Examination of Broad Symptom Improvement due to Mindfulness-Based Stress Reduction for Breast Cancer Survivors: A Randomized Controlled Trial

Lengacher, et al

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Name & Address of Sponsor:

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Name & Address of clinical laboratories, medical/technical departments, or institutions involved in the trial:

University of South Florida, College of Nursing
12901 Bruce B Downs Blvd
Tampa, FL 33612

University of South Florida, College of Medicine
12901 Bruce B Downs Blvd
Tampa, FL 33612

H. Lee Moffitt Cancer Center and Research Institute
12902 Magnolia Drive
Tampa, FL 33612

The Carol and Frank Morsani Center for Advanced Healthcare
13330 USF Laurel Drive
Tampa, FL 33612

Life Hope Medical Office Building
3000 Medical Park Drive,
Suite 140, 1st Floor
Tampa, Florida 33613

SPECIFIC AIMS

Breast cancer survivors are living longer and may be living with many symptoms incurred from the disease and its treatment. Survivors from 1 to 2 years off treatment report continued fatigue, depression, pain and sleep disturbances.[1,2] Symptoms often overlap. When pain is present, it affects mood, and, when fatigue is present, it may add to depression and anxiety. Sleep disturbances reported to persist in survivors have been associated with depression, pain and fatigue, contributing to impaired quality of life. [3,4] In the transition off treatment, worry and fears of cancer recurrence accompany physical symptoms [5] and affect quality of life for both patients and their families years after treatment.[6 ,7-9]

Patients often present with several concurrent symptoms.[10,11] It is believed that symptoms tend to cluster together (two or more concurrent symptoms related to one another and independent of other symptoms)[12] and may have natural associations, similar shared pathways and underlying mechanisms. [13] Emerging evidence indicates stress-related pro-inflammatory cytokines and stress hormones may play a role in the pathophysiology of cancer related symptoms.[7,14]Currently, little is known about how symptoms cluster in breast cancer survivors after treatment, underlying mechanisms, and if interventions can influence multiple symptoms simultaneously.[7,14]

Very few studies have tested interventions during post-treatment survivorship.[15-18] Mindfulness based stress reduction (MBSR), a standardized form of meditation and yoga, has been shown to be effective in reducing anxiety,[19,20] depression [21] and stress in patients with chronic pain.[22] In women with breast cancer, MBSR decreased mood disturbances and stress[23] and significantly improved sleep quality.[24] In an MBSR study of 42 patients with breast and prostate cancer, improvements in quality of life were associated with a decrease in afternoon cortisol levels.[25] Preliminary results from 2 pilot studies conducted by our research team, provide support that MBSR for breast cancer survivors may be effective in markedly reducing symptoms, increasing quality of life, and decreasing fears of recurrence.[26-28] This proposed study builds on our preliminary data of the MBSR Breast Cancer program (BC) to reduce stress, biological markers of the stress response (pro-inflammatory cytokines) and improve physical, and psychological symptoms and quality of life in breast cancer survivors.

Based on recent compelling findings by our group and the existing literature base, the **primary goal** of this application in response to RFA PA-07-074 for the first 2 submissions, and PA-07-070 for this 3rd submission will be to rigorously evaluate the efficacy of the MBSR(BC) among breast cancer survivors. We expect to determine: (1) the extent to which the MBSR(BC) program is efficacious in improving outcomes; (2) whether positive effects from MBSR(BC) are mediated through increased mindfulness and reduced fear of recurrence; and (3) if a subgroup of patients can be determined to derive the most benefit from MBSR(BC).

To achieve this research goal, we propose a 2-group randomized clinical trial among 300 breast cancer survivors who have undergone lumpectomy and/or mastectomy and radiation and/or chemotherapy in the past two years. The MBSR(BC) program will be evaluated against a waitlisted usual care regimen, with patient assessments made at baseline, 6 weeks, and 12 weeks. Formal specific aims are as follows:

Specific Aims. Among breast cancer survivors who have completed treatment within the past 2 years:

Aim (1). Evaluate the efficacy of the MBSR(BC) program in improving psychological and physical symptoms, quality of life and measures of immune function and a stress hormone (cortisol). **We hypothesize** that compared to the usual care regimen, patients randomly assigned to the MBSR(BC) program will experience greater improvements at 6 weeks and sustained improvements at 12 weeks in the following:

- **1a.** Individual psychological symptoms, including depression anxiety, and perceived stress;
- **1b.** Individual physical symptoms, including pain, fatigue and sleep dysfunction;
- **1c.** Quality of life;
- **1d.** Biological stress markers (pro-inflammatory immune cytokines, cellular adhesion molecules, lymphocyte subsets) and a stress-related hormone (cortisol).

Aim (2). Test whether positive effects achieved from the MBSR(BC) program (defined in 1a-1d) are mediated through changes in mindfulness and fear of recurrence of breast cancer. **We hypothesize** that:

- **2a.** Patients in the MBSR(BC) program will report greater increases in mindfulness and larger reductions in fear of recurrence compared to patients assigned to the usual care regimen.
- **2b.** Increased mindfulness will relate directly to improvements in psychological and physical symptoms, quality of life and measures of immune function and a stress hormone (cortisol).

2c. Reductions in fear of recurrence will be associated with improvements in psychological and physical symptoms, quality of life and measures of immune function and a stress hormone (cortisol).

2d. A primary pathway through which MBSR exerts its positive effects (defined in 1a-1d) will be through increased mindfulness leading to reduced fear of recurrence of cancer.

Aim (3). Evaluate whether positive effects achieved from the MBSR(BC) program (defined in 1a-1d) are modified by specific patient characteristics measured at baseline. **We hypothesize** that efficacy of the MBSR(BC) program will be greatest among patients with:

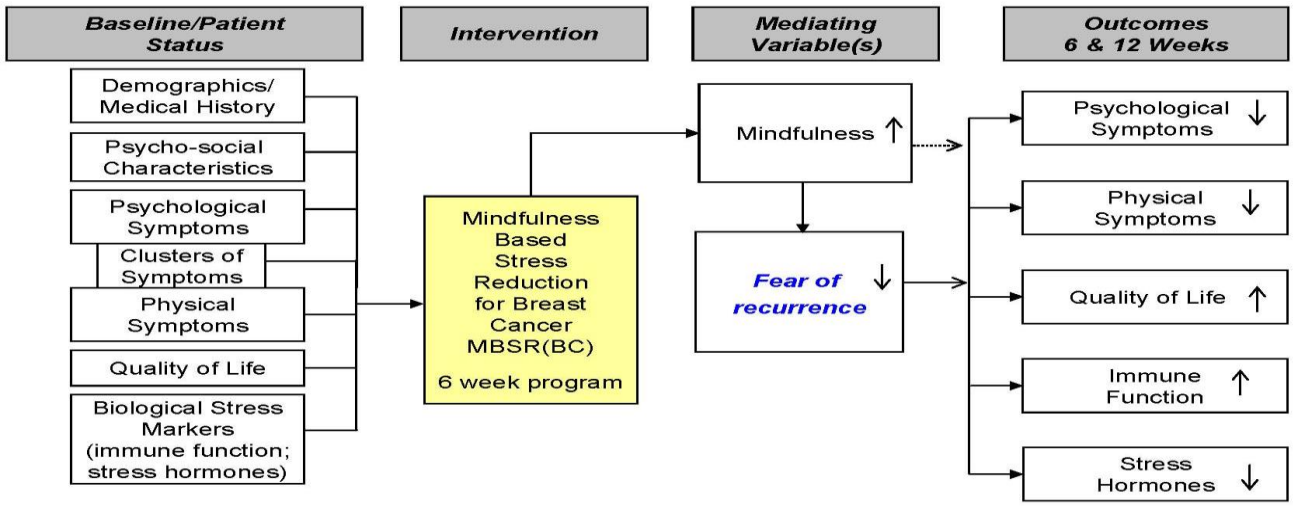
3a. High anxiety, high perceived stress, low optimism and poor quality of life

3b. Specific symptom profiles (i.e. highly distressed patients), as determined by grouping (clustering) patients according to their presenting symptoms.

3c. Particular genetic profiles. Specifically, we will explore whether candidate genetic polymorphisms are associated with severity and chronicity of symptoms (cognitive function, fatigue, depression and pain). These data may be used in the design of a large RCT, potentially customized to patients with specific genetic profiles.

Biobehavioral Logic Model. The theoretical logic model (**Figure 1**) postulates that the MBSR(BC) program improves psychological and physical symptoms, quality of life, and immune function and reduces stress hormones. Changes in psychological (i.e depression, anxiety and stress) and physical (i.e pain fatigue and sleep) symptoms are expected to correspond with changes in quality of life and biological stress markers (pro-inflammatory immune cytokines, cellular adhesion molecules, stress-related cortisol and lymphocyte subsets). Outcomes will be assessed at 6 weeks (immediate post-intervention) and 12 weeks (short-term sustainment). We postulate that the principal mechanism by which MBSR is effective is through increased mindfulness (e.g. awareness) and reduced fear of recurrence. We also postulate that to achieve maximum benefit from the MBSR(BC) program, practice and proficiency in mindfulness is a critically important element. By increasing mindfulness and reducing fear of recurrence, MBSR(BC) may modulate hypothalamic pituitary adrenal(HPA) axis and sympathetic (SNS) and parasympathetic nervous system (PNS) responses resulting in reduced physical, psychological and biological markers of stress and increased quality of life and cellular immune function. Potential covariates, based upon our preliminary data, that may influence the efficacy of MBSR(BC) include: baseline levels of anxiety, perceived stress, optimism and quality of life. Social support is another covariate that may be important. Moreover, the manner in which subjects present with multiple symptoms may influence the efficacy of the MBSR(BC) program. This logic model, developed by Evans (1992)[29] is based upon the Psychosocial Nursing Research Model as a heuristic device for research, and additional pathways not depicted may be plausible.

Figure 1: Hypothesized Biobehavioral Breast Cancer Survivor Symptom Logic Model



Proposed Intervention Effects and Biological Mechanisms. Self-regulating interventions such as MBSR(BC) can interrupt stress responses by increasing mindfulness (e.g. awareness) and reappraising the circumstances (i.e. situation or symptom) as less threatening thus diminishing negative emotional responses that affect immune dysregulation.[30] Many symptoms are exacerbated by stress, including fatigue, sleep disruption, pain, anxiety and depression, the specific outcome variables selected in this study. MBSR(BC) is proposed to reduce these symptoms by increasing awareness to one's emotional and physical response and through this reappraisal regulate stress hormones and cytokine responses. This, in turn, will reduce the intensity and frequency of symptoms and promote parasympathetic responses that facilitate relaxation, sleep, and efficient energy production. According to Miller and Cohen (2001)[30], three conditions must be present to modulate immune function in response to a psychosocial intervention: 1) the person must have encountered an immune-dysregulating stressful experience (e.g. cancer); 2) the intervention successfully reduces stress through reappraisal, reduction of negative emotion and modifying cognition and behavior (e.g. MBSR(BC); and 3) the intervention modulates immune processes that stress has dysregulated (e.g. cytokine and cellular adhesion balance). Our pilot studies of MBSR(BC) provide preliminary evidence for all three conditions. In this proposed study we have selected an intervention with a prescribed dose and intensity known to reduce stress among patients with cancer. We have also selected cytokine and neuroendocrine outcomes with specificity and sensitivity known to be responsive to stress and specific physical and psychological symptoms chosen based on our R-21 findings.

The biological stress markers to be measured in this study are shown in **Table 1**. Stress and accompanying negative emotions result in inflammatory processes and release of pro-inflammatory cytokines stimulated through β-adrenergic receptors.[31,32] As cellular messengers, cytokines stimulate HPA stress responses by directly activating CRH release from the hypothalamus, resulting in a cascade of ACTH release from the pituitary gland, corticosteroids from the adrenal cortex and catecholamines from the adrenal medulla [33,34] which mediate immune function and signal psychological, neuroendocrine and nervous system responses. Cytokines and stress hormones also upregulate cellular adhesion molecules on endothelial cells, altering the adhesive properties of leukocytes which mediate cell to cell adhesion and entry of T cells into the central nervous system.[35,36] Several pro-inflammatory cytokines may also directly stimulate end organ responses, such as IL-6 synthesis and release from the adrenal glands.[37,38]

Cytokines generally function as either pro-inflammatory(Th-1) or anti-inflammatory mediators (Th-2). Pro-inflammatory cytokines, including IL-1, IL-2, IL-6, TNF-α and IFN-γ stimulate inflammation by activating T cytotoxic cells, B cell production of antibodies and complement and acute phase proteins, promoting phagocytosis and increasing vascular permeability and cellular adhesion. Sympathetic nervous system activation under stress releases pro-inflammatory cytokines and PNS activation releases anti-inflammatory cytokines. Cytokines circulate simultaneously through the peripheral and central nervous system resulting in symptoms such as depression and altered sleep, which can in turn impair the balance of cellular (Th1) and humoral (Th2) immune responses.[39-41] Cancer patients may experience fatigue, weakness and other symptoms secondary to an imbalance of cytokines.[13,42]

Cytokines and stress hormones both cause symptoms and are affected by stress responses to psychological and physical symptoms leading to increased cortisol levels and immune changes. [43,44 45] Lymphocytes, monocytes, macrophages and granulocytes are identified to have receptors for cortisol and catecholamines, (neuroendrocrine products of the HPA and SAM axes) which in turn cause changes in cellular cytokine secretion and cytolytic activity.[35]

Several studies have documented that women with breast cancer have dysregulation in several circadian systems and that stress and mood may be an indirect contributor to poorer outcomes.[46] In breast cancer patients, cortisol levels were elevated compared to normal controls, diurnal cortisol profiles were flatter [47-49] and cortisol was related to perceived stress, social support and explicit memory.[47]

In negative and perceived stressful situations (emotional and cognitive responses), the ensuing cascade release of corticotropin-releasing hormone (CRH) adrenocorticotrophic hormone (ACTH), and glucocorticoid hormones (cortisol) results in modulation of cytokine expression and production of inflammatory mediators and other inflammatory molecules.[33]

Table 1. Biological stress markers and expected effects in response to MBSR(BC)

Biological Stress Marker	Hypothesized direction in response to MBSR

Cytokines (pro-inflammatory; Th1): IL-1β**,** IL-1-RA, IL-2, IL-6, TNF- α, TNF-RA, IFN-γ	Decreased
Cytokines (anti-inflammatory; Th2): IL-4, IL-10**,** IL-13,TGF-β	Increased
Cellular Adhesion Molecules (pro-inflammatory): CD11a, CD54, CD62L	Decreased ICAM
Lymphocyte Subsets: CD3, CD19, CD16+56	Increased T, B, NK%
Cortisol	Decreased

Innovation Summary. This proposed research is innovative in: 1) testing an intervention for symptom management in post-treatment breast cancer survivors, a population with few studies and relatively unknown patterns and magnitude of physical and psychological symptoms; 2) determining if positive effects are sustained beyond the initial intervention period; 3) identifying which types of patients and clusters of symptoms MBSR(BC) is more efficacious; 4) testing the role of mindfulness/awareness and fear of recurrence as mediators of the effects of MBSR; and 5) identifying potential biological mechanisms and responses to MBSR. This will be the first study to investigate the prevalence of pro-inflammatory and anti-inflammatory stress-mediated cytokines, cellular adhesion molecule responses, stress hormones, and clusters of patient symptoms over time following breast cancer treatment.

