ACUPRESSURE FOR PERSISTENT CANCER RELATED FATIGUE

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STUDY SCHEMA

5,000 BC Survivors in Michigan Tumor Registry sent letter and study brochure over 3 ½ years

Interested women contact study team

500 Screening Visits

375 BC Survivors found eligible and agree to participate

Randomization and then Baseline Visits

125 Relaxation Acupressure (RA)

25 Drop-outs

6 wks on study performing RA

1 wks pre-treatment observation

4 wks on study no acupressure

100 Women Complete RA Arm

125 Stimulating Acupressure (SA)

25 Drop-outs

6 wks on study performing SA

1 wks pre-treatment observation

4 wks on study no acupressure

100 Women Complete SA Arm

125 Standard of Care (SC)

25 Drop-outs

6 wks on study performing SC

1 wks pre-treatment observation

4 wks on study no acupressure

100 Women Complete SC Arm

Once weekly follow-ups for all 3 arms
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1.0 OBJECTIVES

1.1 Primary Aim
To examine the effect of 6-weeks of RA compared to a regime of SA or standard of care on fatigue as assessed by:

A. weekly self-report using the Brief Fatigue Inventory (BFI), our primary outcome
B. objective daytime physical activity on a wrist worn actigraph using average counts/minute.
C. fatigue patterns assessed 4 times daily using a visual analogue scale recorded on actigraph
D. examine the relationships between improvements in fatigue and improvements in quality of life for SA and RA, as assessed by Long Term Quality of Life Instrument (LTQL).

Hypothesis: BC survivors practicing RA will experience significantly reduced fatigue as measured by: 1. lower BFI, 2. more physical activity and 3. lower daily Actiwatch-S fatigue rating, as compared to women in the SA or standard of care arm. Also, as fatigue decreases quality of life will improve.

1.2 Secondary Aims
2. To date, there are no methodologically strong studies investigating sleep quality in BC survivors. As such we propose to examine the effect of 6-weeks of RA compared to a regime of SA or standard of care on sleep quality as assessed by:

A. monthly self-report using the Pittsburgh Sleep Quality Index (PSQI), our primary outcome.
B. daily sleep/wake diaries and nighttime actigraphy
C. examine the relationships between improvements in sleep quality and improvements in quality of life for SA and RA, as assessed by LTQL.

Hypothesis: Participative and objective sleep quality will improve more following RA compared to SA and SC as indicated by: 1. lower post-treatment PSQI scores, 2 greater sleep efficiency (total sleep time/time in bed*100) and total sleep time by sleep diary and actigraphy at post-treatment. Improvements in sleep quality will be related to improvements in quality of life.

3. Important kinetic parameters required for implementation of a treatment in a clinical setting include the time to onset of a clinically meaningful effect as well as the duration of effect following cessation of the intervention. These factors are currently unknown for acupressure. We propose to compare the time to onset for effects of RA and SA on fatigue and sleep quality during the 6-week treatment period. We will also compare the duration of effect of RA and SA during the 4-week washout period

Hypothesis: It will take 2 to 3 weeks to observe a significant effect of RA on fatigue and sleep, whereas SA may be longer. The effects of RA but not SA on fatigue and sleep will persist at a clinically significant level for at least 4 weeks after stopping treatments.
2.0 BACKGROUND AND SIGNIFICANCE

Once women with BC complete therapy, there is often a period of adjustment to the lack of medical monitoring. Most women complete therapy within one year, and then renew their life without regular medical support. During this time of survival there is the relief of the end of therapy, and also the concern over self-monitoring of symptoms. One of the most common symptoms that persist into post-therapy survivorship is fatigue.

1. Fatigue in Breast Cancer Survivors and Its Negative Sequela

PCRF is among the most common symptoms experienced by BC survivors, yet it remains under-recognized and under-treated. The prevalence of BC-related fatigue after treatment, ranges from 17 to 99%, with rates >60% in most studies. Cancer-related fatigue is associated with reduced physical and psychosocial functioning. Rates of significant PCRF in BC survivors range from 30% to 82% within the first 5 years of diagnosis. BC survivors between 4 months to 10 years after BC diagnosis demonstrate a significantly higher prevalence of fatigue compared to women of similar age who have never experienced BC. Based on BC patient reports, PCRF is more severe, more long-lasting and more disabling than fatigue caused by lack of sleep or heavy exercise. Namely, PCRF is associated with decreased quality of life, decreased sleep quality, and impaired cognition. Further, PCRF is reported by BC patients to be the most distressing and persistent symptom after treatment, which leads to decreased physical functioning and lower quality of life. Beyond quality of life, participative reports of low levels of fatigue at diagnosis in BC survivors predict longer recurrence-free (risk ratio [RR] 1.32, 95% confidence interval [CI] 1.13-1.54) and overall survival (RR 1.23, 95%CI 1.05-1.44) even after adjusting for key clinical and socio-demographic confounders.

Despite the significant negative impact on quality of life and daily functioning BC survivors have few treatment options for PCRF once clear causes for fatigue are identified. Current treatment options often require the availability of a trained practitioner and their associated costs, e.g., psychologist/acupuncturist, or significant motivation on the part of the patient, e.g., regular physical exercise, or have unacceptable side-effects, e.g., corticosteroids. Also, not all treatments are covered by insurance creating further barriers to utilizing current treatments. In contrast, self-administered acupuncture is a very low toxicity and inexpensive treatment that requires minimal instruction to learn. With minimal training (both initially and as part of continuing medical education) acupuncture can be taught by standard clinic staff, e.g., nurse or physician’s assistant. Acupuncture also requires little effort and time on the part of the patient to successfully complete. Self-administered acupuncture can also be carried out in almost any setting including work, home or school, making it convenient and flexible to women’s changing situations.

2. Sleep Disturbances in BC Survivors and its Association with Fatigue: Sleep Disturbances as a Possible Mechanism for Persistent Cancer-Related Fatigue

The causes of PCRF are not yet well understood. One theory is that fatigue is secondary to disturbed sleep patterns, with daytime sleepiness and participative sleep disturbances (defined as reduced sleep quality potentially caused by increased sleep latency, reduced total sleep time and or a participative sensation of non-restorative sleep) being reported to influence perceptions of fatigue. An epidemiological review of insomnia in cancer patients concluded that the presence of an insomnia disorder was a key risk factor that increased the probability of developing chronic and severe fatigue. Cancer patients who report fatigue are 2-½ times more likely to experience insomnia, and several studies have reported significant correlation between fatigue severity and self-reported sleep difficulties in BC survivors, although in one study in BC survivors fatigue had no interaction with sleep duration.
The link between sleep quality and insomnia are particularly important since between 30% to 50% of cancer patients report problems with sleep quality years after the completion of treatment. Moreover, insomnia is particularly frequent in BC patients compared to other cancers, and a survey in BC survivors found that 51% of women were experiencing sleep disruptions and 19% met diagnostic criteria for insomnia. These levels of sleep disruption and insomnia are more than twice the incidence observed in the general public. BC survivors who receive cognitive behavioral therapy for insomnia have improvements not only in sleep parameters but also improved fatigue and quality of life. Although effective, one primary disadvantage of cognitive behavioral therapy for insomnia is that it requires significant expertise and resources to deliver the intervention. Interventions targeted at decreasing fatigue can also improve sleep. However, currently it is unknown to what extent sleep disturbances contribute to fatigue in BC survivors as most studies in this area are correlative in design. Nonetheless, in general, sleep disturbances are positively correlated with fatigue; more severe in fatigued compared to nonfatigued patients; and a significant predictor of fatigue. Similar to fatigue in BC survivors, sleep disruptions and insomnia in particular are associated with significant burdens for the individual, their family and the health care system leading to reduced quality of life, negatively impacting daily activities and increased health care use.

Few studies have examined the effect of an intervention on both fatigue and sleep in BC survivors, despite the strong correlation between these two symptoms. One strength of this proposal is that we will be examining the effect of our intervention on fatigue and sleep individually as well as examining if sleep moderates the relationship between RA and PCRF improvements.

