protocol amendments, and will disseminate this information to the participating centers.

16.2 Informed Consent

The investigator (or his/her designee) will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject will be informed that participation in the study is voluntary, that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment or relationship with the treating physician(s) or institution. The informed consent will be given by means of a standard written statement, written in non-technical language, which will be IRB approved. The participant should read and consider the consent document before signing and dating it, and will be given a copy of the document. No participant will enter the study or have study-specific procedures done before her informed consent has been obtained.

In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the study sponsor and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

16.3 Ethics and GCP

This study will be carried out in compliance with the protocol as described in:

1. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
2. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it.

17. MULTI-CENTER GUIDELINES

17.1 Study Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB

approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below.

17.2 Records Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed.

17.3 Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to the Steering Committee and all participating sites prior to submission for publication or presentation.

18. STATISTICAL CONSIDERATIONS

18.1 Study Design/ Endpoints

This is a three group, phase III randomized controlled trial that will evaluate the short-term outcomes of two distinct group interventions designed for younger women with breast cancer in comparison to a delayed intervention control group.

18.1.1 The primary endpoint will be depressive symptoms as measured by the CES-D score at T2.

18.1.2 Secondary endpoints will include:

- CES-D score at T4 (Amendment May 6, 2019 changed this from co-primary to secondary)
- Other behavioral symptoms including hot flashes, fatigue and sleep disturbance, at immediate post-intervention (T2) and 6 months later (T4).
- Examination of changes in measures of inflammation at T2 and T4.
- Exploration of potential moderators and mediators of intervention efficacy.

18.2 Sample Size/ Accrual Rate

The study is designed to provide 80% power to detect effect sizes for change in the primary outcome, CES-D, in the moderate range for both SE and MAPs compared to the control condition. An anticipated effect size of $d = 0.50$ standard deviation units is based on mean change over time and variability reported in our Phase II mindfulness trial¹³ and other studies.^{19,20,70,71,12} Blinded analysis of early study data indicated a change score SD of 9.1 and a correlation between baseline scores and change scores of -0.51. The familywise error rate will be controlled at 0.05 for two hypothesis tests, one comparing SE to control and the other comparing MAPs to control, using Dunnett's procedure.^{72,73} Using change score SD of 9.2 and correlation of -0.50, we calculated that 58 participants in each arm at T2 would provide 80% power to detect $d = 0.50$. We adjusted to 70 per arm to account for attrition of 10-15%.

Total Expected Accrual: 210 from across the three clinical sites (Protocol Amendment, May 6, 2019)

18.3 Stratification and Randomization

Clinical site and severity of clinical depression at screening will be the only stratification factors used, to account for potential variations across sites in the delivery of the interventions, as well as ensure balance of the primary outcome (depressive symptoms) across the three intervention groups. There are 3 clinical sites and there will be two strata for clinical depression severity. We will use the score of the PHQ-8 obtained at screening as a stratification factor and will have two groups: scores 3-7 and 8 and above. This cut point on the PHQ-8 maps to a score on the CES-D that is below or above 16.⁷⁴ Randomization at each site will occur in cohorts of size 30 (approximately). When a site has enrolled approximately 30 participants, these participants will be randomized 1:1:1 to the three study conditions, so that there will be about 10 women assigned to each group, to ensure adequate group size for the interventions. Each study site will be expected to enroll four study cohorts during the course of the trial. The randomization sequence will be generated by the UCLA coordinating center using permuted blocks.

18.4 Analysis Plan including Secondary Endpoints

Since all outcome measures are continuous and assessed at multiple time points, the data will be analyzed using linear mixed effects models, with fixed effects for time and condition and random effects for individuals. Analyses will be conducted under the intent-to-treat principle, including all participants in their assigned condition, accomplished by fitting models to all available data for each outcome measure, including data of participants with incomplete follow-up. Linear mixed models provide valid inference under a missing at random assumption.⁷⁵ Differences between conditions in change over time will be examined by testing condition-by-time interaction terms. Following recommendations for multicenter trial data analysis,⁷⁶ we will also test for center effects and center-by-treatment interactions. Analyses will control for any participant characteristics with baseline imbalance among conditions or that differ between participants retained and those lost to follow-up. For all analyses, we will conduct diagnostics and effects of outliers and influential cases will be assessed by re-analysis with these cases omitted. All tests will be two-sided.