BACKGROUND AND SIGNIFICANCE

Breast cancer is the most prevalent form of cancer among women. While mortality rates have decreased, the incidence rate remains high and is increasing with 11,850 new breast cancer cases estimated in Florida for 2008, and 182,460 cases nationwide, thereby making breast cancer a major health problem. [50] World cancer rates are expected to double by 2020, increasing the number of persons living with cancer from1.6 million in 2000 to 2.3 million in 2050.[51] Women with breast cancer are among the largest group of female cancer survivors, accounting for 41% of all survivors (NCI Office of Cancer Survivorship). Survivors of breast cancer report continued psychological stress, anxiety, depression, fear of recurrence, and impaired cognitive functioning along with physical symptoms of pain, fatigue and sleep disturbances, which can negatively impact their quality of life after treatment. [8,9] Nonetheless, limited research exists on the type and magnitude of symptoms sustained after treatment ends, and no studies have formally established how symptoms cluster during early phases of survivorship. When treatment ends, emotional distress ensues and existential questions are common as women struggle to face the meaning and purpose of their lives.[52]

Significance. Previous research has focused on examining individual symptoms with few studies assessing clusters of symptoms among breast cancer survivors off treatment. Results from this study will advance conceptual and clinical knowledge of how a stress-reducing intervention impacts symptoms and in whom it may be most efficacious. Determining stress-related biological effects may be applicable to other stress-reducing intervention studies. Longitudinal studies are needed to understand the mechanism of symptoms and how they cluster in breast cancer survivors over time.[7] A greater percent of survivors are younger and in the workforce, and the ability to reduce symptoms would be expected to result in fewer office visits, improved functional performance of roles and a proactive approach to managing health and improved outcomes. This symptom and symptom cluster assessment and intervention model will further our understanding of biology and behavior and test a predictive and personalized model of health care, an important element to transform health and medicine according to Dr. Elias Zerhouni of the NIH.[53]

Review of Relevant Literature

Outcomes: Integration of Psychological and Physical Symptoms, Quality of Life and Biological Stress Markers. Women with breast cancer are at high risk for psychological symptoms (most commonly stress, anxiety, depression, fear of recurrence and physical symptoms including pain, fatigue and sleep disturbances which often are associated with lower health related quality of life. Cytokines have been implicated in multiple diseases and contribute to symptoms of pain, sleep disorders, depression, fatigue and responses to stress.[54,55] Stress hormones, such as cortisol, have been associated with survival and symptoms in several landmark studies.[47,56,57]

Psychological Symptoms

Depression/anxiety. Depression and anxiety remain prevalent in 50% of women treated for early stage breast cancer and more than 50% with advanced stages.[58] For women with a recurrence, 45% experienced depression and/or anxiety.[59] The level of distress varies in intensity depending on the severity of disease and treatment.[5,52,60] Depression has been found to be linked to a higher risk of mortality in survivors,[61,62] and higher

cortisol levels. As cortisol levels rise, depression and depressive symptoms such as anxiety, insomnia and poor memory can be initiated, perpetuated or aggravated.[63]

A pro-inflammatory (Th1) and anti-inflammatory (Th2) imbalance in cytokines has been observed in depressed persons.[64] IL-1, TNF-α and IFN-γ reduce serotonin levels and are well documented in the etiology and pathophysiology of depression.[64-67] Transforming growth factor (TGF-β1) a Th3 response, suppresses pro-inflammatory cytokines (IFN-γ, TNF-α, IL-2 and IL-2R),[68] and in one study, TGF-β1 was lower in response to depression.[64] Significantly higher IL-6 concentrations were found among depressed cancer patients compared to healthy controls.[55] Patients with cancer receiving immunotherapy with cytokines such as IFN-α,[69] IL-2 [39] or IFN-γ, demonstrated sickness behavior that included depression, fatigue and feelings of sadness.[39,40] Symptoms decreased after cessation of therapy [55] and administration of antidepressants that normalize serotonin levels,[67] suggesting direct and indirect roles of cytokines in depression. In the few controlled studies in depressed patients versus normal controls, results showed increases in IFN-γ, IL-1β, IL-1 and IL-2 with depression.[55] We expect that as depression and depressive symptoms are reduced in response to MBSR(BC), cortisol levels and proinflammatory cytokine levels will be lower in the MBSR(BC) group compared to the usual care control group.

Perceived stress. Stress associated with breast cancer can disrupt psychological and biological processes.[70] Acute psychological stress has been demonstrated to lead to short term upregulation of the immune response,[71] and chronic illness has been found to be associated with decreased NK activity, decreased IL-2 and decreased IFN-γ.[72] Andersen and colleagues examined chronic stress in breast cancer patients post surgically and found stress related to lower NK activity and lower T-cell responses [73] and that a post-surgical stress-reducing intervention improved T-cell proliferation.[74] A study of 54 breast cancer post surgical patients showed high levels of psychological stress were significantly related to lower NK activity and IFN-γ.[75] Chronic life stressors in adult males were found to be associated with greater subjective distress, higher levels of epinephrine, lower levels of beta-endorphin and NK cell lysis.[76]

Physical Symptoms

Fatigue. Breast cancer survivors experience moderate to severe symptoms of fatigue years after completion of cancer treatment.[77-79] Factors most frequently associated with fatigue in survivors are pain, sleep, and depression.[80] In a study of 1,957 breast cancer survivors [81] depression and pain were the strongest predictors of fatigue. Although some of the effect of pain on fatigue is mediated by sleep, pain also has a direct effect on fatigue.[82] In a prospective study of factors predicting fatigue in 112 breast cancer patients, physical fatigue was predicted by depression, pain and tamoxifen use; affective fatigue was predicted by depression and anxiety, and cognitive fatigue was predicted by anxiety and pain.[83]

Increases in pro-inflammatory cytokines are related to fatigue and may be chronically elevated in survivors.[14,84,85] In 2 studies of breast cancer survivors 5 years off treatment (n=39, 40), women who were fatigued had higher serum levels of IL-1 receptor antagonist (IL-1 RA), soluble TNF-receptor II (sTNF-RII)[84] and increased numbers of CD4+ T lymphocytes and CD56+ effectors T lymphocytes.[86,87] Fatigued survivors also had higher IL-6, TNF-α, IL-1RA and soluble IL-6 receptor (sIL-6R/cd126) and lower monocyte cell surface IL-6R, activated T lymphocytes and myeloid dendritic cells in peripheral blood.[88] In 2 studies of breast cancer patients on treatment, fatigue clustered with other symptoms and with elevations of soluble intercellular adhesion molecule -1 and vascular endothelial growth factor but not with cytokines (IL-1β, IL-6, TNF-α).[89,90] A recent study in breast cancer survivors demonstrated a functional alteration in cytokine response to lipopolysaccharide stimulation as a biomarker of behavioral fatigue.[88] Lower levels of morning serum cortisol [84]and flatter cortisol slopes were found in breast cancer survivors with fatigue compared to those without fatigue.[86,90] This validated a previous study that found lower levels of morning serum cortisol in fatigued survivors compared to non fatigues survivors[84]suggesting that disturbances in the HPA axis are related to fatigue in survivors. The relationship between fatigue, cytokines and cortisol has been established in several studies of breast cancer survivors off treatment.

Pain. Breast cancer survivors report chronic pain that often interferes with health, physical functioning, work, sleep and quality of life.[91-93] Chronic or localized pain was reported in 25% [94,95] to 30% [96] of survivors 3-5 years later and was higher (49%) among some patients with mastectomy and reconstruction [94,95] which for some was related to a chronic neuropathic pain syndrome.[97] Pain particularly affects young survivors, who express more fear of pain progression and fears of the future.[95] Women with better pain coping strategies have lower levels of anxiety, fatigue and depression.[98] Pain causes strong emotional reactions and stimulates the HPA and autonomic nervous system, characterized by elevations in catecholamines and cortisol [99] and release of

circulating cytokines and cellular adhesion molecules.[100] Perception of pain is influenced by anxiety and previous pain experiences.[100] Peripheral neuropathic pain, a neuroinflammatory response to cisplatin, taxol and vincristine chemotherapy, is the most prominent pain symptom in persons with cancer,[101,102] persisting long after treatment ends. Neuropathic pain is very distressing and difficult to control.[7] TNF-α is released immediately after the nerve damage,[103] upregulating IL-1β, IL-6 and IFN-γ [104-107] as well as anti-inflammatory cytokines.[108] Vincristine elevates GM-CSF, while downregulating TNF-α receptors[109] and paclitaxel increases IL-6, IL-8 and IL-10, with increases in IL-10 associated with joint pain, fatigue, and flu-like symptoms.[110] Although not all survivors have pain, pain is strongly associated with other symptoms and immune dysfunction.

Sleep disturbances. Although insomnia is prevalent among 30-50% of cancer patients, [111] studies in cancer survivors are scarce. In 752 cancer survivors, 47.9% reported sleep disturbances compared to 55.6% of 100 breast cancer patients on treatment reporting sleep disturbances.[112] Insomnia can trigger or result from stress, activating the HPA axis becoming chronic and severe, inducing anxiety and depression and affecting quality of life.[113] Insomnia of 4 days duration was associated with increases in ACTH and cortisol secretion,[114] and chronic insomnia was associated with lower CD3+, CD4+ and CD8+ cells.[115] IL-1β, IL-6 and TNF-α are important regulators of sleep activity,[116] and patients with sleep complaints had higher IL-1α, IL-1β, IL-6, and TNF-α levels.[117] IL-1 induces CRH synthesis, activates the HPA axis and provides the major feedback mechanism in the brain. If HPA activity is reduced, IL-1 is released and induces NREM sleep or slow wave sleep.[41,118] In contrast, anti-inflammatory cytokines IL-4, IL-10 and IL-13 inhibit NREM sleep.[119] IL-6 and TNF-α also are fatigue inducing cytokines and are increased in day time sleepiness.[120] Twenty-seven breast cancer survivors receiving cognitive-behavioral therapy for insomnia exhibited better sleep, less use of medication, lower depression and anxiety, higher IFN-γ upon stimulation with PHA (phytohemagglutinin) and a greater quality of life than 30 subjects in the control group.[121] A pilot study of a cognitive-behavioral intervention also found improvement in sleep disturbances and quality of life in 10 breast cancer patients.[122]

Symptom cluster evidence. The majority of research on symptoms has assessed single concepts.[123] Most research on symptom clusters examined pain, fatigue, depression and sleep among patients on treatment.[124-126] Few studies have examined symptom clusters after treatment ends. In 55 breast cancer survivors, fatigue, pain, emotional distress, and insomnia continued up to 6 months following treatment.[1] In 14 breast cancer survivors, fatigue was related to greater symptom distress, lower activity and poorer physical and social health status; sleep, symptom distress and health status clustered in patterns associated with either lower or higher fatigue.[127] In 15 breast cancer survivors compared to 15 healthy women with hot flashes, sleep duration was shorter for survivors and was associated with fatigue and depression.[128] In two other studies, sleep disturbances were prevalent and clustered only in early stage patients on treatment.[10] A multivariate analysis of 1,957 breast cancer survivors [81] found depression and pain were the strongest predictors of fatigue. Quality of life and symptom clusters were examined in 64 breast cancer survivors who developed lymphedema compared to 64 survivors who did not.[129] A symptom cluster of alteration in limb sensation, loss of confidence in body, decreased physical activity, fatigue and psychological distress was identified, all predicting poorer QOL. Physical symptoms and psychological distress correlated with fatigue and lower quality of life in 25 women with breast cancer.[2] Most of the research on symptom clusters included patients on treatment, and physical symptoms were inter-correlated and often related to psychological symptoms and quality of life.[10,13,82,83,125,130-133] Only one symptom cluster study with biomarkers (serum cortisol, melatonin, serotonin, and bilirubin) was identified. These biomarkers were associated with fatigue, sleep, and depressive symptoms in 22 women with breast cancer receiving chemotherapy compared to 11 women who were cancer free.[134] Conclusions from these studies cannot be generalized because of their small sample sizes and physical symptoms were often highly inter-correlated with psychological symptoms and quality of life.[10,13,83,125,130-133] The challenging work with symptom cluster research is to validate patterns of how symptoms cluster together along with testing innovative interventions that affect not only individual symptoms but the whole cluster of symptoms. [135]

Quality of life(QOL)

A new area for research is investigation of QOL after treatment ends. Although QOL has been studied in numerous trials since the 1980's, only 5 studies were found that provided an intervention designed for post treatment survivorship.[136] Long term survivors continue to have treatment and health concerns related to aging, and co-morbid conditions.[137] Most studies report good overall QOL for breast cancer survivors,[138,139] however, women who have a recurrence [8] or who have had chemotherapy and tamoxifen or both [8,139,140] report lower overall QOL. Compared to healthy controls, survivors generally report poorer physical functioning[8,139,141]

including arm pain, swelling and weakness.[141,142] A critical component of QOL is psychological well being or affective states including anxiety, stress and depression.[143] Survivors indicate that their QOL is related to their level of stress,[138,144] their worry about the future and having little control over the world.[144,145] Risk factors for lower QOL in breast cancer survivors include greater uncertainty and decreased physical functioning with older age,[145] depression [144] and physical symptoms. Protective factors include fewer chronic conditions and physical symptoms, greater emotional support, social support and trait optimism.[4,140,145,146] Studies have shown that depression and associated symptoms such as diminished QOL reduces survival.[147,148] Our preliminary data indicate that MBSR(BC) improved QOL in 17 early stage breast cancer survivors who were in transition from treatment to survivorship, showing a significant improvement after MBSR in general health (p=.003) and emotional well being (p=.03).[26,27]

Mediators: Mindfulness and Fear of Recurrence

Mindfulness/awareness. Mindfulness has been described broadly as a nonelaborative and nonjudgmental awareness of the present moment through which thoughts, feelings, or sensations in the attentional field are accepted and acknowledged but not to be reacted to.[149-151] In the measurement of mindfulness, four components have been identified: 1) the ability to regulate attention; 2) orientation to the present experience; 3) awareness; and 4) a nonjudgmental/acceptance attitude toward experience.[152] Higher levels of mindfulness have been associated with less "under engagement" (experiential though suppression and avoidance) and less "over engagement" (worry, rumination, and overgeneralization) and more emotional intelligence.[153]In a study of 212 college students, higher mindfulness was associated with lower distress and depression and lower levels of thought suppression, worry, rumination and overgeneralizations.[152] Mindfulness was also associated with clarity of feelings, mood repair, attention of feelings and distraction, suggesting the ability to turn into and sit with unpleasant emotions. Higher mindfulness was also associated with cognitive flexibility, problem analyses, plan rehearsal, and less outcome fantasy.

Fear of recurrence. Fear of recurrence mediated patient outcomes in our R-21 preliminary findings. In other studies, fear of recurrence chronically plagues 55-99% of breast cancer survivors.[154-156] In 72 survivors, although fear of the future decreased at 3 to 7 months following diagnosis, it remained elevated at 11 and 15 months and at 6-year follow-up.[157] In survivors 5 years after diagnosis, approximately 70% continued to fear the possibility of recurrence.[158] Fear of recurrence is stronger in younger women, however the type of treatment appears to be unrelated.[158,159] Greater fear of cancer recurrence has been associated with increased cortisol activity.[49] In our pilot studies, 17 breast cancer survivors reported a significant reduction in concerns about recurrence (p<.01) and problems from recurrence concerns (p=.04) after an 8-week MBSR(BC) cancer survivorship program.[26]

Psycho-Social Characteristics

Optimism. There is little empirical data on factors associated with successful adaptation and increased QOL.[160] A small number of studies indicate that one's personal resources of optimism, social support and spirituality may contribute to better adaptation to distress and QOL.[161] Dispositional optimism has been associated with decreased symptoms of anxiety and depression, and increased QOL[162] and is a stable dimension of expectancies about the occurrence of good versus bad future outcomes.[163] Optimists adjust more favorably to life transitions when compared to pessimists[164]and they tend to have more stable coping tendencies when confronted with serious disease.[165] In 80 women with breast cancer, low dispositional optimism predicted anxiety and depression at 6 months after diagnosis.[166] Optimists who experienced anxiety at time of diagnoses had a 6 times greater risk of experiencing anxiety 1 year later, compared to optimists without preoperative anxiety.[167] The relationship of optimism to fear of recurrence and its influence on adaptation to stress has yet to be determined.

Social support. Another resource related to emotional adaptation and QOL in women with breast cancer is social support (the feeling that one has someone to share worries or problems).[168] After treatment, research shows that women with breast cancer report reduced social support from friends, health care providers and family.[169] Research indicates that social support is related to lower levels of anxiety and depression, and social support has been reported as a mediator of optimism and distress in 69 breast cancer survivors.[170,171] Moreover, when social support, intrusive thoughts and QOL were examined in 64 breast cancer survivors, low levels of support were found to be significantly related to cancer-intrusive thoughts, worry, and poorer QOL.[168] In a study of 101 survivors, perceived social support was negatively related to uncertainty, with social support and uncertainty accounting for 27% of the variance in QOL.[172] Thus, the need for social support may be critical during the transition to survivorship.

Summary. There is evidence that physical and psychological symptoms vary in intensity depending on the severity of disease and treatment, with limited studies among survivors, particularly for those in transition off treatment. Although there is evidence of impaired QOL among survivors, the studies are limited with no studies among women who transition off treatment. There is also growing evidence that pro-inflammatory cytokines and stress hormones may be related to symptoms and symptom clusters.[7] Cytokines play a mechanistic role in the pathophysiology of cancer related symptoms, tumor progression and metastasis[173] and can both respond to and induce inflammation,[54] alter neural activity,[174,175] and promote neurochemical cascades that directly affect mood and behavior.[54] Long term effects of daily stress and the relationships between psychological status and immune responses to stress are insufficiently understood due to limited research.[176] Because chronic stress increases cytokines and cytokines are strongly correlated with symptoms of fatigue, sleep disturbances and pain, measures of select pro-inflammatory cytokines are identified to be related to symptoms commonly experienced by survivors of breast cancer.