3. Rationale and Definition for Acupressure

TCM has been practiced in China for over 5,000 years. Until recently, TCM was the primary form of healthcare in China and even now plays a prominent role with TCM hospitals and clinics as well as through the integration of TCM practitioners and units at conventional hospitals.

Acupressure is a TCM technique based on a philosophy similar to that of acupuncture (the placement and stimulation of very fine needles into acupoints). Acupressure involves placing physical pressure by fingers, thumb, elbow, or with the aid of various devices such as pencil erasers on different acupoints points. One advantage of acupressure is the ability to self-administer the treatment. Patients are able to practice acupressure therapy virtually anywhere and anytime. It is safer than acupuncture and less invasive. Acupressure produces fewer side-effects than acupuncture and may be a low-cost alternative as many acupuncture treatments are not covered by insurance plans and thus may be expensive for many patients. Moreover, once a person learns how to administer acupressure he or she requires little or no assistance to complete his or her treatment. In contrast, a trained TCM specialist must administer acupuncture treatments. Individuals trained in acupuncture are often not readily available especially in areas with sparse or poorer populations. Consequently, acupressure becomes the ideal choice in underserved communities where cost of treatments is a factor and access to practitioners of acupuncture is restricted. Acupressure is also a viable alternative to acupuncture in situations where patients (1) cannot come to the clinic to receive an acupuncture treatment, (2) when a more frequent intervention is needed (e.g., once per day) or (3) where needle phobia or safety concerns are an issue.

There are 2 main acupressure approaches: (1) The individualized method where an acupressure practitioner selects acupoints based on the patients’ clinical state and response to acupressure treatment; and (2) The standardized acupressure treatment, which refers to the use of a set of fixed acupoints throughout the treatment course. We will be using the
standardized method as we will be using a Western diagnosis of persistent fatigue and not a TCM diagnosis.

4. Acupuncture and Acupressure for Fatigue

Two previous small studies have indicated that acupuncture/acupressure may be effective in reducing PCRF. Vickers et al. (2004) assessed improvement in post-chemotherapy fatigue following acupuncture in a phase II pilot study in non-depressed, cancer patients. Baseline fatigue scores were high, with approximately half of the sample scoring in the “severe” range using the Brief Fatigue Inventory (BFI). The mean improvement following 8 weeks of acupuncture administered once per week was 31.1% with those younger than 65 years having a greater improvement of 38%. Molassiotis and colleagues conducted a 2 week pilot study to assess the effect of acupuncture, acupressure and sham acupressure on fatigue in a diverse cancer population at least 1 month out from treatment. At the completion of the intervention, there was a 36% improvement in the acupuncture group, 19% in the acupressure group and 0.6% in the sham acupressure group. These effects were sustained 2 weeks after completion of the treatments (22% acupuncture, 15% acupressure, 7% sham acupressure). The study by Molassiotis and colleagues has been the only study to examine acupressure for cancer fatigue among post-treatment patients. Our group examined the effect of self-administered acupressure supposedly having opposing effects on alertness; 1 was relaxing and the other was stimulatory. We also examined 2 different intensity of stimulatory acupressure (low versus high intensity) to examine the effects of duration and frequency on persistent fatigue.

There have also been 4 clinical trials conducted where both sleep quality and fatigue were evaluated following acupressure. Tsay and Chen (2003) assessed the effectiveness of acupressure on sleep quality of end-stage renal disease patients. In a randomized controlled trial, patients were randomly assigned into an acupressure group, a sham acupressure group and a control group. The main outcomes measured were the Pittsburgh Sleep Quality Index (PSQI). The results indicated that PSQI scores of the acupressure group had a significantly greater improvement than the control group. Furthermore, subscales of PSQI were further analyzed and results demonstrated significant differences between the acupressure group and the control group in participative sleep quality, sleep duration and habitual sleep efficiency. However, no differences were observed between the acupressure and sham acupressure groups. Following these findings, Tsay and colleagues (2004) tested the effectiveness of acupressure and acupuncture versus sham acupuncture on fatigue, sleep quality and depression in patients who were receiving routine hemodialysis. The results indicated that patients in the acupressure and acupuncture groups had significantly lower levels of fatigue (p=0.001), better sleep quality and less depressed moods compared with patients in the control group. Harris et al (2005) conducted a single-blind randomized cross-over study on public health graduate students. He compared two types of self-administered acupressure having opposing effects on alertness; 1 was relaxing and the other was stimulatory. Alertness was assessed in the morning and afternoon each of 3 days (study length) using the Stanford
Sleepiness Scale (SSS). The stimulatory acupuncture treatment was superior to the relaxing treatment \( p = 0.019 \). (38) In 85 chronic fatigue patients using acupressure points on the head for 3 courses resulted in 91.8% of the participants experiencing a significant reduction in fatigue. (39)

5. Acupressure, Acupuncture and Sleep Disruption

Over 20 clinical trials have been conducted that examined the effect of acupressure, acupuncture and auricular acupuncture (acupoints found exclusively in the ears) for treating primary and secondary insomnia. (43-48) Despite the heterogeneity of study design, acupuncture techniques, acupoints selection, outcomes and population all of the studies found a positive effect of acupuncture or acupressure treatment on insomnia or sleep disturbances compared to placebo or standard of care. However, along with being heterogeneous, the studies were consistently found to be of poor methodological quality using both the Cochrane and Jahad scales. (44,48) Studies consistently had unreported or improper blinding, randomization, allocation and improper sham procedures. (44) Consequently, methodologically strong randomized controlled studies with large sample sizes and longer follow-up are needed to rigorously investigate the efficacy and safety of acupuncture or acupressure treatment for the treatment of insomnia.

While many different populations with sleep disturbances were investigated none of the clinical trials examined sleep disturbances in cancer patients. One recent open label study did include 11 patients (6 with BC) with cancer who were experiencing insomnia for at least 3 months. (49) While the study found that 67% (4 of 6) of the patients had some level of improved sleep. (49) Methodological weaknesses including lack of blinding, randomization and small sample size greatly limit the interpretation of the results. One strength of this research proposal is a methodologically strong study design for investigating sleep disturbances and also examining these disturbances in an unstudied population, BC survivors. We also propose the novel technique of using self-administered acupressure. Only 3 of the clinical trials examining sleep disturbances used acupressure instead of acupuncture. Two of these studies were conducted in patients with end stage renal disease and 1 in institutionalized residents. (42,50,51) The studies in end stage renal disease are summarized in the acupressure for fatigue section. The study by Chen and colleagues compared acupressure to sham control determining that sleep latency and a total sleep duration score were significantly better than sham treatment \( p<0.01; p<0.0001 \), respectively, but found no difference in sleep quality between groups. (51)

Maladaptive Sickness Behavior Could be a Conceptual Model for PCRF

There are an estimated 2 million women in North America living as breast cancer survivors and PCRF disrupts the lives of an estimated 30 to 80 percent of these women. PCRF is associated with decreased quality of life (91-93), decreased sleep quality (91-92), depression (94) and impaired cognition (95). The mechanism of cancer related fatigue is complex and not well understood making it difficult to identify therapeutic targets and monitor treatments. Some researchers have proposed that maladaptive sickness behavior explains persistent cancer fatigue (96). Sickness behavior occurs when a person is exposed to a bacteria or virus, but also appears to be triggered by both cancer and cancer treatments (97). These various perturbations trigger the immune system to produce pro-inflammatory cytokines such as interleukin 1 and 6 (IL-1 & IL-6), and tumor necrosis factor (TNF) (98). These peripherally released cytokines act on the brain via a fast transmission pathway through the vagus nerves, and a slow transmission pathway involving cytokines originating from the choroid plexus and circumventricular organs causing neuroinflammation (99). Also, peripheral cytokines may enter the brain directly (100) and cytokines produced in the brain can travel to the periphery (100). As a result of the effect of cytokines on both the brain and periphery, people experience symptoms collectively described as “sickness behavior”, which includes fatigue, anorexia, sleep disorders,
depressed mood, anxiety, and cognitive dysfunction (96). Maladaptive sickness behavior is
when these behavioral and physiological affects become chronic as opposed to acute leading to
long term issues such as chronic fatigue (98).