We hypothesize that participants in each intervention will have a greater reduction in CES-D than control participants at post-intervention (T2). Dunnett's procedure, which controls the familywise Type I error when comparing multiple intervention groups to a single control group, will be used to control the familywise error rate at 0.05.⁷² We also hypothesize that participants in the two interventions will have improvements in secondary outcomes (fatigue, sleep disturbance, vasomotor symptoms; CES-D at T4) compared to control, and that MAPs participants will have significant reductions in inflammatory markers compared to SE and control. These will be tested using the mixed modeling approach.

Moderator effects will be assessed using condition-by-moderator-by-time interaction terms in mixed models. Since the study is only powered to detect medium to large moderator effects, these analyses are considered exploratory. Mediation analyses will be conducted by estimating the total, direct, and indirect effects of *X* on *Y* through mediators, singly and together, using published software procedures (e.g., *paramed* in Stata), and 95% confidence intervals will be obtained using bootstrap methods.

No interim analyses are planned.

18.5 Statistical Considerations and Analysis Plans for Inflammatory Biomarkers

To test the hypothesis that the mindfulness intervention reduces NF-kB-related transcriptional signaling and increases glucocorticoid- (GR) related transcriptional signaling, we will conduct promoter-based bioinformatics analyses of genes found to be differentially expressed in standard microarray-based transcriptional profiling of peripheral blood leukocytes. In a pilot study of 65 individuals randomized to MAPS vs Control conditions and tested at baseline and post-intervention follow-up, general linear model

analyses of a Group x Time factorial design identified > 60 transcripts showing > 1.2-fold differential change in abundance over time (approximately 30 showing relative up-regulation in MAPS and approximately 30 showing relative down-regulation). TELiS promoter-based bioinformatics analyses (40) identified an average 40% lower prevalence of NF-kB response elements and an average 60% greater prevalence of GR response elements in the promoters of up-regulated genes relative to down-regulated genes (both $p < .02$). Bootstrap analyses of the sampling distribution of differences identified standard errors for both of less than 10%. Based on these estimates, standard power analyses indicate that the proposed sample size will yield > 90% power to detect a similar difference in the proposed study (i.e., yielding >24 up- and down-regulated genes for TELiS analyses following linear model analysis of differential gene expression using the same Group x Time factorial design with differential expression thresholded at 1.2-fold and FDR controlled at < 5%).

For the exploration of the plasma cytokines and CRP, with the proposed sample size of 70 per group at baseline, we will have over 80% power to detect an effect size of 0.5 in difference in change over time between groups at the $\alpha = 0.05$ level.

18.6 Reporting

The Steering Committee of the trial will develop policies and procedures early in the course of the study regarding reporting of study results, abstracts and publications.

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APPENDIX A: Mixed Model Results from Bower et al.¹³

TABLE 2. Adjusted Means and Results for Psychological and Behavioral Outcomes^a

Outcome	Baseline, n = 71		Postintervention, n = 65		P ^b	3-Month Follow-Up, n = 59		P ^c
	MAPS Group	Control Group	MAPS Group	Control Group		MAPS Group	Control Group	
Primary outcomes								
Perceived stress: PSS	18.05 ± 0.99	18.42 ± 1.12	14.25 ± 1.04	19.15 ± 1.14	.004	17.42 ± 1.09	18.21 ± 1.16	.796
Depressive symptoms: CES-D	14.50 ± 1.58	19.25 ± 1.75	9.99 ± 1.64	18.47 ± 1.80	.095	14.17 ± 1.70	17.92 ± 1.82	.664
Secondary outcomes								
Fatigue: FSI	4.18 ± 0.24	3.56 ± 0.26	3.61 ± 0.25	4.08 ± 0.27	.007	4.15 ± 0.26	3.30 ± 0.27	.572
Sleep quality: PSQI	8.13 ± 0.62	8.39 ± 0.70	6.48 ± 0.65	8.70 ± 0.71	.015	7.27 ± 0.67	7.86 ± 0.72	.647
Pain: BCPT	1.31 ± 0.17	1.56 ± 0.19	1.27 ± 0.17	1.37 ± 0.19	.444	1.17 ± 0.18	1.38 ± 0.19	.881
Hot flashes/night sweats: BCPT	1.24 ± 0.19	1.31 ± 0.22	0.94 ± 0.20	1.53 ± 0.22	.015	1.20 ± 0.20	1.22 ± 0.22	.827
Fear of recurrence: QLACS	11.61 ± 0.86	10.68 ± 0.94	9.67 ± 0.88	10.42 ± 0.96	.128	8.94 ± 0.91	10.26 ± 0.97	.048
Intrusive thoughts: IES	1.59 ± 0.17	1.39 ± 0.19	1.34 ± 0.18	1.34 ± 0.20	.385	1.12 ± 0.18	1.67 ± 0.20	.002
Positive affect: PANAS-PA	29.60 ± 1.03	31.65 ± 1.15	31.99 ± 1.08	30.50 ± 1.18	.033	29.94 ± 1.13	31.99 ± 1.20	.996
Meaning and peace: FACIT	16.86 ± 0.60	17.95 ± 0.67	18.43 ± 0.63	16.53 ± 0.69	.001	18.26 ± 0.65	17.65 ± 0.70	.069