Mindfulness Based Stress Reduction for Breast Cancer (MBSR). MBSR is a clinical program that provides systematic training to promote stress reduction by self-regulating arousal to stressful circumstances or symptoms. The goal of training is to teach participants to become more aware of their thoughts and feelings, through mediation practice and to pay attention and observe thoughts or feeling during stressful situations that contribute to emotional distress.[22,177] MBSR(BC) gives careful consideration to the breast cancer survivors' health status and symptom management for specific emotional/psychological symptoms (anxiety, depression and fear of recurrence) and physical symptoms such as pain and sleep. The MBSR(BC) program has been modified by our group from the original program with specific application to breast cancer survivors and reduction to a 6-week format from an 8-week format. In 3 randomized controlled trials (RCTs) with breast cancer patients, MBSR improved sleep quality[24] and reduced fatigue[178] distress (anxiety, depression, anger and confusion) and perceived stress[23] but did not affect sleep efficiency.[24] In non-randomized studies with cancer patients, MBSR has been identified to significantly improve symptoms of sleep, fatigue, mood, stress and anxiety.[178-181] In non cancer populations, MBSR reduced depression, state and trait anxiety and psychological distress in 78 medical students,[182] reduced depression in 145 depressed patients [21] and reduced chronic pain, stress, depression and anxiety and improved mood and QOL in psychiatric patients.[19,20,22,25,183,184] In 2 longitudinal studies measuring sustained effects of MBSR, 121 psychiatric patients continued to have less psychological distress, anxiety, depression, and physical symptoms at 1 year follow-up[185] and decreases in pain, anxiety, depression and psychiatric symptoms, with activity levels sustained for up to 4 years.[22,183]

Biological effects related to MBSR were measured in the following studies. In a non-randomized pre-post-test study of 49 breast and 10 prostate patients who participated in the MBSR group, IL-4 increased, and IFN-γ, IL-10 and NK production decreased. Significant improvements were observed in stress, QOL and sleep.[186] QOL was associated with decreased afternoon cortisol, but stress was not related to changes in DHEAS hormone levels.[25] In a randomized study of 25 healthy subjects compared to 16 in a waitlisted control group, MBSR reduced anxiety and increased left brain activity, a pattern associated with positive affect and significant increases in antibody titers to influenza vaccine.[187] In a pre-post-test design study of 10 men with prostate cancer enrolled in MBSR and eating a plant based diet, results showed significant decreases in PSA levels.[188] Prior studies are limited by non-randomized designs and small sample sizes.

Summary of Significance and Rationale. This application addresses the criteria in PA-07-070 to support "rehabilitation from cancer and the continuing care of cancer patients." It also addresses the research focus of the office of cancer survivorship to focus on "the health and life of a person with a history of cancer beyond the acute diagnosis and treatment phase." Preliminary data from our R-21 study shows evidence for the efficacy of MBSR(BC) in this population (see Preliminary Data Section). This study builds on previous evidence that MBSR can reduce physical and psychological symptoms, which may influence pro-inflammatory cytokines that are at least partially responsible for negative emotional and physical states.

PRELIMINARY STUDIES

Dr. Lengacher, PhD, RN, Principal Investigator of the proposed application is a tenured Professor at the USF College of Nursing and a member of the Breast Cancer and Psychosocial Oncology Program at Moffitt Cancer Center and Research Institute. The investigative team (see Biosketches) has substantial experience in research with breast cancer patients and assessment of symptoms, immune function, cytokines and neuroendocrine function with emphasis on how MBSR may impact individual symptoms and symptoms in

combination. The team possesses a strong track record of successful recruitment and retention of subjects on extramural and NIH-funded projects. This multidisciplinary team from the H. Lee Moffitt Cancer and Research Institute and USF has strong clinical, statistical and immunological expertise. The two studies below describe recent preliminary work by Dr. Lengacher and her team in evaluating MBSR among breast cancer survivors and serve as the principal basis for this proposal.

Preliminary Study 1: Effects of MBSR in Early Stage Breast Cancer Recovery R-21 (NIH/NCI R21 CA109168-02). The purpose of this recently completed randomized clinical trial was to preliminarily evaluate the effectiveness of MBSR in women with breast cancer as they have transitioned from completing medical treatment to becoming post-treatment survivors. A two-armed randomized controlled design (MBSR versus waitlisted MBSR) was conducted among 84 female breast cancer patients, of which, 82 (97.6%) completed the study. Patients were evaluated at study entry and at 6-week follow-up. This included assessment of stress-related symptoms, emotional distress, functional status, and immune response. The principal findings and conclusions from this study are described below, and in a manuscript submitted to JAMA.

Sample. Demographics of study participants included mean age of 58 years, 12% were Black, 11% were Hispanic, 75% were Caucasian, and 2% were other; 61% were treated with radiation but not chemotherapy, and mean time from cancer treatment completion to study entry was 19 weeks. Baseline characteristics were generally well balanced by random assignment, although the Usual Care group tended to be over-represented by Blacks. These data demonstrate our ability to recruit, randomly assign and retain cancer patients in trials of MBSR.

Outcome analyses. Figures 2 and 3 below show differences in patient outcome scores (baseline to 6-week follow-up) by random assignment. As seen, both study groups tended to improve over time, however, the MBSR group experienced significantly greater improvement in measures of anxiety, depression, fear of recurrence, physical functioning and energy. Additionally, although not statistically significant with this modest sample size, all of the SF-36 subscale measurements and psychological measurements were in the direction favoring the MBSR group. These compelling data have informed our future research objectives including: (1) whether positive effects from MBSR are sustained after the program is completed (i.e. from 6 weeks to 12 weeks); and (2) whether MBSR is particularly effective in subgroups of patients and those with specific symptom profiles, an analysis that could not be reliably performed from this R21 pilot study of 84 patients.

Figure 2. Change in Psychological Status by Random Assignment

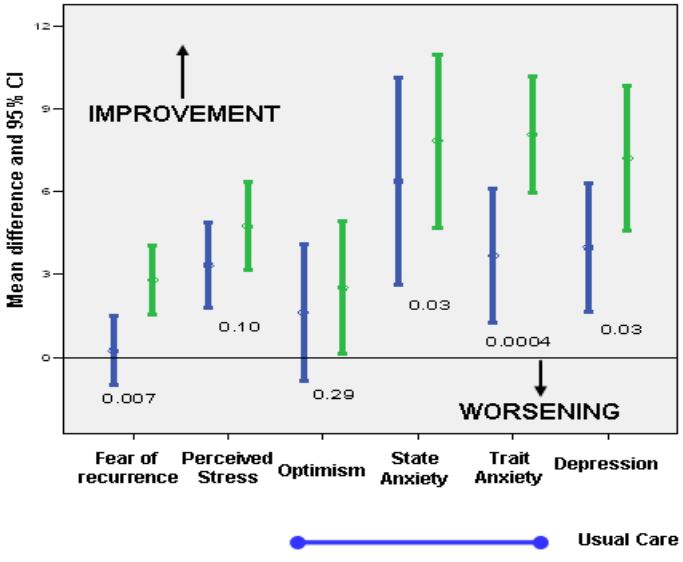
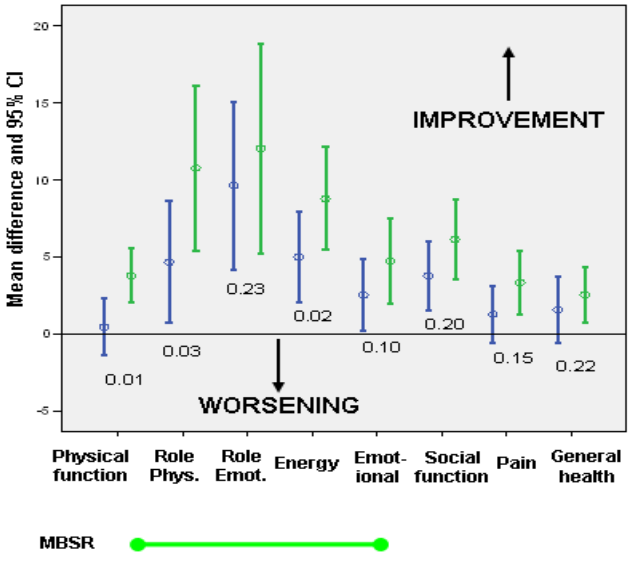


Figure 3. Change in SF-36 Scores by Random Assignment



Mediation analyses. Table 2 shows preliminary mediation analyses (expressed as p-values of path coefficients) for several patient outcomes. As seen, the MBSR program was associated with baseline to 6-week change (reduction) in fear of recurrence (path "A", p=0.008) and a reduction in fear of recurrence was associated with overall lower levels of perceived stress (p=0.02), depression (p=0.03) and anxiety (p=0.0004) at 6 weeks (path "B'). There were strong trends (p ~ 0.05) for indirect effects of MBSR on 6-week outcomes

mediated through changes in fear of recurrence (MBSR indirect effect). Although preliminary, these data suggest that a principal mechanism by which MBSR appears to lead to favorable psychological, physical and QOL outcomes is through reductions in fear of breast cancer recurrence. However, this potential mechanism, as well as others including increased awareness and mindfulness, needs to be evaluated with a larger sample size that permits simultaneous consideration of multiple mediators and covariates (i.e. by the use of structural equation modeling – see data analysis plan).

Table 2. Assessment of Potential Mediators (expressed as p-values) of Positive Effects from MBSR

Potential Mediator		Path	Outcome Measure at 6 weeks (dependent variable) Perceived Stress	Depression	State Anxiety	SF-36 Mental	SF-36 Physical
Δ in perceived stress	A	MBSR → Mediator	0.20	0.20	0.20	0.20	0.20
	B	Mediator → Outcome	---	0.01	0.001	0.0008	0.59
	C	MBSR → Outcome	---	0.02	0.007	0.09	0.09
		MBSR: Direct effect	---	0.04	0.02	0.19	0.10
		MBSR: Indirect effect	---	0.27	0.25	0.24	0.68
Δ in fear of recurrence	A	MBSR → Mediator	0.008	0.008	0.008	0.008	0.008
	B	Mediator → Outcome	0.02	0.03	0.0004	0.004	0.75
	C	MBSR → Outcome	0.006	0.02	0.007	0.09	0.08
		MBSR: Direct effect	0.04	0.09	0.08	0.39	0.12
		MBSR: Indirect effect	0.08	0.10	0.03	0.05	0.76

Immunological analyses. Spearman rank correlations (R_S) were computed between changes in symptoms from baseline to 6 weeks and corresponding changes in immunological markers. Among all patients (n=82), favorable improvements in self-reported anxiety and depression were associated with increases in T-helper (CD4) and B-cell activation (CD-19) counts (**Figures 4 and 5**). Similarly, improvements in measures of general health, social functioning, energy and physical functioning were associated with improvements in multiple immunological parameters, including Interferon gamma (IFN-γ), NK and cytotoxic T-cells (data not shown). Analyses were also restricted to patients with "normal" baseline immunological status, defined as being more than 2 weeks removed since treatment completion with radiation and/or chemotherapy (i.e. to allow restoration of the immune system) and a T-helper to suppressor ratio of 1.5 to 3.0. In these analyses (n=38), larger correlation coefficients were generally observed. There were particularly strong associations between self-reported improvements in general health and increases in T-helper (CD4) counts, and self-reported improvement in physical functioning and increased percentages of IFN-γ (**Figures 6 and 7**).

Figure 4. Correlation between change in anxiety score and increase in T helper cells

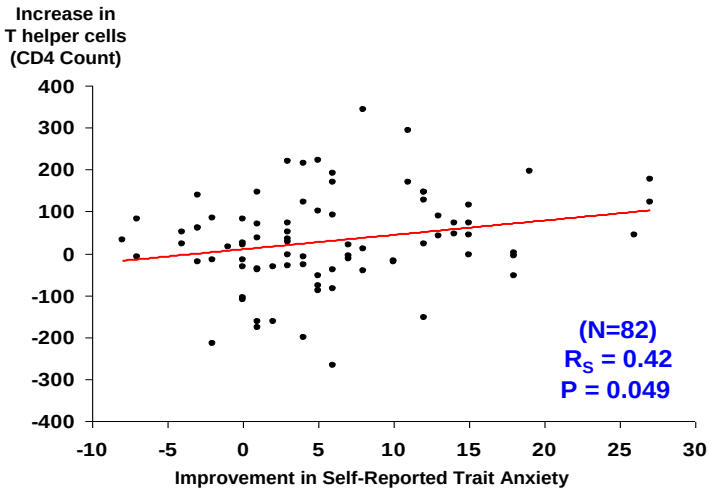


Figure 5. Correlation between change in depression score and increase in B cells

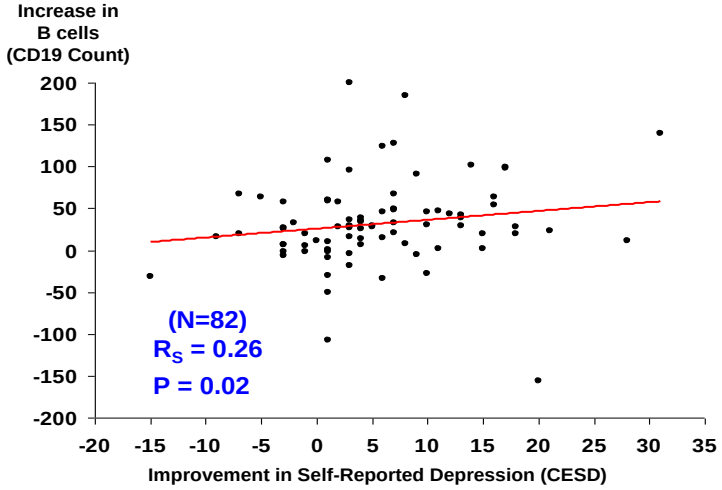


Figure 6. Correlation between change in self-reported general health and increase in T helper cells

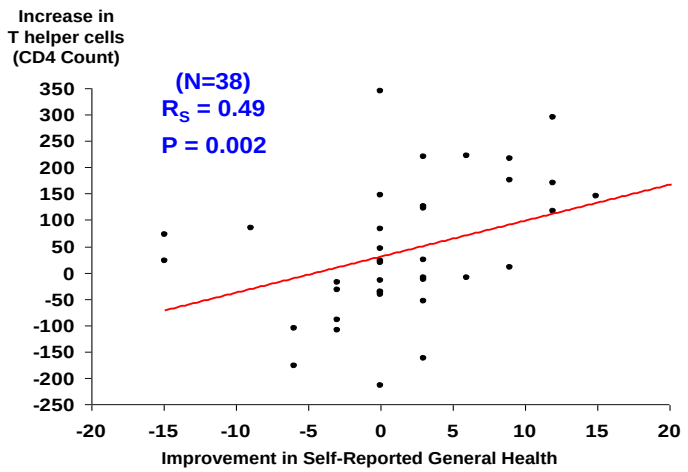
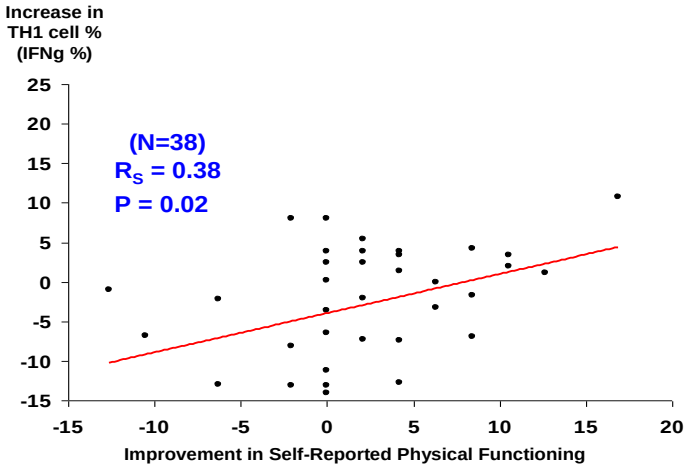


Figure 7. Correlation between change in self-reported physical functioning and increase in Th1 cells



Moderator analyses. Although limited by sample size, we have conducted preliminary moderator analyses to explore whether the effect of MBSR varies by baseline characteristics of the patient. For the outcome variable SF-36 Aggregate Mental Health Score, **Table 3** shows that the MBSR intervention appears to be particularly effective among patients who present with more severe distress including higher levels of anxiety and perceived stress and lower levels of energy and emotional well-being. Similar results were observed for other outcome variables including SF-36 Aggregate Physical Health Score. Of note, within these subgroups, effect sizes for positive benefits from MBSR (expressed as positive values) were very large (>0.90) for several measures including anxiety, perceived stress, physical functioning, pain, general health, energy and emotional status.