**Fatigued BC Survivors Appear to Have More Peripheral Inflammation**

In some BC survivors pro-inflammatory cytokines remain elevated for years after the end
de of cancer treatment even when the person is apparently cancer free (111-114). In particular,
BC survivors with persistent fatigue appear to have significantly higher levels of soluble
inflammatory markers and cellular immune responses such as various T-lymphocytes, IL-6 and
soluble TNF receptors compared to non-fatigued BC survivors (111-113). One study, however,
found contradictory results with no significant correlation between fatigue in BC survivors and
circulating levels of IL-1β.(11) Of note, the women in this study had abnormally high levels of
IL-1β (mean = 1152 pg/ml, range = 9-3,952 pg/ml), above what is observed in other cancers
and healthy individuals (115). These inflammatory immune changes remain after controlling for
age, BMI, depressed mood, cognitive problems, length of time since diagnosis, and treatment
type (111, 112).

**Neural Mechanisms of Fatigue Are Not Well Studied**

The neural mechanisms underlying feelings of fatigue are poorly understood. This lack
of understanding is further deepened when attempting to examine additional symptoms such as
sleep disturbances and pain that often cluster with fatigue. Only a few studies have used
functional neuroimaging techniques to explore these mechanisms and these few studies
focused primarily on people with multiple sclerosis (MS) or chronic fatigue syndrome (CFS).111
This research project focuses on three neurotransmitter systems. The primary excitatory
neurotransmitter (glutamate - Glu) and the primary inhibitory neurotransmitter (gamma-amino
butyric acid – GABA), which were chosen because of their known importance in neural
regulation. It is well known that drugs that block the activity of Glu or enhance or mimic the
activity of GABA are effective analgesics as well impacting fatigue and sleep. We and others
have already used proton spectroscopy to show that Glu levels are elevated in pain and
fatigue processing regions of the brain in several chronic pain states where fatigue and sleep
disruptions are also common co-symptoms.112 In addition, we will also measure the role of
myoinositol (m-inos). We chose m-inos as it is an important marker for astroglial cells, which
are key in maintaining appropriate levels of Glu in the synaptic space.113 Astroglial cells also
appear to be particularly vulnerable to inflammatory cytokines in the CNS.114

Glu as the most common excitatory neurotransmitter in the brain is central to
information uptake and processing.115 Pro-inflammatory cytokines TNF-alpha, interleukin-1beta
(IL-1β) and IL-6 are known to impair astroglial Glu uptake and metabolic supply for the neurons
thereby enhancing Glu transmission.114 By affecting Glu transmission symptoms such as pain,
sleep disruptions, depression, anxiety and fatigue can arise.116

Another neural marker that has been investigated in diseases such as eosinophilia
myalgia syndrome,117 depression113 and cognitive decline,118, 119 which are associated with
fatigue, is myoinositol (m-inos). Brain levels of m-inos, which is decreased in these populations,
is a polyol that serves as a precursor of phosphatidylinositol, the major inositol-containing
phospholipid, and of phosphatidylinositol 4,5-bisphosphate, a key molecule in cellular signal
transduction and120, 121 is considered a marker for astroglial cells.113 Decreased levels of brain
m-inos is associated with severity of adult depression and increases with antidepressant
treatment.113 Also decreased levels are associated with increased pain and fatigue (see
“Preliminary Data).

Of growing interest in pain, depression and fatigue is the main inhibitory central nervous
system (CNS) neurotransmitter GABA. The importance of GABA in pain has similarly been
recognized for some time.112 Similarly, In other disorders such as schizophrenia, anxiety,
depression, epilepsy, and neurodegenerative diseases, an imbalance of Glu:GABA is an accepted theory with strong supportive data explaining the CNS involvement of these disorders. However, little research has examined the role of GABA in effecting clusters of symptoms such as fatigue, sleep disorders and pain in cancer patients.

Perhaps the strongest and most impressive data suggesting a pivotal role for GABA deficiency in pain states with co-occurring sleep disruption and fatigue comes from the recent trials of gamma-hydroxybutyrate (GHB) in FM. Two Phase III trials showed that this compound, which is known to bind only to GHB and GABA-B receptors, is highly effective at improving pain in this condition, with an effect size larger than any of the other drugs studied in this condition. More impressively, these trials all showed similarly impressive effects (p<.001 for all analyses) for improvements in sleep and fatigue. This is the only drug for chronic pain that has shown simultaneous salutary effects for pain, fatigue, and sleep, suggesting it is acting on a basic pathological mechanism in this central pain state.

Resting State Connectivity Fatigue, Sleep and Pain

Resting functional connectivity MRI is a recent adaptation of functional MRI (fMRI) that examines intrinsic connectivity - defined as ongoing neural and metabolic activity that occurs in the resting basal state. Scientific interest in the evaluation of intrinsic brain connectivity has been increasing exponentially in the past decade. Intrinsic brain connectivity may be important for maintenance of synaptic connectivity such as the magnitude and extent of neuronal transmission between brain regions. Intrinsic connectivity involves information transfer between disparate brain regions comprising known primary sensory, executive, and associative networks. FMRI investigations of intrinsic connectivity networks (ICN), brain regions showing correlated activity when the participant is at rest, are conducted with participants simply resting in the scanner. These brain networks are thought to be connected synaptically since the fMRI signal between brain areas in these networks is correlated over time. Specifically, ICN cross-correlation follows known structural monosynaptic and polysynaptic pathways, likely reflecting meaningful neurophysiological activity.

While several ICNs have been identified in healthy subjects and in chronic pain states such as fibromyalgia (FM). However, there is currently no data examining ICNs in cancer patients with fatigue, pain or sleep disruption. This proposal will begin to examine ICNs in these populations comparing and contrasting them to reported research in FM.

3.0 PRELIMINARY DATA

1. Acupressure Modulates Sleepiness in the Classroom

A major challenge to previous acupressure studies was the not being able to detect a specific effect of “true” acupressure compared to “sham acupressure”. Often both the true and sham treatments would have a similar magnitude and direction of effect on the outcome of interest. To address this problem we designed a study where the two acupressure treatments were hypothesized according to TCM theory to have opposing effects, i.e., relaxing compared to invigorating. Thus, we hypothesized that the two groups would have diverging instead of converging effects on the outcomes of interest. We conducted a single-blind randomized crossover study to determine whether self-administered acupressure has a significant effect on sleepiness in a population of healthy student participants in a prolonged lecture situation.(38) Our study utilized 2 active acupressure treatments with hypothesized opposing effects, a relaxation treatment and a stimulation treatment, in a crossover design in which all participants received both treatments on different days. This design was chosen as it avoids the problem of potentially active sham acupressure treatments and maximizes the likelihood of observing an effect of acupressure on sleepiness, since the 2 treatments presumably have opposite effects.
The study population consisted of thirty-nine participants enrolled at the University of Michigan School of Public Health course on clinical research design and statistical analysis.