Abbreviations: BCPT, Breast Cancer Prevention Trial Symptom Checklist; CES-D, Center for Epidemiologic Studies Depression Scale; FACIT, Functional Assessment of Chronic Illness Therapy; FSI, Fatigue Symptom Inventory; IES, Impact of Events Scale; MAPS, Mindful Awareness Practices; PANAS-PA, Positive and Negative Affect Schedule-Positive Affect; PSQI, Pittsburgh Sleep Quality Index; PSS, Perceived Stress Scale; QLACS, Quality of Life in Adult Cancer Survivors; SD, standard deviation.

^a The models were adjusted for marital status, radiation therapy (yes/no), history of smoking (yes/no), and baseline CES-D scores.

^b These are *P* values for group × time interactions testing group differences in baseline to postintervention means. Values in boldface indicate a statistically significant difference.

^c These are *P* values for group × time interactions testing group differences in baseline to 3 month follow-up means. Values in boldface indicate a statistically significant difference.

APPENDIX B: Training of Intervention Instructors

I. MAPS INSTRUCTOR SELECTION, TRAINING, AND MONITORING

Instructor Selection: Diana Winston, director of mindfulness education at the Mindful Awareness Research Center (MARC) at UCLA, will screen all potential instructors. Background/experience should include:

1. Multi day silent retreat experience, preferably with several retreats over many years
2. Completion of some type of structured teacher training related to mindfulness such as Mindfulness-Based Stress Reduction (MBSR).
3. Mindfulness teaching experience over a reasonable period of time (5 or more years is ideal). More specifically, should have experience teaching MBSR courses or the equivalent (rather than general mindfulness as connected to other health/therapeutic practices).

Instructor Training: To learn the MAPs intervention, instructors will participate in an online MAPs class that is accessible anywhere with internet connection. The online course is pre-recorded, and instructors will listen to one 2-hour class each week for 6 weeks at their convenience. Instructors will also have the opportunity to participate in an optional weekly live chat with one of the instructors and other participants. After listening to the recording each week, the instructors will have a 1-2-hour call with Ms. Winston to review and discuss what happened in the class (content, process, etc.). This is the standard procedure for teaching the MAPs intervention to experienced teachers. This will be approximately 18-24 hours of training, and instructors will be compensated for the time doing the training.

Quality Control and Treatment Fidelity: For quality assurance, the MAPs sessions for each instructor will be audio recorded and reviewed by Ms. Winston. This will ensure that instructors are delivering the correct content, are “embodying” the practice, etc. Ms. Winston will utilize a standard quality assurance checklist for this purpose. If Ms. Winston identifies issues with the instructor, she will schedule a call with them to provide feedback, then observe another session.

Instructors will also complete a checklist each week that indicates the main topics to be addressed, whether they were completed, and any issues that were encountered.

Attendance and Homework: The research coordinator will provide attendance sheets for each week that the instructor will be in charge of having participants complete. The instructor or an assistant will also be responsible for monitoring completion of homework and collecting homework sheets.

After the session, the instructor will send an email to the site coordinator to let him/her know who attended the session and who completed/missed homework. The project coordinator will be responsible for following up, contacting women who missed, etc.

II. SURVIVOR EDUCATION INSTRUCTOR SELECTION, TRAINING, AND MONITORING

Instructor Selection: At each site, the PI and Co-investigators will identify and recruit potential nursing clinicians who have experience in patient education, survivorship issues, and oncology. Experience with breast cancer survivors is desirable but not required. Background/experience should include:

1. Past experience delivering education sessions to patients with cancer
2. Experience in managing groups of patients in terms of group dynamics and controlling the flow of conversation.