Table 3. Adjusted Post-Intervention Mean SF-36 Aggregate Mental Health Scores by Random Assignment and Potential Moderating Variables

		Assignment			P-value	
Measure (presented as adjusted means)	N	Usual Care	MBSR	Effect Size	MBSR vs. Usual Care	Interaction
State anxiety						
Below/equal to median	42	58.6	54.8	-0.77	0.20	0.004
Above median	40	43.1	52.1	0.98	0.03	
Depression score (CES-D)						
Below/equal to median	43	54.8	55.5	0.21	0.80	0.50
Above median	39	44.9	51.3	0.76	0.18	
Perceived Stress						
Below/equal to median	42	55.9	55.2	-0.17	0.80	0.09
Above median	40	44.4	51.3	1.73	0.07	
SF-36: Physical functioning						
Below/equal to median	43	48.4	53.5	0.66	0.24	0.99
Above median	39	50.6	53.5	1.30	0.27	
SF-36: Pain						
Below/equal to median	40	48.9	50.3	0.22	0.77	0.22
Above median	42	50.8	56.2	1.31	0.002	
SF-36: General health						
Below/equal to median	53	49.7	50.7	0.12	0.79	0.45
Above median	29	50.4	57.0	1.96	0.01	
SF-36: Energy						
Below/equal to median	37	43.4	49.5	0.98	0.21	0.01
Above median	45	54.5	56.9	0.43	0.16	
SF-36: Social functioning						
Below/equal to median	47	46.8	52.4	0.71	0.13	0.21
Above median	35	54.8	54.0	-0.31	0.80	
SF-36: Role limitations – emotional problems						

Below/equal to median	35	44.2	51.6	0.94	0.12	0.05
Above median	47	55.6	54.4	-0.18	0.95	
SF-36: Emotional well-being						
Below/equal to median	41	43.6	48.8	0.62	0.19	0.05
Above median	41	56.9	57.4	0.16	0.82	

*Adjusted for SF-36 score at study entry, age, black race, stage of cancer, and time since cancer treatment completion. **Reverse scored. ***SF-36 Scores are normed to the general population (mean value of 50).

In aggregate, our R-21 findings provide consistent evidence for MBSR-associated improvements in psychological/physical symptoms. Some psychological and physical states were associated with immune markers. However, corresponding improvements in immunological markers and their clinical significance warrant more detailed investigation. Because the MBSR(BC) program requires instructor training and considerable patient time and commitment, a larger and more definitive evaluation of its true clinical benefit in the setting of breast cancer survivors is warranted, along with specific investigation into patients subgroups most likely to benefit from MBSR, and mechanisms (i.e. reduced fear of recurrence) in which meaningful clinical and immunological improvements could be observed.

Preliminary Study 2: MBSR in Early Stage Breast Cancer Recovery, a Within-Person Pilot Study

This within-person pilot study (i.e. the predecessor to our R21 study without a control group) was designed to: (i) assess the feasibility of MBSR among post-treatment breast cancer survivors; and to (ii) explore the efficacy of MBSR in improving psychological, psychosocial, and general health status among women with early stage breast cancer who recently completed treatment. A repeated-measures pre-test, post-test design was used with patients who received lumpectomy, radiation, and/or chemotherapy.

Sample: Seventeen of 19 women (89.5%) completed the program; mean age 57 (SD=8.9), (range 40-69); 90% were Caucasian, 5% African-American and 5% Hispanic.

Participation, adherence and compliance: Participation: 58 recruited; 27 declined; 31 agreed to attend an orientation session with 19 (61.3%) consenting to participate in classes. Compliance was excellent, 17 of 19 (89.5%) completed the classes. Of the original 19 participants, 82% completed all sessions; absences were due to family and work conflicts. Adherence data showed that 76.5% recorded practice in a diary. Mean minutes practiced per week were 372 for sitting meditation; 139 for walking meditation; 212 for body scan; and 123 for yoga. MBSR Follow-up Evaluation showed that: 88% reported it to be beneficial; 76% reported increased ability to handle stress; 71% reported increased awareness of stress; 77% reported increased coping; and 77% reported increased ability to care for self.

Results related to efficacy: From this pilot within-patient pre/post-test evaluation, the MBSR program indicated significant reductions in anxiety, depression, and perceived stress (**Table 4**). Significant pre/post-test differences were also observed for future concerns and problems related to breast cancer recurrence, and quality of life (general health and emotional well being).

Summary of Research. Past experience and achievements of our team demonstrates successful completion of multi-disciplinary intervention research. We have been highly successful in recruiting and retaining breast cancer patients/survivors and collecting and conducting immunological laboratory assays. Studies by the Principal Investigator have resulted in 6 grant awards, 1 from the National Cancer Institute, the American Cancer Society and the Oncology Nursing Society and 3 grants from local foundations, 20 presentations, and 18 publications resulting from these studies.

Table 4. Mean Instrument Scores Before and After Completion of MBSR (N=17)*

Measure	Score (mean ± SD)		Score Difference		P-Value
	Before MBSR	After MBSR	Mean ± SD	95% C.I.	
Concerns About Recurrence					
Overall concerns about recurrence	11.8 (5.0)	9.1 (4.5)	2.7	0.6 – 4.8	0.01
Problems from recurrence concerns	30.8 (16.4)	23.6 (19.0)	6.9	0.2 – 13.6	0.04
Perceived Stress Scale (PSS)	17.9 (8.1)	13.2 (4.4)	4.6	1.1 – 8.2	0.01
Life Orientation Test (LOT)**	17.3 (3.3)	18.3 (3.4)	-0.9	-1.2 – 0.3	0.14
State Anxiety (STAI)	36.5 (11.3)	31.9 (6.8)	4.6	-0.9 – 10.1	0.09
Center for Epidemiologic Studies Depression Scale (CESD)	9.7 (8.0)	5.0 (3.4)	4.7	1.4 – 8.1	0.009
SF – 36 Health Survey**					
Physical functioning	84.4 (18.4)	87.6 (14.5)	-3.2	-8.3 – 1.8	0.19

Role limitations – physical health	67.6 (39.3)	83.8 (30.5)	-16.2	-37.5 – 5.1	0.13
Role limitations – emotional problems	82.4 (29.1)	86.3 (26.5)	-3.9	-25.7–17.8	0.71
Energy/fatigue	55.6 (28.2)	65.0 (19.3)	-9.4	-21.8 – 3.0	0.13
Emotional well-being	76.0 (15.7)	85.9 (6.7)	-9.9	-15.8 – -4.0	0.003
Social functioning	90.4 (13.6)	93.4 (13.3)	-2.9	-12.2 – 6.3	0.51
Pain	80.4 (18.6)	80.9 (18.8)	-0.4	-7.2 – 6.3	0.89
General health	70.3 (19.7)	77.4 (15.8)	-7.1	-13.5 – -0.6	0.03
Brief Pain Inventory					
Pain severity	1.6 (1.3)	1.5 (1.2)	0.1	-0.3 – 0.5	0.59
Pain interference	1.1 (1.4)	0.9 (0.9)	0.3	-0.4 – 0.9	0.43
Rating of Religiosity	6.4 (2.4)	6.9 (2.0)	-0.5	-1.3 – 0.3	0.18

*Scores represent differences before and after completion of the MBSR program. **Higher scores after MBSR represent improved optimism, and health. CI: confidence interval.

RESEARCH DESIGN AND METHODS

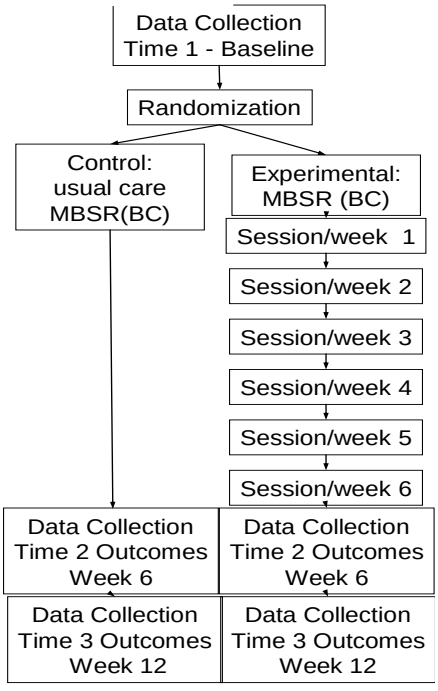
Design. The proposed study will utilize a two-armed randomized design (**Figure 8**). Women with breast cancer who have undergone lumpectomy and/or mastectomy, and radiation and/or chemotherapy will be randomly assigned to receive either: (i) the 6-week MBSR(BC) program; or (ii) Usual Care (UC) guidelines only. The UC group will be waitlisted to receive group MBSR within 6 months after study enrollment. The clinical effectiveness of the MBSR intervention, as determined by measures of psychological and physical symptoms, clusters of symptoms, and QOL will be assessed at pre-test, at 6 weeks to determine immediate effects and at 12 weeks to determine short-term sustainability.

Additional Proposed Scientific Activities to the Parent Grant. In addition to the parent grant procedures (assessment of fatigue, depressive symptomatology, state anxiety, perceived stress, pain, perceived sleep quality, symptom severity, quality of life, mindfulness, fear of recurrence, optimism, social support and immune functioning and salivary cortisol), **objective sleep quality** will be measured by Actigraphy data collected in the three days before each assessment, at baseline, 6 weeks, and 12 weeks. **Genetic polymorphisms** will be examined from previously collected blood for genomic analyses. Thus, the new procedures will fit seamlessly into existing study procedures.

Setting. Subjects will be recruited from the H. Lee Moffitt Cancer Center and Research Institute, a National Cancer Institute designated Center of Excellence located at the University of South Florida, Tampa, Florida. This NCI-designated National Cancer Center serves the largest proportion of breast cancer patients in the greater metropolitan area of Tampa, Florida, and serves a catchment area of nearly 3 million persons. The Principal Investigator has conducted several studies at Moffitt among women with breast cancer and is knowledgeable of and experienced with the institutional requirements for research involving human subjects. She is also a member of the Health Outcomes and Behavior Program and the Breast Cancer Clinical Program at Moffitt.

Sample. A total of 300 study patients will be recruited (see Power Analysis section for sample size justification). To estimate recruitment potential and the time period required to recruit 300 patients, administrative data were obtained from Moffitt. These data indicate that approximately 770, 667, and 826 breast cancer patients were treated in 2004, 2005 and 2006, respectively. Considering our proposed focus on the subset of women at Stage 0, I, II and III and who have undergone lumpectomy and/or mastectomy with radiation and/or chemotherapy (see inclusion criteria below), 657, 499 and 690 patients were treated in years 2004-2006, respectively. Thus, we estimate a potential annual recruitment pool of 615 women (657+499+690)/3) who would be study eligible.

Figure 8. Design Schema



We further conservatively estimate a 30-40% consent rate to participate in the study; this will result in an estimated enrollment yield of 185-246 patients per year. Thus, we believe it is fully feasible to recruit 300 participants with an annual accrual of at least 83 participants. From the 300 participants, we expect no more than 10% loss to follow-up based on our current R-21 trial in which follow-up compliance was 98%. In the unanticipated event that we are unable to enroll 50 subjects within the first 6 months of the study, we will expand our recruitment to one or two hospitals in the area, Tampa General Hospital and/or University Community Hospital. Thus, we fully anticipate enrolling a minimum of 83 subjects annually for a maximum of 4 years of patient recruitment. Finally, while the Moffitt screening data suggest that more than 83 patients could be recruited from this institution each year, assuming a modest 30-40% consent rate, we propose to conservatively enroll a minimum of 83 subjects per year over a 4-year period. This strategy is to be completely realistic and to keep the full 12-week study periods sequential, thereby avoiding overlap in administration of the MBSR(BC) program. Similarly, for consistency, we intend to use a single instructor to administer the MBSR program. We will attempt to enroll the maximum of 24 subjects per group at one time (i.e. 12 in MBSR(BC) and 12 in the usual care control group). This approach may accelerate the time period in which all 300 subjects are enrolled, and hence timely completion of the trial.

A matched comparison group will be recruited through flyers distributed in the USF Health Sciences Center and consist of up to 40 healthy, female volunteers to serve as controls for comparison of biological stress markers to those in the MBSR (BC) and Usual Care (UC) Groups. Inclusion criteria for the matched comparison group will include: healthy, females with no history of cancer who share age 21 or older (and the same demographic profile as those participants in the MBSR(BC) and Usual Care (UC) Groups.)

Inclusion criteria. The primary inclusion criteria are women age 21 or older who have been diagnosed with Stage 0, I, II, or III breast cancer who have undergone lumpectomy and/or mastectomy and are at 2 weeks from end of treatment with adjuvant radiation and/or chemotherapy or are a maximum of 2 years out from completion of such treatment (i.e. to study a full range of residual symptoms). These inclusion criteria were selected to enroll patients who are willing and able to participate regularly and to capture early transition from completion of medical treatment. Eligible subjects must also have the ability to read and speak English at the 8th grade level or above to respond to survey questions. **Note:** We have limited our sample to women age 21 and over and English speaking since, historically at Moffitt, less than 1% of all patients that meet the clinical inclusion criteria have been male or Spanish speaking only, and no patients in the past 3 years were under the age of 21 and diagnosed with breast cancer. Throughout recruitment (i.e. after each MBSR(BC) program), we will review the mix of patients enrolled in the study to verify that sufficient variability exists in clinical history (e.g. stage of disease) and pre-existing levels of symptoms. If the subject pool is unexpectedly homogeneous (did not occur in our R-21 trial) with respect to presenting clinical history, symptom profile, and QOL, we will modify inclusion criteria or oversample patients with specific underrepresented characteristics. In this way, we will ensure that the MBSR(BC) intervention has sufficient opportunity to demonstrate favorable change in patient outcomes in the broad setting of breast cancer patients coming off of treatment.

Exclusion criteria. Patients who have advanced stage breast cancer (stage IV), a severe current psychiatric diagnosis (e.g. bipolar disorder) or recurrent treatment for prior breast cancer will be excluded. Since we anticipate considerable psychological distress among the source population, women with mild yet clinically established depression, anxiety, or other psychiatric conditions will not be excluded from the study.

Instruments. Multiple instruments listed below in **Table 5** will be used in this study to assess the measures of health status and other patient characteristics.

Table 5. Instruments used to measure variables, reliability and data collection points

Variables	Measurements	Data collection Points			Reliability
Outcome Variables		**Baseline**	**6-week**	**12-week**	
Psychological Symptoms					
Depression	CESD Scale	X	X	X	.84 - .92
State Anxiety	State Trait Anxiety Inventory (State Scale only)	X	X	X	.95
Perceived Stress	Perceived Stress Scale	X	X	X	.84 - .86
Physical Symptoms					
Fatigue	Fatigue Symptom Inventory	X	X	X	>.90
Pain	Brief Pain Inventory	X	X	X	.82 - .95

Sleep	Pittsburgh Sleep Quality Index	X	X	X	.77 - .81
Physical and Psychological Symptoms					
Symptom Severity	MDASI	X	X	X	.82-.94
Quality of Life					
Quality of Life	MOS-SF-36	X	X	X	.83 - .93
Biological Stress Markers					
Immune Function	Pro-inflammatory and anti-inflammatory IL-1β, TNF-α, IL-6, IL-10, IL-1-RA, TNF-RA, IL-8, IFN-gamma Cellular adhesion markers CD11a, CD54, CD62L, CD45RA, CD45RO Lymphocyte subsets (CD3, CD19, CD16+56)	X	X	X	N/A
Stress Hormones	Cortisol (salivary)	X	X (wk 1 MBSR Group)	X (wk 6)	N/A
Mediating Variables					
Mindfulness	Cognitive and Affective Mindfulness Scale-Revised	X	X	X	74 -.77
Mindfulness	Five Facet Mindfulness Questionnaire	X	X	X	.72-.92
Fear of Recurrence	Concerns about Recurrence	X	X	X	.87
Psychosocial Variables					
Optimism	Life Orientation Test	X	X	x	.74-.78
Social Support	MOS Social Support Survey	X	X	X	.97
Descriptive Variables					
Demographics	Age, ethnicity, education, marital status, occupation	X	X	X	N/A
Clinical History	Diagnosis, Treatments, Medication, Lifestyle behaviors	X	X	X	N/A

*Previous experience indicates 120-135 minutes to complete all questionnaires.

Outcome Variables

Psychological Symptoms

Depression will be measured by the Center for Epidemiological Studies Depression Scale (CES-D), a 20-item measure of depressive symptomatology.[191] Respondents rate how frequently they have experienced each depressive symptom during the previous week on a four-point scale. A total depression score is computed with higher scores indicative of more depressive symptoms. This instrument has been used in several cancer studies and despite having a mix of psychological and physical symptom items, is principally a measure of emotional/psychological status. Reported coefficient alpha reliability is .92 for breast cancer subjects.

State Anxiety will be measured by the State Anxiety Inventory (Y1 state scale only) that contains a 20-item Likert scale that measures present experience of anxiety. Internal consistency reliability for this scale is .95.[192]

Perceived Stress will be measured by the Perceived Stress Scale.[193] This is a 14-item, Likert-type instrument that assesses how often in the past month one appraises life situations as "stressful." Items are scored as (0) never to (4) very often. Internal consistency reliability is reported to range from .84-.86.