Methods: Acupressure regimens promoting mental stimulation or relaxation were utilized in a crossover design with participants randomized to either Sequence I (day 1 stimulation – day 2 relaxation – day 3 relaxation) or Sequence II (day 1 relaxation – day 2 stimulation – day 3 stimulation). Each regimen was taught to all study participants by 2 members of the class who were previously trained in acupressure. Each regimen consisted of a 15-minute self-administered session of acupressure at either 5 stimulatory or 5 relaxation points (3 minutes each). The stimulatory point formula consisted of Si Shen Chong and bilateral – Large Intestine 4 (LI 4), Stomach 36 (St 36), Kidney 1 (K 1), and Urinary Bladder 10 (UB 10). These points were chosen based on their ability to reduce sleepiness in TCM theory.(52) The relaxation point formula was selected based on treatment of insomnia in TCM theory and contained Yin Tang and bilateral Anmian, Heart 7 (Ht 7), Liver 3 (Liv 3), Spleen 6 (Sp 6).(52) All points were stimulated using either the thumb or forefingers to massage in both clockwise and counterclockwise directions. The style of acupressure administered in this investigation was highly simplified as to allow for the training of participants and to allow for the limited study time period. The primary outcome was the difference between afternoon and morning scores on the Stanford Sleepiness Scale (SSS) (afternoon score – morning score).(53) The SSS was administered 2 hours prior to and 3 hours after each acupressure regimen. The 3 hour endpoint was chosen because this was the end of the class period where students were most likely to be fatigued.

Data were analyzed using the PROC MIXED procedure of SAS (version 8.2). This model incorporated the fixed effects of sequence (I or II), period (day 1, 2, or 3), treatment (relaxation or stimulation), and other covariates, as well as the random effects of participant within sequence.

Results: There were no differences in gender (I:9 male vs. II:12 male; χ²=0.199; p=0.656) or race (I:14 white vs. II:12 white; χ²=1.857; p=0.173) between the 2 sequences. A mixed model regression analysis using the change in SSS as the dependent variable was performed and the following variables were retained from the model: treatment (p=0.019), day (p=0.004), AM caffeine (p=0.083), hours of overnight sleep (p=0.042), and AM upsetting event (p=0.071). No significant carry over effects between days or treatments were detected. The least squares means for the stimulation and relaxation acupressure treatments were 0.570 and 1.127, respectively, with a significant difference in change in alertness scores between the 2 acupressure treatments. The mean difference between morning and afternoon SSS scores are presented by treatment, sequence, and day in Figure 1 above. The relaxation acupressure treatments consistently produced higher values, corresponding to more sleepiness than the stimulation acupressure treatments regardless of sequence or day. These data indicate that our 2 acupressure formulas have differential effects on alertness and/or sleepiness in healthy normal participants. In support of this interpretation, more participants in the relaxation acupressure group took naps (p=0.048) during day 1.

2. Acupressure Specifically Reduces Persistent Fatigue in Cancer Survivors
Since our preliminary study demonstrated specific effects of acupressure on sleepiness in healthy controls and differential effects of opposing types of acupressure (relaxing versus stimulatory), we next performed a pilot randomized single-blinded controlled trial of acupressure in cancer survivors experiencing moderate to severe PCRF, as defined by ≥4 on the BFI, with the similar opposing acupressure treatments (relaxing and stimulatory). We chose not to have a no-treatment control group for this pilot study. This was a feasibility study where we were investigating effect size, dose or intensity of acupressure on fatigue and the impact of the two opposing acupressure treatments in a diseased population. We anticipated adding a no-treatment control group in the design of our next study if there was a significant and clinically meaningful effect of acupressure on fatigue.

Methods: Cancer survivors were eligible to participate if they had completed all cancer related therapies with the exception of hormone therapy at least 12 weeks prior to enrolling in the study and had no evidence of active disease. Potential participants were excluded if they had other causes of fatigue such as anemia, malnutrition, or chronic fatigue syndrome. Participants were randomized to one of three treatment groups: 1. relaxation acupressure (RA; n=14), 2. high intensity stimulatory acupressure (HIS; n=15), and 3. low intensity stimulatory acupressure (LIS; n=14). Participants performed acupressure for 12 weeks between 3 to 14 times per week depending on group. The stimulatory point formula consisted of unilaterally Si Shen Chong, Conception Vessel 6 (CV 6); and bilaterally Large Intestine 4 (LI 4), Stomach 36 (ST 36), Spleen 6 (SP 6) and Kidney 3 (KI 3). These points were chosen based on their ability to reduce fatigue in TCM theory. The relaxation point formula was selected based on treatment of insomnia in TCM theory and contained Yin Tang and bilateral Anmian, Heart 7 (Ht 7), Liver 3 (Liv 3), Spleen 6 (Sp 6). All points were stimulated for one minute using either the thumb or forefingers to massage in both clockwise and counterclockwise directions. The style of acupressure administered in this investigation was highly simplified as to allow for the training of participants and to allow for the limited study time period. Fatigue was measured with the BFI on a weekly basis. The effect of group on change in BFI was assessed with ANOVA and linear regression. Correlations were also made between compliance and change in BFI.

Results: There were no significant differences in any baseline study outcome across groups (all p>0.10). The change in BFI was significantly different across treatment groups, with greater reductions in the relaxation acupressure group (See Figures 2 and 3; mean±SD reduction in BFI: RA 4.0±1.5, HIS 2.2±1.6, LIS 2.7±2.2; p=0.027). In a linear regression model with change in BFI as the dependent variable, the group difference remained significant after adjusting for age, cancer type, cancer stage, and cancer treatments (p=0.013). Across all groups, greater time spent performing acupressure was associated with greater reductions in fatigue (r=-0.39; p=0.037). Participants were blinded to treatment groups (p=0.62).

Self-administered relaxation acupressure engendered greater reductions in fatigue when compared to either high or low intensity stimulatory acupressure. This effect was not modified by relevant clinical or...
demographic variables. Across groups, these reductions in fatigue were on the order of 45% to 70%, which were clinically relevant and could represent significant improvements in quality of life for cancer survivors. Given results from our acupressure trial on sleepiness in the classroom, we hypothesize that the relaxation acupressure treatment may be improving sleep quantity and/or quality. This effect may then lead to a reduction in daytime fatigue, one of proposed hypotheses. Alternatively, the stimulating acupressure treatments could also have improved daytime alertness while having no effect on nighttime sleep. These two theories will be tested in the proposed study by examining actigraphy data captured during periods of wakefulness and sleep. Self-administered acupressure holds significant potential for being a cost-effective low toxicity self-care treatment for PCRF, one of the most troubling symptoms for cancer survivors.

4.0 STUDY DESIGN AND METHODS

4.1 Participant Selection

4.1.1 Study Population

Women, 18 years of age and older, with a diagnosis of breast cancer will be recruited into this study. Eligible patients will meet the following eligibility criteria:

4.1.2 Inclusion Criteria

- Age 18 or older;
- With a diagnosis of breast cancer;
- Have completed all cancer-related treatments (i.e., surgery, chemotherapy, radiotherapy, immunotherapy, etc.) except for hormonal therapy and or herceptin at least one year previously;
- Be apparently cancer-free;
- Able to self-administer treatment at the specified points;
- And have a complaint of persistent, moderate to severe fatigue despite standard treatments [defined as ≥ 4 on the Brief Fatigue Inventory (BFI)].

4.1.3 Exclusion Criteria

- Pregnant, wanting to become pregnant or lactating women;
- Diagnosed with anemia [defined as hemoglobin levels out of reference range] or receiving treatment for anemia;
- Diagnosed with any comorbidities likely to cause significant fatigue (i.e., moderate to severe heart failure, hypothyroidism);
- Currently taking medication for insomnia;
- Have an initiation, a cessation or change of dose (up to three weeks prior to the study’s start) of any chronic medications or dietary supplements or any planned change of chronic medications or dietary supplements during the study;
- Or have received acupuncture or acupressure treatment in the previous 6 months;
- Received a cancer diagnosis other than breast cancer within the past 10 years;
- Diagnosed with fibromyalgia prior to a breast cancer diagnosis;
- Untreated Major Depressive Syndrome;
- Melanoma (non-early stage) within the past 10 years which required treatment greater than surgery;
• Regular 3rd shift, overnight workers.

Women who contact the study team via phone call or email and express interest will be scheduled for a screening visit. Screening visits will occur at the Michigan State University County Extension office located in the county of the women’s residence and to be conducted by a study nurse, or at the MCRU spaces located at the University of Michigan. The final element of eligibility will be a medical history, physical, screening labs, screening questionnaire and examination of concomitant medications conducted at the screening visit.