3. Knowledge of common cancer survivorship concerns

Instructor Training: To become familiar with the curriculum and intervention program, instructors will be provided a training manual that covers the content of each seminar lecture, including references and resources. The annotated slide set for each of the 6 lectures will be provided, and they will be asked to review pre-recorded lectures for each seminar that will be delivered and role-modeled by several of the investigators. They will be asked to follow along using the slide notes. Subsequently, we will hold a two-hour in-person training meeting at each study site that will review the goals and objectives of the seminar series and answer any specific questions about the content of the lectures. In addition, the session will focus on group management strategies and how to address and management of depressed or distressed participants during the course of the seminar series.

Quality Control and Treatment Fidelity: For quality assurance, the sessions for each instructor will be audio recorded and reviewed by site PIs. This will ensure that instructors are delivering the correct content and managing the group process. Each site PI will utilize a standard quality assurance checklist for this purpose. If the PI identifies issues with the instructor, s/he will schedule a call with them to provide feedback, then observe another session.

Instructors will also complete a checklist each week that indicates the main topics to be addressed, whether they were completed, and any issues that were encountered.

Attendance: The research coordinator will provide attendance sheets for each week that the instructor will be in charge of having participants complete.

After the session, the instructor will send an email to the site coordinator to let him/her know who attended the session. The project coordinator will be responsible for following up, contacting women who missed, etc.

APPENDIX C: Mindfulness Awareness Practices (MAPS) Curriculum that was adapted for younger breast cancer survivors

Mindful Awareness Practices (MAPs) for Daily Living: A 6-Week Program

Designed by Diana Winston and
Dr. Susan Smalley

For information, contact www.marc.ucla.edu

Week 1- What is Mindfulness?		
Sitting with Relaxation/Arrival Meditation	Add reflection on motivation	5 minutes
Fill out Research?	Students fill out mindfulness surveys	
Dyad Introductions	-name, -who you are -why you're here/motivation	5 minutes
Go-Round Introductions	-name -something about yourself -why you're here/motivation	15 minutes +
Introductory Lecture	<ul style="list-style-type: none"> • What MARC is • Logistics- bathroom, parking, break, room issues. • Making up class (missing class, etc.) • Describe each class/order, sequential • If you are a therapist... • Experiential—applicable to life • Speak and create community, learn from each other • Mindfulness is... <ul style="list-style-type: none"> - Present time awareness - No automatic pilot - Counteract busyness • Read “Sweet Nothing” • Science and benefits <ul style="list-style-type: none"> - Physical health - Mental health - Attention - Brain research • Don't believe me 	20 minutes
Grape Eating Meditation		10 minutes
Dyad sharing	IF TIME, DEPENDS ON TIME SPENT WITH RESEARCH SURVEY	5 minutes
Group Sharing	Points: <ul style="list-style-type: none"> • Making ordinary extraordinary • Notice more than we normally do • May judge, that's normal • Try it at home 	5 minutes
BREAK		10 minutes

Introduce Mindful Sitting Practice	<ul style="list-style-type: none"> • Spend time teaching different sitting postures • Breath meditation Offering different anchors: abdomen, chest, nostrils 	10 minutes
Group Sharing	Points from Sitting Practice <ul style="list-style-type: none"> • Monkey mind, completely normal • It's difficult and is a skill we learn over time • Muscle • Sleepiness is normal, find another time of day to practice • Many different states, sometimes odd, come and go 	10 minutes
Getting a Home Practice Going	<ul style="list-style-type: none"> • Time of day to practice • Where to practice • Using the CD • Encouragement to do it everyday • Be kind to yourself if you don't • Read research on "proficiency" 	10 minutes
Closing Comments		2 minutes
Appreciation Meditation		2 minutes