Physical Symptoms

Fatigue will be measured by the Fatigue Symptom Inventory (FSI).[194] This is a 14-item self-report measure that reports severity, frequency, and daily pattern of fatigue, as well as perceived interference with QOL. Items include 4 indicators of fatigue experienced in the past week and are measured on separate 11-point scales (0=Not at all fatigue; 10=Extreme fatigue) as well as current fatigue. Perceived interference is a 7-item scale that uses separate 11-point scales to assess the degree to which fatigue in the past week was judged to interfere with: (i) general level of activity, (ii) ability to bathe and dress, (iii) normal work activity (iv) ability to concentrate, (v) relations with others, (vi) enjoyment of life, (vii) and mood. These interference ratings can be summed to obtain a total perceived interference score. Two items measure duration of fatigue, defined as the number of days in the past week and the mean percentage of time each day the respondents felt fatigued. The final item provides qualitative information about diurnal variation in the daily experience of fatigue. The 7-item interference subscale was found to have excellent internal consistency (alpha > .90). Test-retest reliability over

3 to 12 week intervals among cancer patients was also favorable (r=.35-.75). Convergent validity was demonstrated by significant positive correlations measures between the FSI and (POMS-Fatigue Scale) and significant negative correlations between the FSI and measures of psychological functioning (e.g., SF-36 Health Survey). Construct validity has been demonstrated on measures of anxiety and depression.

Pain will be measured by the Brief Pain Inventory,[195] which contains 9-items that examine pain intensity and interference in patients. Items 1-6 assess type of pain, location of pain in the body and severity of pain during the past week, on average and at present. Items 7-8 refer to medications and their usefulness in relieving pain. Item 9 assesses the severity of pain interference in patients' daily activities. Reliability coefficients for the BPI Severity and Interference scales were high with reliability coefficients ranging from .82 to .95.

Sleep will be measured by the Pittsburgh Sleep Quality Index (PSQI).[196] This instrument measures sleep quality of patients and contains 19 self-rated questions and 5 questions rated by the bed partner or roommate of the patient. Questions refer to patients' sleep habits, quality of sleep, potential use of medicine for sleep, and QOL and activities due to sleep. The 19 self-rated questions produce 7 component scores that are summed up for a global sleep quality score. Each of the 7 component scores are scored on a 4-point scale. The overall reliability coefficient for the global PSQI was .80 and ranged from .70 to .78 for the sleep disturbance component.

Psychological and Physical Symptoms will be measured by the MD Anderson Symptom Inventory (MDASI), which is a self-administered questionnaire which measures current symptom experienced by the patient and severity of the symptom. Patients are asked to assess their symptoms from 0 to 10 to rate the presence and severity; 0 is labeled "not present" and 10 is labeled "pain as bad as you can imagine." MDASI has 13 core symptom items that are rated based on their presence and severity and 6 symptom interference items that are rated based on the level of symptom interference with function. Internal consistency, calculated by α, has been shown to range from 0.82-0.94. This shows a high level of reliability.*

Quality of Life will be measured by the Medical Outcomes Studies Short-form General Health Survey (MOS SF-36), which is a 36-item health status measure that uses Liker-type response formats.[197] This self-report measure includes 8 subscales that measure the following: Physical Functioning, Physical Role Functioning, Bodily Pain, General Health, Vitality, Social Functioning, Emotional Role Functioning, and Mental Health. Subscale scores range from 0 to 100 with higher scores indicating a more favorable health status. Reliability estimates have been reported in several studies with several different patient populations. Estimates of internal consistency reliability range from 0.62 to 0.94, the majority of scores have exceeded 0.80. Test-retest reliability estimates range from 0.43 to 0.90. Factor analysis indicates two dimensions of the instrument, physical and mental health status, that account for 82% of the reliable variance of the measure.[197]

Mediating Variables

Mindfulness will be measured by the Cognitive and Affective Mindfulness Scale-Revised (CAMS-R), [152] a self-report 12-item Likert-type scale. Items query mindfulness approaches to thoughts and feelings and respondents rate how each item applies to them (1=Rarely/Not at all; 4=Almost always). The 12-item total mindfulness score had an acceptable level of internal consistency (alpha .74-.77). The CAMS-R subscales measure the four domains of mindfulness (attention, present-focus, awareness, acceptance/non-judgment). Mindfulness will also be measured by the **Five Facet Mindfulness Questionnaire**. This is a 39-item instrument based on an exploratory factor analytic study of five independently developed mindfulness questionnaires. It analyzes five factors of mindfulness, which includes observing, describing, acting with awareness, non-judging of inner experience, and non-reactivity to inner experience. Questions are scored as (1) "never or very rarely true" to (5) "very often or always true." [198] Construct validity of the FFMQ are significantly correlated with meditation experience except for the acting with awareness subscale. Internal consistency for all facets ranged from adequate to good (α=0.72 to 0.92).[199]

Fear of Recurrence will be measured by the Concerns about Recurrence Scale.[156] This is a 30-item Likert-type instrument that measures the extent and nature of women's fears about the possibility of breast cancer recurrence. It is composed of 2 sections. The first section has four items that assess "worry" related to recurrence, scored as (1) "I don't' think about it at all" to (6) "I think about it all the time." The second section has 26 items that assess "what it is" and extent to which they worry about each item all are scored on a five point scale. Overall internal consistency reliability is .87 for breast cancer subjects.[156]

Psycho-Social Characteristics

Optimism will be measured by the Life Orientation Test-Revised (LOT-R).[200] This instrument contains 6 target Likert items and 4 filler items. Only target items will be measured. The average score is derived from the 6

target items. It assesses "generalized expectancies for positive versus negative life outcomes" scored on a 5-point scale, ranging from (0) strongly disagree to (4) strongly agree. Optimist scores are defined as those above the median (18) with pessimists defined as below 18. Coefficient alpha reliability ranges from .74-.78.
Social support will be measured by the Medical Outcomes Social Support Survey.[201] This instrument contains 19 items assessing 4 categories (subscales) of social support: tangible, affectionate, positive social interactions, and emotional or informational. These are scored on a 5 point Likert-type scale ranging from (1) for none of the time to (5) for all of the time. The items identify how often each type of support is available to subjects if needed. An additional item identifies the number of close friends/relatives. Internal consistency reliability is 0.97 for the full instrument and .91-.96 for the subscales.

Biological Stress Markers

In our model are measures of pro-inflammatory and anti-inflammatory cytokines and a stress hormone (cortisol). Extracellular secretion of cytokines and cellular adhesion surface markers on leukocytes are viewed as indicators of immune function and cortisol levels are indicators of stress hormones. In the current study, approximately a minimum of 10 ml of blood will be collected in anticoagulant (heparinized) from patients between 10-12 am at baseline, 6 and 12 weeks. Blood samples will be taken from participants in the 2 groups: MBSR(BC) intervention and Usual Care. We hypothesize that MBSR will influence immune responses triggered by emotional distress and anxiety following coming off treatment for breast cancer. For the matched control comparison group, 10 ml of plasma will be obtained for the measurement of plasma cytokine levels and 3 ml will be obtained for cellular adhesion markers.

Measurement of plasma cytokine levels. Out of the 10 ml, 2 ml of plasma will be obtained from heparinized venous blood for the cytokine analyses. All cytokines and chemokines will be determined using the Duoset ELISA technique from R&D Systems (Minneapolis, MN). The first step is to bind unlabeled capture antibody to medium-bind 96 well EIA plates (Corning-Costar; Cambridge, MA). For this, the capture antibodies for IL-1β (4μg/ml; R&D), IL-1RA (10μg/ml; R&D), IL-6 (2μg/ml; R&D), IL-8 (CXCL8) (4μg/ml; R&D), IL-10 (2μg/ml; R&D), IFN-γ (4μg/ml; R&D), TNF-αRI (4μg/ml; R&D), TNF-αRII (2μg/ml; R&D) and TNF-α (4μg/ml; R&D) will be diluted in PBS. Depending upon the antibody combinations, the plates will be incubated for 2 hrs at 37ºC or overnight at 4ºC and blocked for 1 hr with 0.5-3% BSA in PBS containing 0.05% Tween 20. For cytokine and chemokine testing, dilutions of serum samples or cytokine standards will be added to the coated plates for 2 hr, followed by the addition of biotinylated antibodies (0.1-1μg/ml) to cytokine/chemokines for 1 hr and then the addition for 30 min of streptavidin-horseradish peroxidase (HRP; 1:1000; 50μl, BD Pharmingen). The plates will be washed 3-5 times between additions of the above reagents. The peroxidase substrate, tetramethylbenzidine (TMB) (Sigma, St Louis, MO), will be then added, and the reaction allowed to develop for 5-45 min and then stopped by the addition of 1 N sulphuric acid. The OD of the chromogenic substrate will be read at 450 nm on an Emax Microplate reader (Molecular Devices; Sunnyvale, CA) and the OD units converted to cytokine or chemokine protein units by means of a standard curve run for each plate. This procedure can be done with 2 ml of blood plasma per specimen.

Measurement of cellular adhesion marker expression. Three ml of heparinized peripheral blood will be collected by venipuncture simultaneously with the sample collected for cytokine levels. As an indication of cell activation, we will measure the quantitative expression of cellular adhesion markers CD11a (leukocyte adhesion molecule), CD54 (intercellular adhesion molecule-ICAM-1), CD62L (L selectin adhesion receptor), CD45RA and CD45RO on leukocyte subsets which will be analyzed using multi-color flow cytometry on a FACScalibur 4 color flow cytometer (Becton Dickinson, San Jose, California). Fifty microliters of sample will be dispensed into each of 4 tubes (one for each adhesion marker and one for an isotype control, along with CD3, CD19 and CD16+56) to allow for evaluation of expression on different lymphocyte subsets. Expression on monocytes and granulocytes will be accomplished by gating on appropriate populations utilizing forward vs. side scatter plots to differentiate lymphocytes, monocytes and granulocytes. Quantitative expression will be monitored by determining the mean fluorescence intensity of the marker and normalizing the instrument with each run using quantitative beads (Bangs Labs, Fishers, IN).

Measurement of salivary cortisol & IL-6. Participants will collect saliva in their mouths and drool the saliva into 50 ml conical Falcon, over 5 minutes, without coughing or clearing their throat. The collection tube will be marked with the time, date and participant number. The RA will then tap the tube to reduce bubbles, and secure the cap on the tube. Tubes of saliva will be transported in a soft-sided cooler in specimen transport bags with biohazard labels and transferred to the Health Sciences Laboratory. Once transferred, samples will be transferred to 15mL conicals, centrifuged at 3000 R.P.M. for 15 minutes, and the supernatants pipetted into

Fisherbrand siliconized/low retention microcentrifuge tubes (Fisher Scientific), and stored in the -80° C freezer in the College of Public Health Laboratory until assayed for cortisol. Saliva will be assayed using a High Sensitivity Salivary Cortisol Enzyme Immunoassay Kits from Salimetrics, Inc. (State College, PA) according to kit instructions (Salimetrics Inc Catalog No. 1-0102/1-0112 96-Well Kit, Updated: 6/23/04). Intra-assay coefficients of variation, inter-assay values, and assay sensitivity will be calculated. Cortisol values will be examined for outliers and any raw data that falls outside the physiological range will be excluded from analyses. For measurement of IL-6, saliva will be assayed using a high sensitivity IL-6 ELISA kit (Abcom). IL-6 values will be examined for outliers and any raw data that falls outside the physiological range will be excluded from analyses.

Intracellular cytokine measurements. Three mL of heparinized whole blood will be incubated in 1 mL amounts for 5 hrs with PMA (5 ng/ml, Sigma Chemical, St. Louis, MO), ionomycin (500 ng/ml, Sigma), and brefeldin A (1 µ?□g/ml; BD Biosciences). The PMA/ionomycin stimulates intracellular cytokine production and the brefeldin A inhibits cytokine transport out of the cell. Following incubation, the RBCs in the samples will be lysed by ammonium chloride buffer and the PBMCs processed for surface and intracellular staining. For surface staining, all tubes are Fc-blocked with isotype-controlled antibody of irrelevant specificity for 20 min at 4° C. Next, two tubes will be treated with CD45 perCP, CD4 APC, and CD3 FITC for 20 min at 4° C. The third tube will be treated with appropriate antibody isotypes to serve as controls for positive and negative. All tubes are washed 2X in staining buffer, resuspended in Cytofix/Cytoperm (BD Biosciences), and incubated for 20 min at 4° C. The cells are then washed 2X in Perm/Wash Buffer (BD Biosciences) and resuspended in either anti-IFN-gamma PE, anti-IL-4 PE, or isotype control and incubated for 30 min at 4° C in the dark. The cells in the 3 tubes are then washed and analyzed by flow cytometry for $CD4^+$ cells that are either Th1 or Th2 positive using Cellquest software (BD Biosciences).

Assessment of Genetic Polymorphisms. Previously, presently and future collected blood is drawn for immune functioning measurement, this will be used to measure genetic polymorphisms. Genomic DNA will be extracted from peripheral blood leukocytes and amplified by PCR using the Qiagen DNA extraction kit (Qiagen, Valencia, CA) with modifications. Twelve candidate single nucleotide polymorphisms (SNPs) in twelve genes (fatigue: ACE (intron16 insertion), IL-1β(511C/T), IL6(-174G/C), IL8 (-251T/A); UGT1A1 (Tandem repeats in promoter) Depression: 5-HTTLPR (-1438G/A), BDNF (val66met), COMT (val158met), PROKR2 (intron1), Pain: TNF-α (-308G/A), PTGS2 (exon10 +837), and NFKBIA (exon 6 +50) will be genotyped. A simple, accurate, and high-throughput allelic discrimination analysis method will be used. This technique uses fluorescent-labeled probes and is similar to the procedures used in Dr. Jong Park's laboratory in a previously published study that measured polymorphisms.[189,190] For quality control purposes, 3% of all samples screened by allelic discrimination will be randomly verified by direct sequencing. All scoring will be done by readers blinded to randomization.

Demographic Data Form, Clinical Medical History Form, Use of Stress Reducing CAM Survey

Demographic data. Standard socio-economic demographic data will be collected on participants to allow for description of the sample. Data will include age, gender, ethnicity, highest level of education completed, marital status, income status, and employment status.. Demographics will be gathered at baseline and updated at 6 and 12 weeks. A chart audit will be completed through use of medical records to verify all medical and treatment information. The matched control group, will only complete the demographic data form.

Clinical history form. A Standard Clinical History form will be collected at baseline, 6 and 12 weeks to determine if there are any new problems and treatment related to problems. Data collected will include site of cancer diagnosis, date of cancer diagnosis, date treatment ended, date treatment ended, number of weeks on radiation, and number of weeks on chemotherapy. As part of the clinical history form, a social history will be gathered including information on lifestyle health behaviors, use of alcohol, caffeine, smoking behavior, medications (including antidepressants, Tamoxifen and aromatase inhibitors) and exercise.

Concomitant use of stress reducing therapies will be measured by the Stress Reducing Technique Subscale of the Use of Complementary Alternative Therapies Survey (UCATS) developed by the Principal Investigator.[202] This includes assessment of frequency and intensity of use of other mind body and stress reducing therapies based on 12 Likert items. Internal consistency reliability is 0.86 for the total survey and 0.79 for the Stress-Reducing Techniques Subscale. Intensity of CAM use is measured in hours per week.

Procedures

Approvals. Human subjects and institutional review board approval will be obtained prior to enrolling participants**.** Approvals will be obtained from the Institutional Review Board at Moffitt Cancer Center and Research Institute and the Institutional Review Board of the University of South Florida.