4.1.5 Method of Participant Randomization, Stratification and Blinding

This is a randomized parallel group clinical trial with three study arms. Our randomization scheme will be created by our study statistician and blocked by Michigan County. This will be a single-blinded study. Participants, investigators and all study staff except the person teaching the acupressure will be blinded. The person teaching the acupressure to participants will know to which group participants are assigned. However, the person teaching the acupressure points will not collect study outcomes from participants. Eligible patients will be randomized into one of these three groups: relaxing acupressure, stimulating acupressure or standard of care in a 1:1:1 ratio for a total of 375 patients with 125 randomized into each acupressure group. Study participants will be stratified at randomization into one of two strata based on the women’s sleep quality at baseline (strata 1 = PSQI score of <8; strata 2 = PSQI score ≥8). A PSQI of 8 or greater in BC survivors indicates poor sleep quality (65) (This will allow for an equal distribution of women with sleep quality issues compared to those with normal sleep quality across the three treatment arms.

4.1.6 Recruitment

The primary recruitment method for this study will be the Michigan Tumor Registry, a database maintained by the Michigan Cancer Surveillance Program within the Michigan Department of Community Health. We will request Michigan Tumor Registry data for women diagnosed with breast cancer in the last 4 years (2006 through 2010) and for 5 counties in Michigan: Wayne, Washtenaw, Ingham, Genesee and Kent. These counties represent significant population centers (Detroit, Lansing, Flint, Ann Arbor and Grand Rapids) and areas of racial and ethnic diversity.

In addition to the Michigan Cancer Surveillance Program, information about the study will be posted on the University of Michigan’s “UM Clinical Studies” website (www.umclinicalstudies.org/Flyers/information about the study will also be made available to breast cancer clinics, support centers, and hospital registries located in Wayne, Washtenaw, Ingham, Genesee, Kent, Oakland and Alpena counties. Medical Directors of these clinics and registries will be notified in advance of the study through introductory emails, letters or presentations from the study staff. We will then work collaboratively with these centers to reach eligible participants.

Finally we will advertise to our target audience (woman breast cancer survivors) through general media outlets (ie. press advertising, press releases).

Upon contacting the Study team to register their interest, either through the Study 1-888 number, via email, or in-person, the study candidate will be asked a short number of questions to confirm their diagnosis/fatigued state and confirm their potential eligibility and interest in the study. Once their interest is confirmed the study coordinator will schedule the screening visit.
Involvement of Healthcare Providers
Prospective Subjects’ healthcare providers will receive a letter from the Michigan Tumor Registry Cancer Surveillance Program Director explaining the study and soliciting their input regarding a particular patient’s suitability for the study.

In addition we plan to contact healthcare providers throughout the Michigan counties of interest and make them aware of the study and ask for their assistance in advertising the study to their patients. Initially we will solicit collaborations from clinics that study investigators have an existing relationship.

Patient Contact
The study team will provide the Cancer Surveillance Program with a list of zip codes for the regions of interest, from which a randomized pool of potential candidates will be identified. The Cancer Surveillance Program will then contact the candidates in 4 batches over the course of the year and identify patients interested in participating in the study whose information will be then passed to the study team.

Registry staff will contact the reporting hospital to confirm the diagnosis and validate vital status and physician of record. They will then write to the physician as a courtesy and to again confirm diagnosis and vital status, and to determine any significant co-morbidities (ie. dementia, recurrent cancer) that may preclude the patient as a suitable study candidate. Finally the registry then contacts the patient in writing up to three times to inform them of the study, and to obtain their authorization to release their information to the study team.

Potentially eligible women identified through the Cancer Surveillance Program or via other means (physician referrals, local hospital registries etc.) will also receive the introductory letter from study team contact information and a study brochure (either in-person or via mail). If no response is received a reminder letter will be sent out to increase potential participation rates. If still no response a third and final reminder letter will be sent.

Women may also contact the study team directly via phone call or email and express interest in participating.

4.1.7 Participant Reimbursement
Participants who complete all study visits (baseline, Week 3, Week 6 and Week 10) will be entered into a drawing for a $99 Visa gift card. Their chance to win the gift card will depend on how many other women complete all study visits.

Participants who consent for the optional brain imaging scan will receive $50.00 per scan (once at Baseline, and at Week 6).

4.2 Study Intervention
The study will utilize individual instruction by acupressure educators to teach study participants about the acupressure intervention. Acupressure educators are local study staff (located in the county were the women are being recruited from the cancer registry) made up of nurses and physician’s assistants who have been trained by the study co-principal investigator Richard Harris, who is a professional acupuncture practitioner. Dr. Harris will meet with the local
acupressure educators for an initiation training session. At this session he will explain the basic
philosophy of TCM and acupressure, demonstrate both sets of study acupressure on himself
and on the educator. He will also give the educators a DVD of a person performing the
acupoints, laminated illustration of acupoints along with a written description of where the points
are located. He will also ask the educators to demonstrate the correct location of the acupoints
on themselves as well as proper pressure and stimulation techniques. Dr. Harris will make a
site visit to observe the acupressure educator performing both sets of acupoints (stimulating and
relaxing) on themselves. He will note how many acupoints are correctly located and make any
needed corrections. He will also ask them to apply the correct amount of pressure and
stimulation on a point on himself. Dr. Harris will have a checklist that interveners must match at
a 95% rate. After the acupressure educator has enrolled two participants Dr. Harris will return
to the site to check for the efficacy of the acupressure educators and then twice yearly
afterwards. These assessments of the acupressure educators are how we will measure their
treatment fidelity. Acupressure educators can request additional clarification and instruction as
needed.

From our previous study (See preliminary data) participants can be taught to perform their
acupoints within 15 minutes. Acupressure educators will meet with each participant separately
and demonstrate the location of each acupoint on themselves and on the participants.
Participants will also be given a DVD of a person performing the acupoints, laminated illustration
of acupoints along with a written description of where the points are located. Participants also
have the acupoints marked on them with adhesive colored dots to reinforce the location of the
acupoints for the first few days. At the end of the session participants are asked to demonstrate
the location of all their acupoints to the educator and appropriate adjustments are made.
Acupressure educators also demonstrate on the participant the appropriate level of pressure to
apply on the acupoints and the correct stimulating motion. Participants are then asked to
stimulate points on the educator until it is determined that they are using the correct pressure
and stimulation. Participants are told and given a handout with the following information for
correctly performing their acupressure:

“Once you have identified the pressure point location, use the pad- not the
tip- of your index finger to apply pressure. Place your index finger on the
selected point and turn it in a clockwise direction. Apply firm pressure to the
point using a light to moderate touch depending on your sensitivity. The
points may feel somewhat tender to the touch, and pressure should be
enough to illicit that sensation. There should be a distinct feeling around or at
the site of pressure. This may be felt as numbness, warmth, tingling, aching
or buzzing sensation. If no sensation is felt, try applying more pressure.
Please note that some points are more sensitive than others, and in fact you
may not feel any sensation at certain points.

Pressure should be applied for 3 minutes per point. Treatments are done
every day, once per day. Pressure points should be done in the order
provided, starting from the head down to the feet. Apply pressure to ONE
point at a time. If a point is located on both sides of the body, apply pressure
to the RIGHT side, followed by the LEFT side prior to proceeding to the
following point.

Do NOT lose contact with the point. If you need to, you may take a break in
between points for a couple of minutes. Please do NOT take a break in the
middle of applying pressure to a point.

Acupressure can be performed sitting, standing or lying down.”
Participants may return at any time to be retrained or ask clarifying questions.