Week 2- Listening, Embodiment and Obstacles		
Sitting with Relaxation/Arrival Meditation	Add reflection on motivation	5 minutes
Dyads Check-In	- introduce yourself, names - how was your practice this week?	5 minutes
Questions and Answers	- how often did you practice poll - read how much practice it takes (harmonica, etc.) - how was your practice this week? ANY QUESTIONS/Comments?	15 minutes
STOP	Teach acronym and practice it	5 minutes
Listening Meditation	Play 5 minute music selection and ask them to observe their mind. How do they listen?	5 minutes
Dyad Sharing	What happened in this exercise?	5 minutes
Group Sharing	What happened for you Bring out: <ul style="list-style-type: none"> • Things that happen in our mind when we listen: analysis, image, association, memory • Whatever happened, no problem • Reaction? Notice how we respond to stimuli • Most important is being conscious 	10 minutes
Walking Meditation	Basic Instructions and short circle walking	10 minutes
Group Sharing	How did it go?	10 minutes
BREAK		10 minutes
Breath/Body/Sound Meditation	Introduce hearing and awareness of sensations with primary focus on breath	10-12 minutes
Group Sharing	What happened? Q & A	10 minutes
Obstacles Lecture	Talk on sleepiness, restlessness, doubt, craving and aversion. Learn to recognize and feel in your body.	20 minutes
Optional if time: Movement Meditation	General mindful stretching, may include flying. Sharing about experience	10 minutes
Closing Comments	Homework: <ul style="list-style-type: none"> • Continue on with 5 min CD • Practice walking meditation (optional) 	5 minutes

	<ul style="list-style-type: none"> • Notice reactions—craving and aversion 	
Appreciation Meditation		2 minutes

Topics to additionally convey this week:

An explanation of what is an anchor

Week 3- Working with Pain		
Sitting with Relaxation/Arrival Meditation		10 minutes
Questions and Answers	- how often did you practice poll - how was your practice this week? ANY QUESTIONS/Comments?	15 minutes
Science Lecture	Guest Speaker	30 minutes
Break		10 minutes
Pain Lecture	<ul style="list-style-type: none"> - MBSR and pain - Pain is inevitable, suffering is optional - Different ways of relating to pain - catastrophize, macho, space - Difference between pain itself and overlay - Pain is not monolithic - Making it worse with resistance, fear, self judgment 	10 minutes
Ice Cube Meditation	<ul style="list-style-type: none"> - be playful, have fun - what is physical experience? - how is mind relating to the pain? - use it as a microcosm to see your relationship to pain 	10 minutes
Dyad Sharing	What happened in this exercise?	5 minutes
Group Sharing	What happened for you Bring out: <ul style="list-style-type: none"> • Way past informs future • Difference between reaction and actual experience • Stories we tell ourselves about pain 	10 minutes
Body Scan/Pain Meditation	Lead 5 min body scan followed by 5 minute pain meditation: <ol style="list-style-type: none"> 1. locate pain or discomfort 2. find neutral/pleasant place 3. explore pain as physical manifestation 4. go back to pleasant 5. notice if there is an overlay/reaction 6. go back to pleasant 7. explore one more time, bring loving kindness 	10-12 minutes
Group Sharing	What happened? Q & A	10 minutes

Closing Comments	Homework: <ul style="list-style-type: none">• Move on to 12 min CD• Explore your reactions to pain	5 minutes
Appreciation Meditation		2 minutes

Topics to additionally convey this week:

Formal v. informal practice

Week 4- Working with Difficult Emotions, Cultivating Positive Emotions		
Sitting		5 minutes
Dyads Check-In	- introduce yourself - how was your practice this week?	5 minutes
Questions and Answers	- how often did you practice poll - how was your practice this week? ANY QUESTIONS/Comments?	15 minutes
Emotions Lecture	- we aren't taught culturally about emotions - now kids learning it in school - we learn from our families -energy in motion -RAIN	20 minutes
Q & A		10 minutes
Movement Meditation	Lead them in gentle mindful yoga type stretches	8 minutes
Group Sharing	What happened?	5 minutes
Break		10 minutes
Emotions Meditation	1. 5 min of breath med 2. Work though RAIN with current or remembered emotion	12 minutes
Group Sharing	What happened?	10 minutes
Loving Kindness Lecture	- natural state available to any of us - not saccharine - unconditional - try it—think of loved one, get feedback - ok if you don't feel it, part of the practice - creativity in practice - does it work?	5 minutes
Loving Kindness Meditation Practice	- loved one - loved one to us - us to us - to anyone you are drawn to	10 min
Closing Comments	Homework: <ul style="list-style-type: none"> • Continue with 12 min CD • Bring Loving Kindness into your life 	2 minutes
Appreciation Meditation		2 minutes