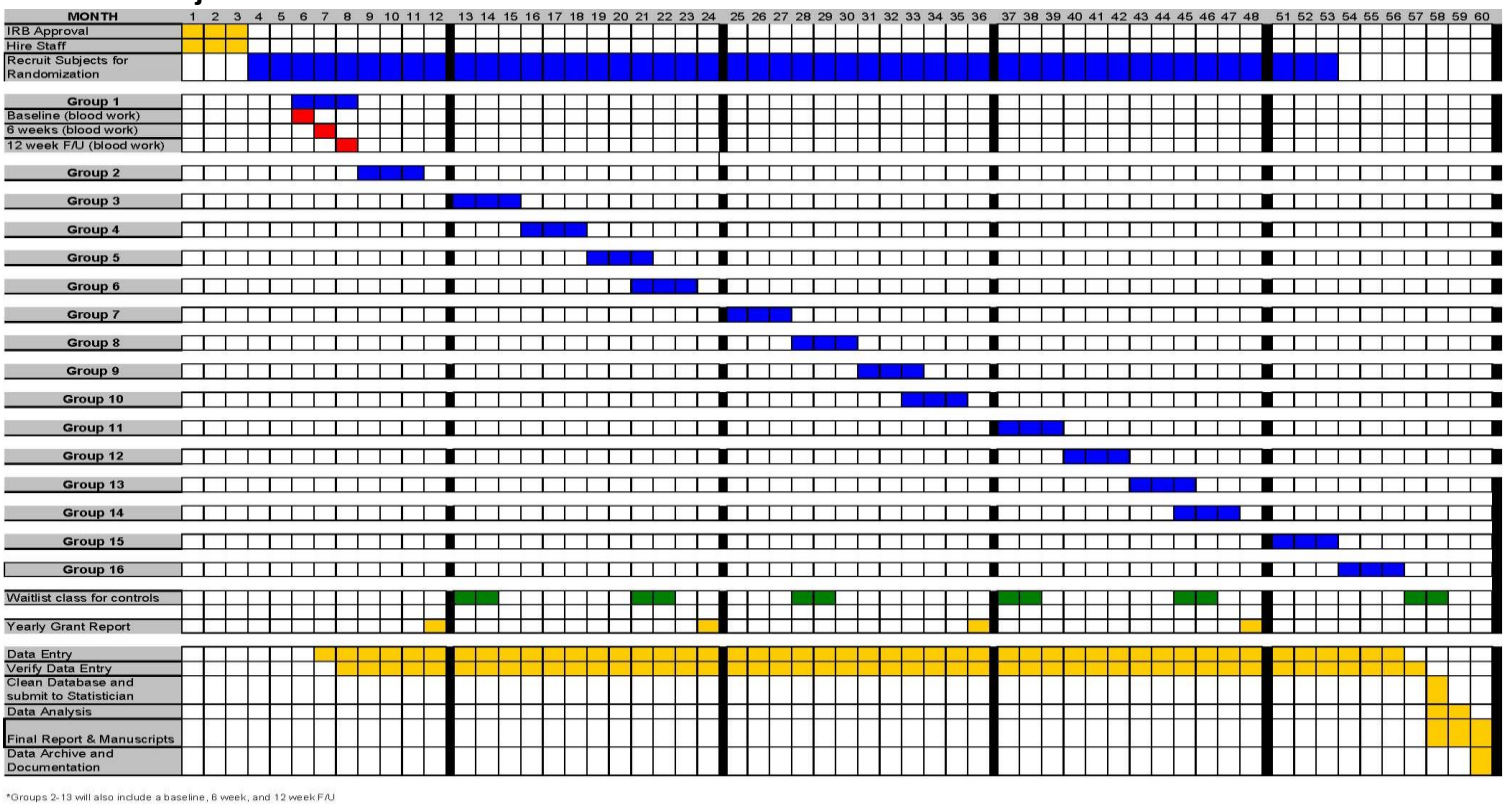
Protocol/Data Collection Procedures

Recruitment and screening. Three hundred(300) women age 21 years and older who meet the stated inclusion criteria will be recruited from the Moffitt Cancer Center and Research Institute and the Carol and Frank Morsani Center for Advanced Healthcare at the University of South Florida (as previously described in the Sample subsection). Recruitment will commence after patient completion of breast cancer surgery and near completion of treatment, up to 2 years off treatment. The Principal Investigator is a member of the Moffitt Breast Cancer and the Health Outcomes and Behavioral Program and has working relationships with physicians and nurses at Moffitt. Health practitioners will assist and be trained in screening for interest in enrollment and will identify eligible patients during routine patient care. They will be provided with a script to explain a brief overview of the MBSR study. Flyers and brochures describing the study will be distributed to patients via advertisements within the cancer center. The distribution of how participants were contacted and participation rate will be tracked. The Morsani Center staff will also utilize the Breastcare Database in order to identify potential participants in the study. Patients who express an interest in the study and meet the study inclusion criteria will be asked to sign a participant interest form. An orientation session will then be scheduled in which consent and baseline measures will be obtained by the principal and co-investigator and research assistants. The research assistant will undergo training to ensure that the recruitment guidelines are followed for enrollment into the study. To maximize enrollment and minimize patient dropout, it will be emphasized that, irrespective of the random assignment, all subjects will have the opportunity to participate in the MBSR(BC) program (i.e. either initially or following a wait period) and that the timing of the intervention has been selected to assist in the critical transition period when formal medical care and support has ended. All critical elements of the study will be reviewed with the patient including the 6 week MBSR(BC) schedule, the 3 time points in which blood will be drawn, the 2 time points for collection of saliva and the self-report questionnaires to be completed.

Participants in the matched control group will be recruited through the distribution of flyers in the USF Health Sciences Center.

Project Timeline. The timeline for this 5 year project is presented in **Table 6** below. Start up time is expected to take 3 months, recruitment, baseline data collection, administering the intervention, and data collection is expected to take 51 months for 16 sessions. Final data entry, screening and cleaning the data, data analysis, writing reports, abstracts and publications will take 4 months.

Table 6: Project Timetable



*Groups 2-13 will also include a baseline, 6 week, and 12 week F/U

Randomization. At the initial orientation session, the assigned randomization will be determined by use of a blocked randomly generated number scheme developed by Dr. Kip, the project methodologist. Following randomization, each subject will be given a corresponding visit schedule. Random assignment will be in a 1:1 ratio to one of two conditions: (i) the formal (in-class) 6-week MBSR(BC) program to commence within 1-week of the orientation session; or (ii) Usual Care (UC) guidelines with waitlisted MBSR(BC) which will ultimately be offered within 6 months of enrollment into the study. Subject randomization will be stratified by type of surgery, (lumpectomy versus mastectomy), breast cancer treatment (chemotherapy with or without radiation versus radiation alone), and stage of breast cancer (Stage 0/I versus II/III). This, along with the blocking mechanism, will be done to help insure balanced distributions of baseline factors between the 2 study groups (e.g. pre-existing levels of anxiety, immune status, etc.). Participants assigned to MBSR will be enrolled in a minimum of 5 to 6 participants, which is adequate for this type of research (per consultation Saki Santorelli).

Data collection procedures for the quantitative measures. Data collection intervals for participants will include a baseline assessment at the initial orientation, an assessment at the end of the 6 week intervention period, and a follow-up assessment 12 weeks after baseline enrollment.

Baseline assessment phase (orientation session). At the baseline orientation session, a limited overview which includes specific details of the MBSR(BC) program will be provided. All critical study elements defined in the informed consent form will be carefully reviewed with the patient, including the 6-week schedule of the MBSR(BC), the 3 time points for blood draws, 2 time points for cortisol collection and the questionnaires to be completed. In addition to conducting randomizations at the baseline session, baseline data will be obtained. A research assistant will accompany patients to the laboratory area at Moffitt for blood draws in the morning for immune function measures and stress hormones. The blood will be transferred by the lab assistant to the Health Sciences Center Immunology Laboratories, adjacent to Moffitt where it will be prepared for cytokine and flow cytometry. Flow cytometry will be performed at the Health Sciences Center/Tampa General Hospital flow cytometry laboratory. All blood will be drawn between 10-12 a.m. at baseline, 6 weeks and 12 weeks. After the blood is drawn, the Principal Investigator and research assistant will then administer the measures of psychological and physical symptom status, QOL and mediators along with demographic and clinical history surveys. Baseline assessments will be done prior to randomization, hence all data collected at this time will be blinded to future assignment. Lab technicians will be blinded at each data point.

Intervention and follow-up phase. Subjects assigned to the MBSR(BC) group will be scheduled for 6 weekly (2-hour sessions) conducted by a trained professional leader in MBSR(BC) (see protocol below for the 6 weekly sessions). Class sizes will consist of a minimum of 5 to 6 participants. In addition to the repeated assessment of blood studies and psychological symptoms, physical symptoms, QOL and mediators at 6 and 12 weeks, MBSR(BC) participants will also be instructed to record their meditation, yoga, walking meditation, and body scan practice time in a daily diary during the intervention period as well as during the subsequent 6-week period after the intervention. For subjects randomized to the Usual Care control group, repeated assessment of blood studies and measures of psychological symptoms, physical symptoms QOL and mediators will be performed at the end of 6 weeks and 12 weeks. At the end of 12 weeks, the Usual Care group will be offered the MBSR(BC) intervention to occur within 6 months after the completion of the study.

Usual care condition: The Usual Care group will consist of standard post-treatment clinic visits and will not be modified by study participation. We will not encourage or discourage use of CAM, yet we will specifically ask participants not to use or practice meditation or yoga techniques, or participate in MBSR during the study. The frequency and intensity of subject participation in other stress-reducing techniques will be assessed by the stress-reducing subscale of the UCATS survey.

Orientation, week 1(MBSR(BC) group only) and week 6 collection of saliva. At orientation, salivary cortisol will be collected 2 hours apart for both the MBSR(BC) and Usual Care group at the same time of day as the MBSR(BC) session. At week 1, salivary cortisol will be collected for the MBSR(BC) group only just before and within 20 minutes after the MBSR(BC) session. At week 6, salivary cortisol will be collected for the MBSR(BC) group just before and within 20 minutes after the MBSR(BC) session, and saliva will be collected for the Usual Care group 2 hours apart at the same time of day as the MBSR(BC) group. Participants will be told to avoid

dairy products, caffeine and smoking one hour before each collection. Samples will be placed on ice and assayed with each pre- and post-test in the same batch.

Experimental conditions (overview of intervention sessions). The MBSR(BC) intervention is modeled on program developed by Jon Kabat-Zinn and colleagues at the Stress Reduction and Relaxation Clinic, Massachusetts Medical Center.[19,22] Mindfulness is the capacity to bring full attention, moment to moment awareness. MBSR was developed to assist patients in management and adaptation to physical and emotional consequences of illness through the self-regulatory process of meditation to assist persons in taking an active role in stress reduction, and symptom management, including psychological (anxiety, and depression) and physical symptoms such as pain and sleep. The goal of training is to teach participants to become more aware of their thoughts, feelings and emotional reactions to symptoms through meditation practice, and to pay attention and observe the thoughts or feelings during stressful situations that contribute to emotional distress. Patients are taught to bring awareness to the thoughts and emotions associated with symptoms such as pain and anxiety and to separate the emotional experience from the sensory experience, thus learning their perception can influence symptom experience and through MBSR one can eliminate the fear attached to pain and reduce suffering. Thus, by promoting self-regulation through the practice of meditation coupled with additional components of the program such as body scan, one can cope with the distress of symptoms and illness including cancer. See MBSR(BC) Manual pages 14 and 41. The overall goal of this program is to teach breast cancer survivors how to more fully improve their health and QOL, complementary to traditional care.[203] The objectives are to: 1) allow survivors the opportunity to examine and develop an understanding of their personal response to the symptoms and distress and find a means to modify that response; 2) encourage survivors to take an active part in their healing process; 3) teach opportunities for self care through mastery of MBSR; 4) increase feelings of well-being and wholeness; and 5) provide an environment that is supportive to self disclosure about the meaning of cancer and that allows for learning of new skills as a cancer survivor.
Intervention components. The intervention consists of 3 processes: 1) educational material related to relaxation, meditation, the mind-body connection and a healthy lifestyle for survivors; 2) practice of meditation in group meetings and homework assignments; and 3) group processes related to barriers to the practice of meditation, application of mindfulness in daily situations and supportive interaction between group members. Participants receive meditative training [19] in 4 types of meditation techniques that emphasize focusing attention to the breath: 1) sitting meditation, which involves an awareness of bodily sensations, thoughts and emotions while focusing on attention to breathing; 2) body scan which consists of observing any sensations in the various regions of the body from the head to toes while focusing attention to breathing; 3) Gentle Hatha Yoga which consists of various postures and stretches that increase awareness and balance and strengthens the musculoskeletal system: and 4) walking meditation, which increases awareness with walking activity. MBSR(BC) program is a weekly, 2-hour session, for 6 weeks duration. The six weekly 2-hour sessions in the MBSR(BC) intervention include: week 1, overview and rationale of the MBSR(BC) intervention; week 2, visualization and guided body scan; week 3, awareness of pleasant events, visualization, body scan and yoga posture; week 4, awareness of unpleasant events, visualization, body scan and yoga posture; week 5, application of MBSR to awareness of thought processes; and week 6, beginning of independent action. Participants are requested to formally meditate (mindfulness practice, including yoga and body scan exercises) for a minimum of 15-45 minutes per day, and allocate 15-45 minutes for informal practice. Six-week programs have been implemented in several studies. CD's will be provided on the six-week program to assist patients with meditation, yoga and body scan. For a detailed description of the MBSR(BC) weekly intervention sessions and description and the MBSR(BC) Training Manual.

Training of Staff. Dr. Cecile Lengacher received training in MBSR from Jon Kabat Zinn and Saki Santorelli along with our instructor Dr. Manolete Moscoso who has extensive experience and practice in mindfulness meditation. Another instructor will be hired if needed. A curriculum established by Jon Kabat-Zinn and Saki Santorelli will be used as the basis for the standardization of the classes. All investigators and research assistants will complete the federal requirements for training in the protection of human subjects and documentation will be provided to the IRB and NIH. This includes completing the NIH Training module. http://phrp.nihtraining.com. With respect to carrying out the study, a training manual was developed for the R-21 pilot study and will be revised for the nurse recruiter and research assistant (RA) who will be trained by the PI on recruitment and participation of patients into the study, monitoring of progress and data collection. Our current R-21 research study coordinator Melissa Molinari Shelton and our Research Assistant, Michelle Barta

have 2 years experience with the pilot project along with other co-investigators and consultants. New personnel hired will receive 10 hours of training before recruitment begins. Training will include 2 hours of background information on the project and 6-8 hours on recruitment procedures for the study, obtaining informed consent and methods to assist with data collection. The RA will assist with data management, and will be trained for observational methods to assess implementation of the MBSR(BC) program (described below).

Integrity of the Intervention and manipulation checks. Meetings with the primary instructor(s) implementing the intervention will be scheduled at regular intervals for systematic review. A structured observational method will be used to evaluate the MBSR instructor adherence to the intervention protocol. If there is more than one instructor (not currently planned), all classes will be audio tape-recorded to insure consistent compliance by the instructors with intervention protocols. A trained research assistant will use an observational checklist to determine content coverage in the 3 main components of MBSR(BC) (sitting meditation, body scan and yoga) as well as interactional components of the process (teacher to student, student to teacher, student to student support). Inter-rater reliability will be established by comparing PI observations with the research assistant observations on 4 sessions. The checklist will be validated by a panel of experts in MBSR. For each session, at the completion of the observation, the research assistant will complete a post-observation report to record the personal reaction to the class instructor and class participants. These data will be used to check on whether the coding scheme is discriminating among individuals to whom the observer has very different reactions. Finally, the research assistant will be asked to write a paragraph about unusual or disturbing events including environmental variables that may have affected the observation. The PI will convene bi-weekly meetings with the research team to share helpful suggestions for adhering to the protocol and to ensure that the MBSR(BC) intervention is implemented as effectively as possible. To determine the fidelity of the MBSR(BC) intervention, a participant manual will be used that includes a daily diary. At each data interval, the data collector (research assistant) will check the manual to determine to what extent the participant is recording homework in the diary. Completion of the daily diary will be monitored on a weekly basis for the intervention group.

Integrity of the data. The study coordinator will insure that patients admitted to the study meet all the study criteria by doing a random review of 1 to 2 cases per month. To ensure that the study questionnaires are answered completely, data collectors (as stated above) will be instructed to review each form as the subject completes it, and to monitor full completion of all sections and questions. This will occur in a similar manner for MBSR(BC) and Usual Care subjects.

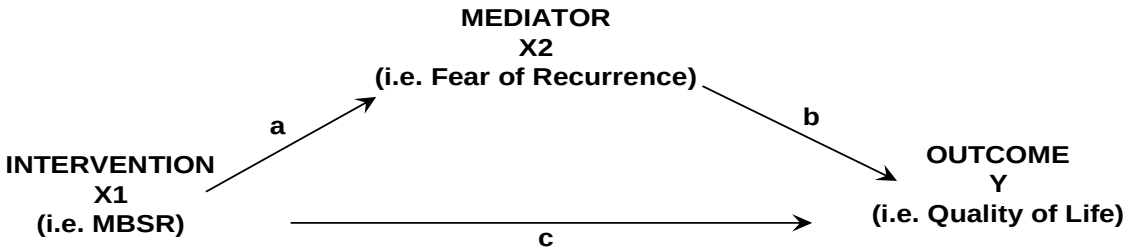
Data Analysis Plan.

The data analysis plan coincides with the 3 proposed specific aims. Prior to formal hypothesis testing, the distributions of all explanatory and outcome variables, as well as covariates, will be examined. For outcome variables with skewed distributions, appropriate transformations (e.g. square root, logarithmic, etc.) will be performed to satisfy normality requirements for parametric multivariable linear modeling. This will include choosing the transformation which yields the lowest Anderson-Darling score. In instances in which appropriate transformations cannot be achieved, non-parametric methods will be used.