Acupoints were chosen by consensus of 4 acupressure practitioners and based on a previous study design in students with sleep disturbances as well as TCM theory for treating insomnia and fatigue. Practitioners had all been in practice for at least 2 years actively seeing patients. They also had been trained as and received one of more of the following degrees; a Naturopathic Doctorate (ND), a masters in TCM or Oriental Medicine and a license of acupuncture (L.Ac.) or a diploma in acupuncture (Dipl. Ac.). Practitioners were asked to choose a set of relaxing and stimulating acupressure points based on a Western diagnosis of fatigue that could be reasonably reached by participants, i.e., not the middle of the back, and not so many points that it would take an excessive amount of time to complete a treatment.

a. Relaxation Acupressure. In addition to standard of care participants will be asked to apply pressure on each of following points (bilaterally where indicated). There are 5 acupoints with 4 of the acupoints performed on both the left and the right sides of the body giving a total of 9 points to stimulate. Each of the 9 acupoints will be stimulated for 3 minutes per point giving a total treatment time of 27 minutes done once daily. The acupoints are:

- **Yin tang (Unilaterally):** This point is located on the forehead, between the eyebrows.
- **Anmian (Right and Left/bilaterally):** Located on the posterior aspect of the neck.
- **Heart 7 (HT7) (Right and Left/bilaterally):** Located on the palmer surface of the hands on the wrist crease.
- **Spleen 6 (SP6) (Right and Left/bilaterally):** This point is located on the inside of the lower leg.
- **Liver 3 (LIV3) (Right and Left/bilaterally):** This point is located on the foot.

b. Stimulating Acupressure. In addition to standard of care participants will be asked to apply pressure on each of following points (bilaterally where indicated). There are 6 acupoints with 4 of the acupoints performed on both the left and the right sides of the body giving a total of 10 points to stimulate. Each of the 10 acupoints will be stimulated for 3 minutes per point giving a total treatment time of 30 minutes done once daily. The acupoints are:

- **Si Shen Chong (Unilaterally):** Located at the top of the head.
- **Conception Vessel 6 (CV6):** Located two finger widths below the navel on the centerline.
- **Large Intestine 4 (LI4) (Right and Left/bilaterally):** Located on the back of the hand.
- **Stomach 36 (ST36) (Right and Left/bilaterally):** Located on the lower leg below the knee on the outside of the leg.
- **Spleen 6 (SP6) (Right and Left/bilaterally):** This point is located on the inside of the lower leg.
- **Kidney 3 (K3) (Right and Left/bilaterally):** This point is located on the inside of the ankle.

c. Standard of Care. Participants will be asked to continue doing whatever their healthcare providers advise for PCRF. We anticipate that most women will be treated per the National Comprehensive Cancer Network (NCCN) Clinical Guidelines for Fatigue V1.2009 (NCCN Guideline for fatigue).(66) These guidelines recommend mostly supportive care such as use of stress management or cognitive behavioral therapy; short naps and possible use of stimulants and sleep medications. Participants will be asked to continue any current treatment and not to start or stop treatments over the course of the study. All treatments for fatigue will be recorded.
### 4.2.1 Study Visits

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<th>Screening Visit (within 60 days of baseline)</th>
<th>Baseline Visit (Week 0) (+/- 1 week)</th>
<th>Daily (Days -7 to -1 &amp; 1 to 70)</th>
<th>Week 3 Visit (+/- 1 week)</th>
<th>Week 6 Visit (+/- 1 week)</th>
<th>Weekly Phone Calls (Week 1, 1-2, 4-5 &amp; 7-9)</th>
<th>Final Visit (Week 10) (+/- 2 weeks)</th>
<th>Long-Term Follow-Up (&gt;22 weeks)</th>
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1. Complete Blood Count; blood for correlative tests, blood for future DNA analysis
Acupressure for Persistent Cancer Related Fatigue
Study Protocol: Version 12

2 HADS = Hospital Anxiety Depression Scale; BFI = Brief Fatigue Inventory; and PSQI = Pittsburgh Sleep Quality
Index; LTQL = Long Term Quality of Life Instrument; BSAPQ = Breast and Surrounding Areas Pain Questionnaire;
GSE = General Self Efficacy Scale; BPI = Brief Pain Inventory; VAS for Pain = Visual Analog Scale for Pain Severity,
3 The sleep diary is given as part of the study log book.
4 Participants are randomized to one of three treatments: Standard of Care; Relaxation Acupressure; or Stimulating
Acupressure
5 Data file downloaded at these visits
6 Does not apply to standard of care arm
7 Urine pregnancy test, as appropriate, performed any time between Screening Visit and Group Randomization
8 Optional blood for inflammation markers (IL-1b,IL-1a, IL-1Ra, IL-6, IL-6R, TNFa, TNF-R1, TNF-R2, CRP)

a. Study Visits and Contacts.

Screening Visit (to determine eligibility): Upon contacting the study coordinator to register
their interest, the study candidate will be asked a short number of questions to confirm their
diagnosis/fatigued state and confirm their potential eligibility and interest in the study. Once their
interest is confirmed, the study coordinator will schedule a screening visit with the study nurse in
the county extension office closest to candidate’s home location. Once scheduled, the candidate
will be provided a copy of the informed consent document to review, as well as a medical &
treatment history and concomitant medication form to review and complete prior to their
screening visit. These will not be collected from the subject until they consent to be a part of the
study and have signed the informed consent document.

Written informed consent will be obtained at the beginning of the study visit. A physical exam
including vitals will be performed. Sociodemographic information, medical history and
concomitant medications will be collected. Laboratory tests (CBC), cytokines, and urine
pregnancy test will be obtained. To ensure the accuracy of the blood test, it will be sent to a
laboratory which is local to the MSU Extension Office (e.g. a Quest Diagnostics [Madison, NJ]
service facility, a laboratory at Michigan State University’s Sparrow Health System [Lansing, MI],
University of Michigan’s Health System). Participants will also be asked to complete the HADS,
PRIME-MD, BPI, VAS for Pain, PSQI, Berlin Questionnaire and BFI. We will also ask subjects
seen at the University of Michigan MCRU facility, if they would be willing to donate a small
sample of blood (~5ml) to bank for future DNA analysis. Subjects at the MCRU facility will also
be asked whether they would be willing to donate an additional sample of blood (~5ml) for the
testing of markers of inflammation (IL-1b, IL-1a, IL-1Ra, IL-6, IL-6R, TNFa, TNF-R1, TNF-R2,
CRP). The additional blood samples will only be obtained once they have consented. Subjects
seen at one of the county extension offices will be offered these opportunities, however they will
need to travel to the MCRU facility and undergo a separate blood draw if they wish to donate a
blood sample. The optional blood sample for DNA analysis will be frozen as whole blood in an
EDTA vial for future analysis. The optional blood sample for markers of inflammation will be
frozen as either serum or plasma until assayed by the Cancer Center Immunology Core. The
subject may also choose to consent for two optional brain imaging tests. A 14-day sleep diary
will be given to participants to complete the 14 days immediately following their screening visit.
This sleep diary will be collected at their week 3 visit. Women will be shown how to enter the 3
or 4-time daily fatigue rating.

Eligible participants scheduled for their baseline visit within 60 days.

Mailing of the 1st Activwatch/Logbook: The study team will mail an Activwatch, logbook and
instructions to eligible participants. They will be instructed to wear it for one week prior to their
Baseline Visit. This will allow the study team an opportunity to capture important baseline/pre-
treatment data.
Baseline Visit (Week 0 +/- 1 week): Participants will fill out the LTQL, BFI, PSQI, BSAPQ, BPI, GSE Scale and Therapy Evaluation Questionnaire. Participants will receive their acupressure instruction including a handout describing acupressure, and illustrations of the proposed acupressure points.

All future visits and contacts calls will be scheduled at this visit to maximize study participation.

In addition, if the subject is randomized to an acupressure group, and previously consented for the optional brain imaging test, the first MRI scan would be conducted at this visit.

Week 3 Visit ( +/- 1 week): Participants return to their study site. A BFI and any adverse events will be collected. Data from the last 28 days from the actiwatch will be downloaded. Participants will be tested for the accuracy of locating their acupoints and the skill of correctly stimulating the points (self-efficacy measure).