Week 5- Working with Thoughts, Mindful Interactions		
Sitting		5 minutes
Dyads Check-In	- introduce yourself - how was your practice this week?	5 minutes
Questions and Answers	- how often did you practice poll - how was your practice this week? - how was your informal practice? ANY QUESTIONS/Comments?	15 minutes
Thoughts Lecture	<ul style="list-style-type: none"> • Thoughts are most difficult • don't believe everything you think • top 10 list • meta-cognition study • multiple techniques—self-talk • disidentification • Train platform analogy* • Tools: <ul style="list-style-type: none"> - label - feel in body - count - tag line • Not about getting rid of • Long term process • John Nash Story • Our relationship shifts 	20 minutes
Q & A		10 minutes
Walking Meditation	Can let them do individual walking	8 minutes
Group Sharing	What happened?	5 minutes
Break		10 minutes
Thoughts Meditation	1. 5 min of breath med 2. 5 min of MIND LABORATORY - what are your thoughts doing? - get curious about them 3. Clouds and sky	15 minutes
Group Sharing	What happened?	10 minutes
Mindful Interactions Lecture	Guidelines for Listener: <ol style="list-style-type: none"> 1. Full attention 2. connect with body 3. observe internal reactions Guidelines for Speaker: <ol style="list-style-type: none"> 1. authentic, from the heart 2. connect with body 3. can verbalize what you're aware of 	5 minutes

Interactions Practice	Dyads: What brings me joy? Partner A, B then sharing, maintaining mindfulness	10 min
Closing Comments	Homework: <ul style="list-style-type: none"> • Move on to 17 min CD • Be aware of interactions 	2 minutes
Loving Kindness Meditation	For partner and for class	2 minutes

Topics to additionally convey this week:

An explanation of what is an anchor

Week 6- Wrap Up		
Sitting		5 minutes
Dyads Check-In OPTIONAL	- introduce yourself - how was your practice this week?	5 minutes
Questions and Answers OR: FILL OUT SECOND HALF OF SURVEY/EVALUATION FORMS	- how often did you practice poll - how was your practice this week? - how was your informal practice? ANY QUESTIONS/Comments?	15 minutes
Mindful Practice Period	15 minutes sitting (full instructions) 10 minutes sitting 5 minutes sitting	30 minutes
Break		10 minutes
Resources	See other sheet	25 minutes
Closing Council	<ul style="list-style-type: none"> • Mindful talking practice • Native origin, but within all cultures • Speaking from your heart • Listening from your heart • Only speak when you have stone • You can pass • Be spontaneous • Pay attention to time 	20 minutes
Loving Kindness Meditation	Final, for class and world	2 minutes

APPENDIX D: Survivorship Education Curriculum

Week 1: Breast Cancer 101: a review and issues of importance to younger women

- Heterogeneity of breast cancer and its treatment
- Breast cancer as a chronic disease; cancer prevention and control
- Medical management for breast cancer survivors; having a survivorship care plan
- Medical and psychosocial perspectives that are important to wellness and life after cancer

Week 2: Quality of Life in Breast Cancer Survivors

- Quality of life after breast cancer treatment: what domains are affected?
- Common side effects of breast cancer treatment that can persist after treatment: fatigue, depression, sleep disturbance, cognitive dysfunction, infertility risk, chemotherapy-related amenorrhea, hot flashes
- How to find help in managing these symptoms

Week 3: Energy balance, Nutrition, and Physical Activity

- Obesity, weight, and breast cancer
- Physical activity and cancer survivorship
- Energy balance, changes associated with the menopause
- Nutrition and healthy eating for breast cancer survivors
- Vitamins and special diets

Week 4: Cancer in the Family: Cancer Genetic Predisposition Testing and Counseling for Breast/Ovarian Cancer Syndromes

- Hereditary breast and ovarian cancer
- Taking a family cancer history
- Genetic testing and counseling
- Difference between tumor and germline genetics/genomics

Week 5: Relationships and Work-Life Balance

- Talking to children
- Talking to partners, current and potential
- Work-life balance

Week 6: Body Image, Menopause and Vaginal Health, Sexuality & Intimacy/ Moving Forward

- Body image and breast cancer
- Sexual dysfunction among breast cancer survivors
- Managing menopause related vaginal changes
- Rebuilding a positive body image
- Intervention strategies