Specific Aim #1: Evaluate the efficacy of the MBSR(BC) program in improving psychological and physical symptoms, QOL and measures of immune function and stress hormones. For this aim, analysis of covariance (ANCOVA) will be used to compare adjusted mean outcome scores (physical symptoms, QOL, immune function, stress hormones**)** between patients assigned to the MBSR(BC) program versus patients assigned to the Usual Care regimen. The "intent to treat" principle will be used, and all outcomes will be considered of equal importance (i.e. no secondary outcomes). There will be 2 post MBSR(BC) outcome assessment periods - one at 6 weeks immediately upon completion of the program and one at 12 weeks. This design, coupled with initial baseline assessment, will result in 3 separate measures and hence the opportunity for repeated measures analysis. We view the 2 post MBSR outcome assessment periods as representing separate questions, thereby warranting separate analyses. First, the efficacy of MBSR(BC) will be evaluated using the 6-week assessment period as the outcome period of interest. For this ANCOVA, the baseline value of the outcome variable of interest (e.g. baseline anxiety score) will be included as a covariate, along with all other potential confounding variables that are not adequately balanced by random assignment (as described below). This will provide an assessment of the efficacy of MBSR(BC) in improving patient outcome (i.e. reduced anxiety) in the short-term and above and beyond improvements that occur simply

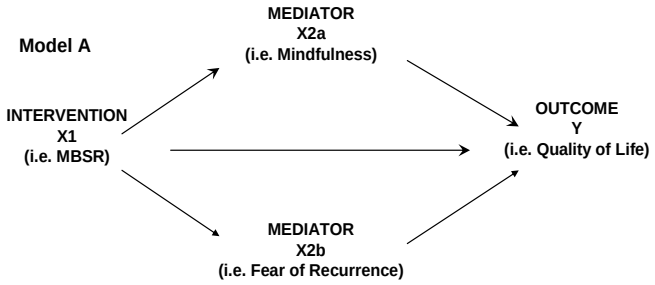
due to increasing time since treatment completion (as measured in the Usual Care group). In the second analysis, the 12-week assessment period will serve as the outcome period of interest, again including baseline status of the outcome variable of interest as a covariate along with potential confounding variables. This will provide an assessment of the short-term sustainability of MBSR(BC) in improving patient outcomes. Acute changes in salivary cortisol levels (i.e. immediately before and after an MBSR(BC) session versus matched control sessions) will also be compared by random assignment by use of ANCOVA. In addition, "mixed models" for continuous outcomes [204] which use random effects to induce correlation over time between observations (i.e. at baseline, 6-weeks, and 12-weeks) on the same patient, will be used. This approach will allow for a range of possible covariance structures (e.g. exchangeable, autoregressive), and the random effects structure described above can account for across-patient heterogeneity regarding rates of change, while facilitating estimation of fixed effects, MBSR in particular. Thus, this analysis will test whether the rate of change in patient outcomes (e.g. anxiety) varies over time significantly between the MBSR and Usual Care regimens.

Specific Aim #2: Test whether positive effects achieved from the MBSR(BC) program (defined in specific aims 1a-1d) are mediated through changes in mindfulness and fear of recurrence of breast cancer. For this aim, we seek to identify "how" MBSR may be effective in improving psychological and physical symptoms, QOL and measures of immune function and stress hormones. In other words, do specific variables mediate the efficacy of MBSR(BC)? As shown in our preliminary R-21 analyses, reduced fear of recurrence of cancer may be one mechanism (mediator) by which MBSR is effective. Moreover, we now propose to directly measure mindfulness and awareness achieved from MBSR which, in theory, may be expected to mediate the effects of MBSR. Thus, these 2 variables will be the primary potential mediators evaluated using multiple methods. To illustrate, the MBSR(BC) program will be treated as the primary explanatory (predictor) variable hypothesized to have direct effects on patient outcomes, such as QOL at 6- and 12-weeks. Change in fear of recurrence is postulated to be associated with both the MBSR(BC) program and patient outcomes at 6- and 12-weeks, thus mediating the relationship between MBSR and patient outcomes (i.e. indirect effect of MBSR on patient outcomes). This is depicted in the simple path diagram below.



In this diagram, MBSR (X1) is assumed to have both a direct and indirect path to the outcome QOL (Y). "c" is the direct path and "a -→ b" is the indirect path, passing through the mediating variable change in fear of recurrence (X2). These paths will be expressed as standardized beta coefficients in regression modeling, including path analytic methods[205] and sequential regression techniques. [206] Thus, the direct and indirect paths will be compared directly with each other to assess the strength of mediating effects. A parallel approach will be used to evaluate changes in mindfulness and awareness as mediators of patient outcomes.

In addition, we seek to evaluate the relative contributions (and pathway sequence) of changes in mindfulness and fear of recurrence simultaneously as mediating the effects of MBSR, while also controlling for covariates that may be imbalanced (largely unexpected) despite random assignment. This multivariable, multi-pathway approach will require a more comprehensive and flexible approach, specifically, use of structural equation modeling (SEM) for this application.



Briefly, SEM is a theory-based confirmatory technique with two main parts: a structural model that shows potential causal dependencies between endogenous and exogeneous variables; and a measurement model that shows relations between variables and their indicators.[207,208]

In this study, we will focus on the structural model (i.e. path analyses) while retaining the flexibility for development of a full model with multiple covariates represented and modeled as latent variables. Specifically, the 2 basic models of principal interest (identified as "A" and "B" above) (without covariates) will be formally tested. This will help to define "how" MBSR may be effective. In addition, the use of SEM in this framework permits specification of error terms: that is, estimates of reliability of each measure in the model (i.e. see **Table 5**). This will help to better estimate the true magnitude of path coefficients for Models A and B. Finally, assessment of model superiority (i.e. Models A and B) will be evaluated by examining individual path coefficients and overall model chi-square adjusted goodness of fit statistics.

Specific Aim #3: Evaluate whether positive effects achieved from the MBSR(BC) program (defined in specific aims 1a-1d) are <u>modified</u> by specific patient characteristics measured at baseline. To identify variables that modify (interact) with the efficacy of MBSR(BC), multiple analytic approaches will be used. First, conventional subgroup analyses will be conducted to evaluate MBSR(BC) versus Usual Care. The a priori-defined subgroups of interest, based on our R-21 analyses and specific aims, will include: (1) baseline levels of psychological status and health (anxiety, perceived stress, optimism and QOL) categorized as above or below the median; and (2) specific symptom profiles (i.e. patterns of symptoms), as determined by symptom cluster analyses and described below. In essence, all of these subgroups represent different aspects of disease severity and patient stage of recovery. In addition, interaction terms will be used to formally test whether the efficacy of MBSR is modified by the a-priori defined variables. However, we will place a premium on interpreting the results of potential moderating variables based on absolute measures of effect (e.g. adjusted means) rather than statistical significance alone which is influenced heavily by the number of patients in each subgroup evaluated.

"Cluster analysis" [209 210] will be used whereby patients presenting with similar individual symptoms (e.g. high depression, high anxiety) will be grouped (clustered together), and the efficacy of MBSR(BC) will be evaluated within each individual cluster of patients. The cluster analysis will be based on 6 symptom scores: depression, state anxiety, perceived stress, fatigue, pain and sleep. We will standardize each of the 6 scores to have the same mean and variance. We will cluster them into k clusters, with k ranging from 2 to 5, and choose a final clustering size based on the distinctiveness of the clusters. As the k+1 cluster groups differ from the k cluster group only by two groups being combined together, our choice will principally be made by the distance between the clusters that are being combined compared to the distance between cluster members when the groups are considered separately. We will then look at the differences in the averages for each of the 6 scores between the clusters. As cluster analysis is designed to separate subjects by their score profiles, it is to be expected that some spread in the average scores will occur. Thus, p-values derived from pairwise comparison lack the strong meaning they have for a priori groups of subjects. Still, these p-values will provide the relative strength of the separations and allow us additional insight into which factors drive the clusters that are produced. The clustering method we will use is an agglomerative, cluster analysis using the average linkage on the squared Euclidean distances of the standardized scores.

Other analyses. In addition to our specific aims and hypotheses to be formally tested, we seek to examine among all patients the extent to which changes in patient symptoms and QOL are associated with clinically relevant changes in biological markers. Initially, changes from baseline to 6 weeks, baseline to 12 weeks and 6 weeks to 12 weeks in distributions of symptoms and biological markers will be plotted by use of kernel density estimates. This will provide an overall picture as to the extent and distribution of symptom and biological marker change over time. Second, Spearman rank correlation coefficients will be computed between change in symptoms, QOL scores and biological marker values. These estimates will be computed at both 6 and 12 weeks and by correlating changes in symptom scores from baseline to 6 weeks with changes in biological markers from baseline to 12 weeks. This will help to identify the temporal sequence of events: that is, whether specific changes in symptoms tend to precede or occur concurrently with changes in biological

markers. In addition, for biological markers that have established "normal" reference ranges, including T-helper cells and NK cells, subgroup analyses will be performed among patients with "abnormal" values at baseline. Specifically, log binomial regression will be used to assess the adjusted relative risk of achieving a "normal" value within the established reference range in relation to change in symptoms and adjusting for baseline biological marker level and potential confounding variables (as described below). Similarly, using both the 6 week and 12 week measurements for assessment of return to "normal" biological marker levels, moment-based Generalized Estimating Equations (GEE) [211] an alternative quasi-likelihood approach for discrete outcomes, will be used. Similar to the mixed models for continuous outcomes, different covariance structures can be specified to account for within-patient correlation (multiple observations).

Statistical issues. Based on the data analysis plan and repeated measurements, several statistical issues warrant separate discussion.

Confounding. Due to the stratified random assignment scheme to be employed, we do not anticipate appreciable imbalances between the 2 study groups among baseline variables that may be prognostic of outcome (e.g. baseline anxiety). Nonetheless, we will assess potential confounders (covariates) that may require statistical adjustment, and if so, include these in multivariable models (e.g. ANCOVA, SEM). Specifically, we will fit an initial linear regression model that includes the MBSR intervention as a separate indicator variable (hence Usual Care as the referent group), along with the baseline value of the outcome of interest (i.e. symptom score). We will then fit a second model that adds a potential confounding variable, such as baseline anxiety level. If the parameter estimate (beta coefficient) for the MBSR indicator variable changes by $\geq$10%, this is an indication of confounding and need for statistical adjustment.[212] We favor this approach since it is relatively invariant to sample size, a feature not present in stepwise regression procedures.

Multiple comparisons. We have proposed multiple outcome measures to evaluate the efficacy of MBSR. We recognize that, without statistical correction, the probability of a type I error is increased due to multiple comparisons. On the other hand, the majority of the proposed outcome measures are believed to be relatively distinct from each other in terms of clinical measurement and unit of measurement. Therefore, as a compromise, a fixed type I (alpha) error rate of 0.01 will be used for all analyses to sufficiently guard against a type I error, while not imposing undue statistical power (sample size) requirements on the study.

Missing data. Missing data due to participant dropout is always a concern. We believe that subject withdrawal will be minimized in this study because of the following: 1) routine contact will be made with participants in the process of scheduling and verifying the baseline, post assessment at 6-week and 12-week visits; 2) requiring attendance at an orientation session with a blood draw helps to insure subject commitment after baseline; 3) participants will be paid $50 upon entry into the study, $50 at the end of 6 weeks and $50 at 12 weeks upon study completion; and 4) performance in our R-21 trial in which subject retention was 98% at 6-week follow-up. To minimize item-specific missing data on the battery of self-report measures, the Principal Investigator and/or research assistant will review all forms at the time the subject completes them to identify any missing data elements or problems completing the forms. Analytically, assuming that the amount of missing data is low (as experienced in our R-21 trial), missing values will be imputed (filled in) by either unconditional or conditional mean imputation; these relatively simple approaches perform well when the overall percentage of missing data is low.[213] Alternatively, multiple imputation methods may be considered for unanticipated circumstances when the amount of missing data is not low, yet still suitable for imputation. The matched comparison group will receive $10 for participation in the biological cytokines.

Power Analysis and Sample Size Justification

As described below, our proposed sample size of 300 patients has been selected to be able to conduct a reliable, rigorous evaluation of the efficacy of MSBR(BC) overall and within key subgroups of interest.

For specific Aims #1 and #3, we propose to compare adjusted mean outcome scores separately at 6-weeks and 12-weeks of follow-up between the 2 randomly assigned groups. As seen in **Table 7,** the full cohort of 300 subjects (with an effective N of $\geq$300 taking into account up to 10% loss to follow-up despite only 2% in our R21 study) will provide 90% power (type I error rate of 0.01) to detect an effect size (between group difference in adjusted means / standard deviation) of 0.45. For interpretation, an effect size of 0.2 has been classified as "small", 0.5 as "medium", and 0.8 as "large".[214] For our a priori defined subgroups of interest which will be categorized as above or below the median, a medium effect size of 0.64 will be detectable at 90% power, assuming a conservative type I error rate of 0.01. For the cluster analysis, we hypothesize that 3 clusters will emerge with the following potential interpretations (i.e. patient profiles) and probabilities: patients generally

high on most symptoms (30%); patients generally low on most symptoms (30%); and patients with a mixed symptom profile (40%). The following power analyses are based on these hypothesized results. Within each cluster, effect sizes of 0.71 and 0.83 will be detectable as shown in Table 7. In addition, in a full model of all patients, we can treat cluster assignment as an ordinal main effects term (i.e. ranking based on symptom severity), treatment assignment as a binary main effects term, and the interaction term treatment assignment x cluster assignment. This may enhance statistical power for this analysis. While the power calculations were based on using a 2-sample t-test, we will use the Wilcoxon rank sum test with normal scores, which asymptotically has equal power to the t test if the raw data are normal, and greater power otherwise.

Table 7. Effects Sizes Detectable at 90% Power for the Total Cohort and Key Subgroups

Patient group	N per group	Total N	Effective N*	Effect Size Detectable @90% Power
All Patients	165	330	300	0.45
Baseline symptom status (e.g. depression score)				
Above median (50%)	82	165	149	0.64
Below median (50%)	83	165	149	0.64
Symptom cluster analysis				
Cluster 1 (e.g. high on all symptoms)	49	99	89	0.83
Cluster 2 (e.g. mixed symptom profile)	66	132	119	0.71
Cluster 3 (e.g. low on all symptoms)	49	99	89	0.83

*Conservatively assumes 10% loss to follow-up and based on type I error rate of 0.01.

Finally, in the mixed model assessment of rate of change in symptoms by random assignment, we expect to observe greater power due to simultaneous use of baseline, 6-week, and 12-week symptom scores in the analysis, unless there is a very high within-patient correlation among these serial measurements. Thus, the proposed sample size of 300 patients, and based on very conservative assumptions (i.e. 90% power, type I error rate of 0.05, 10% loss to follow-up), will be adequately powered to detect medium to large differences in efficacy (i.e. symptom improvement) between the MBSR(BC) and Usual Care groups.

For specific Aim #2, we will use the full sample size as used in Aim #1. Because SEM builds upon classical linear modeling approaches (e.g. ANCOVA), we would expect the sample size selected for Aim #1 to be sufficient for Aim #2 analyses. Nonetheless, guidelines exist for ensuring adequacy of sample size for SEM. Among the most conservative recommended criteria is a minimum of 15 to 20 cases per measured variable or indicator.[215-217] As depicted above in Model B, we identify 4 measured variables of interest, along with potential (but unexpected) covariates to minimize confounding. Based on our proposed sample size of 300 subjects, we anticipate few appreciable imbalances of potential confounding variables, perhaps 4 at most. Therefore, with a model of 8 measured variables, the minimum required sample size for use of SEM is approximately 160 subjects (i.e. 8 x 20). Thus, our proposed sample size of 300 subjects should be fully adequate to evaluate potential mediating variables in the framework of SEM.

For our proposed additional ("other") analyses and again assuming a conservative type I error rate of 0.01, a modest correlation coefficient of 0.22 between change in symptoms and change in biological markers will be detectable at 90% power. In subgroups analyses, as defined above, modest correlation coefficients ranging from 0.25 to 0.48 will be detectable at 90% power. Finally, in log binomial regression analyses restricted to patients with "abnormal" biomarker levels at baseline and using a conventional type I error rate of 0.05, we seek to compare the percentage of patients that achieve "normal" (reference range) biomarker levels at follow-up (**Table 8**). We assume that 30% to 70% of patients will have "abnormal" values at baseline and that 30% to 70% of patients in the Usual Care group will achieve "normal" values at follow-up. Given these assumptions, the sample size of 300 patients will be able to detect modest to large relative risks ranging from 1.26 to 2.13 at 90% power. In other words, if MBSR(BC) is observed to be 1.3 to 2.1-fold better than Usual Care in achieving "normal" biomarker levels, the study will have 90% power to detect this effect as statistically significant using a conventional p-value of 0.05.

Table 8. Relative Risks of Return to "Normal" Biomarker Levels Detectable at 90% Power

% Abnormal at baseline	Total N	Effective N*	Relative Risk Detectable Based on % of Usual Care Subjects with Return to Normal Values		
			30% success	50% success	70% success

70% of patients	231	208	1.73	1.43	1.26
50% of patients	165	148	1.85	1.51	1.29
30% of patients	99	89	2.13	1.63	1.35

*Conservatively assumes 10% loss to follow-up.