Week 6 Visit (+/- 1 week) (Marks the end of doing acupressure and the beginning of the washout phase): Participants return to their study site. A BFI, PSQI and any adverse events will be collected. Participants will also be asked to complete the LTQL, BSAPQ, BPI, HADS and GSE Scales. Data from the last 21 days from the actiwatch will be downloaded. Participants will be tested for the accuracy of locating their acupoints and the skill of correctly stimulating the points (self-efficacy measure). An assessment of blinding will also be performed and the 14-day sleep diary will be given to be returned at the Final Visit. Participants will be asked to stop any acupressure treatment for the next 4 weeks. If subjects consented for the optional blood sample for markers of inflammation at the Screening Visit, then the 2nd drawn will be performed at this visit. It will be frozen as either serum or plasma until assayed by the Cancer Center Immunology Core.

In addition, if the subject was randomized to an acupressure group, and previously consented for the optional brain imaging test, the second MRI scan would be conducted at this visit.

Weekly Phone Calls/Visits (Weeks 1-10): All participants will be contacted once per week (except during study visit weeks). During the contact, a BFI will be administered. Participants are able to miss up to three follow-ups during their time on study. Participants will be asked about completion of study logs and/or sleep diaries and about any adverse events. We will also ask participants if they are having any problems locating the points and provide instruction if any difficulties arise. If a phone call is insufficient to help locate points, the participant can arrange to visit the acupressure educator for further instructions.

Final Visit (Week 10) (+/- 2 weeks): Participants return to their study site. All participants will complete the BFI and PSQI as well as the LTQL, BSAPQ, BPI, HADS and GSE Scales. Sleep diaries from the previous 14-days, study logs and actiwatches will be collected.
4.2.2 Study Measures

Hospital Anxiety Depression Scale (HADS, 3 minutes): Given at the screening, week 6 visit, final visit, and during long-term follow-up; this 15-item questionnaire is a widely used instrument to measure depression and anxiety, which was developed especially for populations with physical illness. A meta-analysis of studies using HADS reported a mean Cronbach’s α of 0.83 for anxiety and 0.82 for depression. (68)

Primary Care Evaluation of Mental Disorders (PRIME-MD, 15 minutes): Will be administered at screening. It is a 26-item self-administered questionnaire that screens for five of the most common groups of psychiatric disorders in primary care: depression, anxiety, alcohol, somatoform and eating disorders. The scale has good accuracy, sensitivity and specificity. (107)

Brief Fatigue Inventory (BFI, 2 minutes): Will be administered once weekly for all 11 weeks and once during long-term follow-up. The BFI was developed at the MD Anderson Cancer Center to screen cancer patients for fatigue. The BFI assesses the severity of fatigue and the impact of fatigue on daily functioning in patients with fatigue due to cancer and cancer treatment. It has been shown to have good reliability (Cronbach’s α = .96) and to correlate well with other measures of fatigue. (54) The instrument consists of a one-page fatigue assessment tool that contains 9 items, each measuring the severity of fatigue on a 0-through-10 scale, and is calculated from the mean of completed items. A BFI of 4 or above is considered moderate fatigue while a score of 6 and above is severe fatigue.

Actiwatch-Score (Actiwatch- S) to collect daytime and nighttime physical activity and symptoms: The Actiwatch-S [Mini Mitter, Bend, OR] collects daytime and nighttime physical activity and symptom levels in the moment (as opposed to retrospective recall). Participants will wear the Actiwatch-S for all weeks of the study. The Actiwatch-S is a small waterproof device about the size of wrist watch (28 x 27 x 10 mm weighing 17 grams) that is worn continuously on the non-dominant wrist. An accelerometer monitors the occurrence and degree of motion and measures the number of movements that exceed 0.01g gravitation force. Activity data are downloaded to computer and sleep/wake activity is estimated using Actiware® – Sleep software. It is important to emphasize that actigraphy does not measure sleep per se, but a behavior that is highly correlated with sleep—level of activity. Sleep episodes, both intended and unintended, can be reliably identified when low activity occurs in the presence of other indicators of sleep, such as self-reported sleep. (69-71) Participants will be instructed to wear the actigraph at all times except if engaging in physical activities that could damage the device. If the actigraph is removed, removal and replacement times are recorded on the log book. A limitation of actigraphy is that it can mistakenly identify quiet wakefulness as sleep. For this reason, actigraphy is always accompanied by a daily log book to assist with scoring the activity data. The Actiwatch-Score actigraphs will be downloaded to computer via an electronic interface and analyzed for sleep/wake and daytime activity state using on-board Actiware® – Sleep software. The software uses a validated algorithm to compute standard parameters of sleep/wake and activity cycles for each day of recording. The primary outcomes for nighttime...
actigraphy will be total sleep time (total minutes scored as sleep by the Actiware algorithm) and
sleep efficiency (total sleep time/time in bed*100, %).

It has also more recently been used by members of our research team to examine daytime
physical activity by measuring activity patterns,(56,57,59) and the effects of a physical activity
intervention.(59) By using data from the Actiwatch-S this study will gather objective measures
on fatigue and sleep enhancing and supplementing self-report data. A review of the reliability
and validity of accelerometers including the Actiwatch has recently been published by Dr.
Murphy.(72) The Actiwatch has also been used in the above cited research articles to assess
fatigue. The method of symptom reporting along with a log book for double data entry has
yielded approximately 94% completed data on symptoms in our previous studies. The
assessment of fatigue using this method improves upon existing recall-based methods of
symptom reporting in which people tend to underreport or report only peak or recent
symptoms.(60)

Actiwatch-Score (Actiwatch-S) to collect fatigue severity:
Four times daily participants will indicate on a scale from 0 = “no fatigue” to 10= “The most
severe fatigue” their fatigue severity at that moment. These scores will be entered into the
Actiwatch-S upon completion of their acupressure treatment, once in the morning (6 to 10 AM),
one in the afternoon (2:00 to 6:00 PM) and once in the evening (7:00 to 11:00 PM).

Long Term Quality of Life Instrument (LTQL, 5 minutes): The LTQL is a 34 items
questionnaire that is self administered for evaluating functional impairment and the perceived
effect of that impairment on quality of life in BC survivors. LTQL is composed of four sub scales
that encompass the four domains of quality of life: somatic concerns, spiritual/philosophical
views of life, fitness and social support. (106)

Breast and Surrounding Area Pain Questionnaire (BSAPQ): For measuring pain in the area
of the breast (defined as the breast, armpit, side of the body, or arm on the operated side) on
either the operated breast or the area from which the breast was removed we will be using the
BSAPQ. This questionnaire was developed in a large cohort of women who had received breast
cancer surgery to determine the presence, frequency and severity of pain in the breast region.
(109)

Brief Pain Inventory (BPI, 5 minutes): The BPI will be used to assess average clinical pain at
baseline, at the end of treatment period, at the end of the study, and again during the long-term
follow-up. The BPI has validation support for use in both cancer and chronic non-malignant
forms of pain.

Self-Efficacy Scale (GSE, 4 minutes): The construct of Perceived Self-Efficacy reflects an
optimistic self-belief (Schwarzer, 1992). This is the belief that one can perform a novel or difficult
tasks, or cope with adversity -- in various domains of human functioning. Perceived self-efficacy
facilitates goal-setting, effort investment, persistence in face of barriers and recovery from
setbacks. It can be regarded as a positive resistance resource factor. Ten items are designed to
tap this construct. Each item refers to successful coping and implies an internal-stable
attribution of success. Perceived self-efficacy is an operative construct, i.e., it is related to
subsequent behavior and, therefore, is relevant for clinical practice and behavior change. The
scale was created to assess a general sense of perceived self-efficacy with the aim in mind to
predict coping with daily hassles as well as adaptation after experiencing all kinds of stressful
life events. (110)
**Pittsburgh Sleep Quality Index (PSQI, 8 minutes):** PSQI will be administered at screening, week 6, week 10, and during the long-term follow-up. This widely used 19-item questionnaire evaluates sleep disturbance over the past month. It yields a total score and 7 component scores: sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleep-promoting medication; and daytime dysfunction. In women with breast cancer, Cronbach’s alpha for the global PSQI is 0.80. A score >7 in BC patients suggests poor sleep quality. The scale has adequate psychometrics. The primary outcome will be the total PSQI score at screening, week 6, and week 10, although we will conduct exploratory analyses on the PSQI subscales.