Methodological issues and limitations. We recognize the dedicated commitment that patients must make in participating in this study. Asking participants to attend 6 weekly sessions in addition to study orientation and 3 blood draws and 2 time points for cortisol collection is time consuming and may not be feasible for women who work full time, have family responsibilities or lack travel accommodations. Feasibility and accessibility are important factors in complementary and alternative medicine (CAM) trials of women with breast cancer. [218] Understanding these limitations, we have conservatively estimated our consent rate to be 30-40%. We acknowledge the potential bias in recruiting women particularly interested in MBSR because of the commitment required and excluding those who may be interested but who are unable to participate. This is an inherent methodological concern across CAM studies. However, our sample would not be atypical of the general population who use CAM. If the findings demonstrate the efficacy of MBSR in a sample interested and available, future study would make more extraordinary attempts to include a more comprehensive sample.

Based on our R21 data, in particular findings from the Usual Care group, we expect that over time after radiation therapy and/or chemotherapy, women will tend to have less emotional distress and improved QOL. Fatigue is known to continue at least 2 weeks post radiation therapy and may continue for months afterward and improvements in immune function may occur with increasing time from chemotherapy. With respect to evaluating MBSR(BC) we will control for this expected improvement with a randomized design and by stratifying analyses by time since treatment. If MBSR(BC) is shown to consistently improve symptoms and QOL above and beyond Usual Care, we can conclude that these effects are due to the intervention and not simply time alone. Lifestyle and treatment factors also are known to influence immune outcomes, such as smoking, poor nutritional state and tamoxifen and aromatase inhibitors. Although we cannot control for all of these factors, we anticipate that these factors will remain stable over 12 weeks and that a sample of 300 patients will be generally sufficient to reliably balance the 2 random assignment groups on known and unknown confounding factors. While diaries will be collected, we recognize the difficulty in determining actual and accurate recordings of yoga and meditation practice, the degree to which assignments are completed, and whether the literature provided was actually read. We have selected daily diaries and a post assessment question determining subject's actual completion of these assignments as the most feasible method for this study. Other options, such as having a family member record actual compliance, seemed disrespectful and intrusive. Another limitation is the potential burden of subjects completing self assessment instruments. From previous studies we have determined the approximate time to complete all assessments is 120 minutes. Although this seems lengthy, 82 of 84 participants in our R-21 study (98%) received fair compensation and were motivated and willing to complete all instruments.

Summary. The proposed study is important and novel in that it will rigorously evaluate the efficacy of MBSR(BC) in improving residual symptoms and quality of life in breast cancer survivors off treatment. In addition, our proposed aim to examine over time changes in symptoms and QOL in relation to pro-inflammatory cytokines and other biological stress markers is novel. This study builds on our preliminary studies of the MBSR(BC) program to reduce stress and physical and psychological symptoms, and improve QOL in breast cancer survivors. We have demonstrated the feasibility of recruiting and retaining breast cancer survivors, have preliminary evidence that a 6-week MBSR(BC) program helps reduce some symptoms over the short-term, and that MBSR may affect cellular immune function and cytokines released in response to stress. However, more precise evaluation of the clinical implications of immune effects requires a larger more definitive study. In addition, both the immediate (i.e. 6 weeks) and short-term sustained (i.e. 12 weeks) effects of MBSR require evaluation. If both immediate and short-term sustained beneficial effects are observed, this would provide the rationale for even longer term evaluation. The clinical and biological measures we have proposed, coupled with our preliminary data and proposed sample of 300 patients, will provide for a valid analysis. The complexity and chronic nature of the symptoms experienced among breast cancer survivors, their high risk of morbidity and psychological distress, and the prior lack of adequately powered efficacy studies testing MBSR validate the important need for this study.

PROTECTION OF HUMANS SUBJECTS

Human Subjects Involvement and Characteristics. This is a single site study, where 300 participants will be recruited from which we expect 300 participants to complete the study. Women receiving breast cancer treatment will be recruited from the H. Lee Moffitt Cancer Center and Research Institute. Inclusion criteria include: age 21 or older diagnosed with breast cancer, defined as Stage 0, I, II, or III and having undergone lumpectomy and/or mastectomy, and adjuvant radiation and/or chemotherapy and being end of treatment to 2 years post-treatment. In addition, eligible subjects must also have the ability to read and speak English at the 8th grade level to respond to the survey questions. Exclusion criteria include: advanced stage breast cancer (stage IV), a severe current psychiatric diagnosis (e.g. bipolar disorder), or recurrent treatment for prior breast cancer. Subjects will be asked to: (i) participate in a 6-week, 2-hour per week, Mindfulness Based Stress Reduction Program; (ii) complete a variety of questionnaires; and (iii) have 8 ml of blood drawn. These measurements will be made at 3 intervals: baseline, 6 weeks and 12 weeks. Participants will also be asked to provide at 3 time points, a saliva sample at the orientation, first week (for the MBSR(BC) group only) and week 6 of the intervention.

Sources of Research Data. The research data to be obtained consists of scores from psycho-social self report questionnaires, 8 ml of blood, as well as saliva. The questionnaires take approximately one and one half hours to complete. In addition, existing medical record data will be reviewed to obtain information about the participants' disease history and treatment regimen. These data will be obtained by the Principal Investigator or co-investigators upon admission to the study. A research assistant will serve as coordinator and will be trained by the Principal Investigator on recruitment and coordination of the project.

Potential Risks. The risks associated with participation in this study are deemed to be low. Specifically, the principal potential risk appears to be minimal possible injury resulting from blood being drawn. To prevent excessive bleeding, pressure will be applied to the site where the needle is inserted and a band-aid will be applied to prevent infection. A bruise may form at the site where the needle is inserted, this is easily treated and if this should occur, it poses no significant risk. In addition there is a potential for muscle soreness that might result due to the yoga exercises. The likelihood of these outcomes is considered to be small since the prescribed yoga regimen is designed to be very low level and within each person's capacity. Moreover, the potential bruising and muscle soreness are usually not serious and recovery is rapid. If a patient has a port, and if the patient requests that blood be drawn from her port, then these are the known risks. The risks associated with blood being drawn from vascular access of implanted ports are infection, blockage, and air in the line. Clean technique will be followed. The port will be flushed afterwards. This procedure will be supervised by an experienced RN. There are no other known or anticipated risks of physical, mental, or social injury to those who will participate in the study.

If participants are found to be depressed or anxious, they will be referred to their social worker where they will be seen by appropriately trained and licensed mental health professionals. To protect against a loss of confidentiality, procedures will be taken to maintain confidentiality of participant information and data. All participants who participate in the study will have the opportunity to withdraw at any time.

Recruitment and Informed Consent. Potential participants who meet the inclusion criteria will be recruited from the breast cancer treatment center clinics at the H. Lee Moffitt Cancer Center and Research Institute and the Carol and Frank Morsani Center for Advanced Healthcare at the University of South Florida. The Principal Investigator is a Moffitt member and has established working relationships with health professionals at Moffitt, the primary source of patient recruitment. Health practitioners at Moffitt will be provided with a complete description of the study aims and protocol. Consistent with current HIPAA regulations, patients will be contacted by Moffitt or Morsani members and health practitioners who will identify eligible patients during routine patient care, and they will provide a brief overview of the MBSR study. Multiple recruitment methods will be used. For consistency in recruitment, a script will be developed to describe the study and the recruitment process. Second, flyers and brochures describing the study will be indirectly distributed to patients via advertisements within the cancer center. The distribution of how subjects were contacted and participation rate will be tracked. The Morsani Center staff will utilize the Breastcare Database to identify eligible participants for the study. Patients who express interest in the study and meet the study inclusion criteria will be asked to

sign a participant interest form. Each research assistant will undergo training to ensure that they follow recruitment and enrollment guidelines for the study. The Principal Investigator or the research assistant will explain details of the study. This will occur after conclusion of treatment. For women who express an interest in participating in the study, an orientation session will be scheduled for the period from 2 weeks from end of treatment to 2 years after completion of treatment -- this is where a combined HIPAA and consent document will be obtained. This timeframe coincides with the initial transition from conventional treatment to adaptation to one's daily life and activities. To maximize enrollment and minimize patient dropout, the research assistant and Principal Investigator will emphasize that, irrespective of the random assignment, all participants will have the opportunity to participate in the MBSR(BC) program (e.g. either initially or following a wait period). Moreover, it will be emphasized that the timing of the intervention has been selected to assist in the critical transition period when formal medical care and support has ended. All critical elements of the study will reviewed with the patient, including the 6-week schedule of the MBSR(BC) program, 3 time points for blood draws to be taken, 2 time points for saliva collection and the questionnaires to be completed. Completion of the questionnaires will take place following the group orientation session.

Procedures for Minimizing and Protecting against Potential Risks. Safeguards with regard to the participants' experience of uncomfortable feelings during the data collection have been considered. First, participation is totally voluntary and does not affect treatment. The place for discussion of the study will be a comfortable setting in the clinic environment. The research assistant will arrange the time and place for recruitment; the Principal Investigator is experienced in enrolling patients into clinical studies. A co-investigator and the interventionist are trained clinical psychologists experienced in clinical trials. If participants are found to be depressed, they will be referred to their social worker where they will be seen by appropriately trained and licensed mental health professionals.

To protect confidentiality, each participant's data will be protected with the utmost care. Data records for each participant will be identified by a unique study code number that does not contain personal identifying information. Names, code numbers and telephone numbers will be kept in locked secure files, separate from the study data. Likewise all physical study data will be kept in locked storage and all electronic study data will be password protected with access restricted to approved personnel. Because this is a prospective study, anonymity is not possible. Confidentiality is possible and will be maintained. Confidentiality will be further maintained by reporting only group data in study publications and presentations.

With regards to other potential risks, several procedures are designed to protect against or minimize risk of injury or soreness related to the yoga training. These include providing participants with information on to how to avoid these risks as part of the intervention materials and having the interventionist review potential risks and their avoidance with each participant during the course of study participation. Also, we will protect against or minimize these risks, by instituting a Data Safety Monitoring Plan (see below).

Risks Versus Potential Benefits and Importance of the Knowledge to be Gained. Participants may experience improvements in their emotional distress, fatigue, perceived health status and immune and stress hormone levels. The risks associated with participation in this study are deemed to be low. There is a small risk associated with the blood collection, and a risk of loss of confidentiality is possible. There are no other known or anticipated risks of physical, mental, or social injury to those who will participate in the study. If participants are found to be depressed, or anxious, they will be referred to their social worker where they will be seen by appropriately trained and licensed mental health professionals. The findings of this study will provide researchers and clinicians with knowledge regarding the potential effectiveness of MBSR(BC) in breast cancer, immune recovery and symptom management. Also this intervention may provide direction for future research in the mechanisms of stress reducing interventions and their potential impact on treatment and education of breast cancer survivors.

Data and Safety Monitoring Plan. In order to insure the safety of participants and the integrity of the study, a data and safety monitoring plan will be put into effect. All investigators of the proposed study will meet federal guidelines and complete the requirements for training with completion of the training module at http://phrp.nihtraining.com. All policies for the IRB from Moffitt Cancer Center and Research Institute and the

University of South Florida will be adhered to. As part of the data and safety monitoring plan, all adverse events will be reported at Moffitt through the Cancer Center's clinical trials management system, Oncore, per established policy. This policy includes specific timelines for reporting events that are stipulated by the University of South Florida's Institutional Review Board. In addition to the University IRB the Moffitt Cancer Center's Protocol Monitoring Committee reviews all adverse events for the investigator-initiated trials as they occur. The Principal Investigator will be responsible for completing all required summary reports and reporting any adverse events that are documented on the safety/adverse events form or are reported by the study interventionist. Adverse events will also be reported immediately to the participant's oncologist in the unlikely event that any medical intervention might be necessary.

Prior to initiation of the study, the proposed procedures will be reviewed for protection against risks by the University's IRB. In addition, the Moffitt Cancer Center's Scientific Review Committee will review the study procedures to ensure their scientific merit, safety, legality, and technical feasibility per established policy. These committees are empowered to suspend or close studies with major deficiencies and provide direction to investigators in the development of corrective action plans to rectify and meet identified deficiencies.

As part of the Protocol Monitoring Committee function, accrual is monitored for clinical trials on a semi-annual basis at which time accrual figures are reviewed. The Moffitt Cancer Center employs an internal audit program to address retention of participants, adherence to protocol, and data completeness. This audit program is reviewed and governed by the Protocol Monitoring Committee. All active trials not audited or monitored regularly by an external sponsor undergo a minimum of 1 internal audit annually. A specific function of the Protocol Monitoring Committee is to review and monitor gender and minority accrual for each study. If after 6 months we fail to enroll at least 50 subjects, we will initiate recruitment at additional sites at Tampa General Hospital and/or University Community Hospital.

INCLUSION OF WOMEN AND MINORITIES

All study participants will be women treated at the H. Lee Moffitt Cancer Center which directly serves the Hillsborough County and Central Florida area yet also includes patients from throughout the state and the southeastern United States. Our primary catchment area is defined as the 7 counties in closest proximity to the Center (Hernando, Hillsborough, Manatee, Pasco, Pinellas, Polk and Sarasota counties). These counties account for 70.46% of all patients seen at the Center. This data received from FCDS were based on facility admissions (inpatient and outpatient at hospitals and free-standing therapy centers). Male and female patients less than 21 years are excluded because they comprise less than 1 percent of all breast cancer patients.

Table 9a, 9b and 9c below reflect the data related to race (ethnicity) of patients having breast cancer during 2004, 2005, and 2006 at Moffitt Cancer Center. Since 76-85% were White and 7-10% are of unknown race, minority representation is low. To increase minority participation, we propose a number of steps. First, our expanded inclusion criterion, which includes mastectomy and chemotherapy patients, should increase our pool of potential minority patients. Our experience and data indicates that minorities present with a more advanced illness.[219] Second, special effort will be taken to ensure that all minorities are approached to participate by a minority co-investigator with experience on our current research team and recruitment efforts at Moffitt South (where more minority patients are treated) will be increased. Dr. Versie Johnson-Mallard, who is experienced in minority recruitment and retention in our pilot studies, will be added as a co-investigator. Third, accrual of patients by race/ethnicity will be closely monitored, and if we are falling short of our target goal of $\geq$20% minorities, we will expand enrollment to an additional site at Tampa General Hospital and/or University Community Hospital in Tampa. Our recruitment of minorities has been very successful at this point in time, due to efforts of the PI in pilot studies and Dr. Versie Johnson-Mallard. Our current R-21 pilot study has 24% minorities. Moffitt South at Tampa General Hospital and University Community Hospital have a higher representation of minorities than Moffitt, due in part to serving the indigent and underinsured. Moffitt is committed to the inclusion of all patients and special efforts for the institute have been implemented, see Moffitt Efforts below. Finally, if these efforts do not prove to be effective, we will cap accrual of Caucasians at 80% of the total sample targeted and only recruit minorities thereafter.

Table 9a. 2004 Breast Cancer Patients by Race (Moffitt)

Race	Total	Percentage
White, not of Hispanic origin	616	79
Black, not of Hispanic origin	36	5
Hispanic	38	5
Asian	14	2
Unknown/other	75	9
Total	**779**	**100**

Table 9b. 2005 Breast Cancer Patients by Race (Moffitt)

Race	Total	Percentage
White, not of Hispanic origin	516	76
Black, not of Hispanic origin	41	6
Hispanic	46	7
Asian	8	1
Unknown/other	71	10
Total	**682**	**100**

Table 9c. 2006 Breast Cancer Patients by Race (Moffitt)

Race	Total	Percentage
White, not of Hispanic origin	703	85
Black, not of Hispanic origin	57	7
Hispanic	3	<1
Asian	9	1
Unknown/other	54	7
Total	**826**	**100**

Moffitt Efforts: Moffitt Cancer Center is committed to providing all patients with outstanding cancer care regardless of race, gender, ethnicity, physical and mental ability, sexual orientation, age, economic class, religion, education or family/marital status. The newly established Office of Institutional Diversity & Research (OIDR) directs and monitors all Moffitt programs to advance the organization's commitment to diversity and inclusion and supports Moffitt's efforts to recruit and retain the most talented and productive employees and faculty of diverse backgrounds, and facilitates diverse patient access and research participation. It also encourages increased health disparities research, fosters mutually beneficial community relationships, facilitates sustained commitment to and accountability for leveraging diversity, and creates an atmosphere of respect and inclusion through education in diversity management and cultural competence.

Targeted/Planned Enrollment Table

Targeted/Planned Enrollment Table

This report format should NOT be used for data collection from study participants.

Study Title: MBSR Symptom Cluster Trial for Breast Cancer Survivors

Total Planned Enrollment: 300

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	30	0	30
Not Hispanic or Latino	270	0	270
Ethnic Category: Total of All Subjects *	300	0	300
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	1	0	1
Black or African American	30	0	30
White	268	0	268
Racial Categories: Total of All Subjects *	300	0	300

* The “Ethnic Category: Total of All Subjects” must be equal to the “Racial Categories: Total of All Subjects.”

INCLUSION OF CHILDREN

This study will be conducted in the State of Florida where the age of a consenting adult is established as 18 years of age; however, since no patients in the past 3 years have been diagnosed with breast cancer under the age of 24 years, only patients 21 years and older will be recruited into the study.

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