**Sleep Diary (5 minutes):** The sleep diary will be given to participants at the screening visit which is to be completed 14 days after; and again at the week 6 visit which is to be completed 14 days prior to the Final Visit. Sleep diaries are simple, non-invasive, self-report measures that provide night-to-night information on sleep pattern, quality, and relevant daytime behavior. The diary takes 2 minutes or less to complete each day. The following sleep parameters will be self-reported on the diaries: bedtime, rise time, sleep onset latency (time to fall asleep for the first time), number and duration of nighttime awakenings, and naps (start and end times of previous day’s naps). Daily caffeine, alcohol, drugs, and nicotine intake will also be recorded. The primary outcome variables – total sleep time (minutes spent asleep each night) and sleep efficiency (total sleep time/time in bed* 100) - are derived from the information provided on the diaries.

**Visual Analog Scale for Pain Severity (VAS Pain, <1 minute):** The VAS for Pain will be given at the screening visit. It contains only one question which asks about overall pain intensity within a one week period and ranges from no pain up to worst possible pain. Participants are asked to place a tick mark along a solid 10cm line.

**Berlin Questionnaire (3 Minutes):** The Berlin Questionnaire is a 10 item questionnaire that asks questions to determine the likely presence or absence of sleep apnea. The scale has good accuracy, sensitivity and specificity. It will be given at the screening visit.

**Therapy Evaluation Questionnaire (2 minutes):** The Therapy Evaluation Questionnaire is a 7 item questionnaire asking about the subject’s perception of the treatment on a 7-point scale ranging from “not at all” up to “very”. It will be given twice; once at the baseline visit and also at the week 6 visit.

**Adverse Events:** Toxicity will be graded according to NCI Common Toxicity Criteria version 4.03.

**Treatment Fidelity and Self-efficacy Measure:** Participants will be evaluated at week 3 and week 6 for their ability to accurately locate and stimulate their acupoints. The acupressure educator will ask the participant to identify each of their acupoints and to stimulate 1 point on the educator. The number of acupoints correctly located will be recorded on a case report form as will the adequacy of stimulating the acupoints (recorded as “yes” or “no”). Participants will be corrected and asked to relocate acupoints as needed. Participants will also be asked to record when they have completed their acupressure treatments and for how long they performed the treatment.

**Assessment of Blinding:** At the week 6 visit participants who were randomized to the 2 acupressure arms will be asked which type of acupressure they thought they were performing, stimulating or relaxing. They will also be asked several questions relating to why they believed...
they were randomized to that treatment including, “was it the location of the acupoints” and “was it the way the treatment worked”.

**Logbooks:** A logbook will be used for double data entry and to verify actiwatch data (both movement and recording when acupressure was performed). The log book will list the fatigue rating along with other information to obtain more complete data. To assist in analysis of physical activity data, we will ask about physical activity in the day (5 hour blocks of time) and during the night. Participants will also record their wake and sleep times.

**Cytokines:** Samples will be stored at -80°C until assayed. We will measure markers of inflammation (IL-1β, IL-1α, IL-1Ra, IL-6, IL-6R, TNFa, TNF-R1, TNF-R2, CRP) using an ELISA assay. This quantitative ELISA-based test has distinct capture antibodies absorbed to each well of a 96-well plate in a defined array. Manipulation of the range of the standard curves and exposure time allows for reliable comparisons between fatigued and non-fatigued participants of both low and high level cytokine concentrations in plasma and serum. The Cancer Center Immunology Core who is currently running this type of assay will analyze the samples.

### 4.2.3 End of Study Letter

After all participants have completed the study, the study team will send out a letter letting the participants know what study arm they were randomized into and giving them an option to receive the published manuscript with study results via email or through the post.

### 4.2.4 Brain Imaging

**Brain Imaging – Spectroscopy:** Consenting participants will undergo conventional magnetic resonance imaging (MRI) of the brain on a 3.0T MR scanner (General Electric Medical Systems, Milwaukee, WI). Single-voxel spectroscopy will be performed using the following parameters: point resolved spectroscopy, repetition time 3,000 msec, echo time 30 msec, flip angle 90°, number of excitations 8, field of view 16 cm, with a volume of interest of 2 × 2 × 3 cm. During each session, 4 separate single-voxel spectroscopy sequences will be performed, once with the VOI placed in the right anterior insula, once in the right posterior insula, once in the superior frontal gyrus, and once in the anterior cingulate.

Participants will be at rest during the H-MRS session. The raw data from each single-voxel MR spectroscopy sequence will undergo manual post-processing using H-MRS software (LCModel; Stephen Provencher, Oakville, Ontario, Canada). LCModel uses a linear combination of individual spectra obtained from pure molecular species to fit the experimental spectra. Values for Glu and myo-inositol will be calculated as absolute concentrations using the water signal for normalization. Resulting metabolite absolute concentrations will be reported in arbitrary institutional units.

Since our voxels incorporate CSF, and the volume of CSF dilutes H-MRS-derived metabolite values, we will correct our metabolite levels for CSF volume for each participant. For this we will use Voxel Based Morphometry, a toolbox that operates within the image analysis program Statistical Parametric Mapping. Dr. Harris will be conducting the analysis of the MRI data at the Chronic Pain and Fatigue Research Center at the University of Michigan. The MRIs will not be read for clinical purposes. If a gross brain abnormality is detected the participant will be referred to their primary care provider for further work up and tests. The MRIs will occur at the University of Michigan University Hospital in the research MRI scanner. Consenting participants from both Treatment Arm A and Treatment Arm B will undergo brain imaging at the time of Baseline (Week 0), then again at the time of their Visit 4 (Week 6).
Brain Imaging – Resting State: Resting fMRI scans (10min), performed with subjects resting comfortably in the scanner with eyes open, will be completed at the beginning of the fMRI scan session. In order to quantify intrinsic brain connectivity, functional MRI data will be analyzed with both a dual-regression ICA approach and seed-voxel approach. These approaches are complementary, as they quantify intrinsic brain connectivity on a network level (dual regression pICA) and a more specific region-focused level (seed-voxel). Physiological data will also be collected simultaneously to the fcMRI data, using a pulse oxymeter and chest plethysmograph as cardio-respiratory fluctuations are known to influence fMRI intrinsic connectivity estimation within several brain networks.

5.0 REPORTING ADVERSE EVENTS

5.1 Definition
An adverse event (AE) is any condition which appears or worsens after a participant is enrolled in an investigational study. An AE does not necessarily have a causal relationship with the study agent.

5.2 Definition of Acupressure-related Toxicity
Toxicity will be graded as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 (see Section 5.5), and appropriate action will be taken. The possibility that a given adverse event is related to study treatment will be classified as one of the following: not related, unlikely, possible, probable, or definite. Any adverse event determined to be possibly-, probably- or definitely related to the study agent will be deemed a treatment-related toxicity event.

5.3 Frequency
Toxicity will be monitored by participants for the duration of the study. All participants will be questioned regarding toxicity during the weekly progress phone calls and on their last visit. All participants will be instructed to contact the study coordinator via phone call or email at any time during the study.

All participants will be contacted via telephone (at a predetermined time convenient for participants) or email during each week of the study to solicit any adverse reactions. Return calls will be attempted within the week if study participants are not available via phone at this first call.

5.4 AE Reporting and Data Elements
All adverse events that occur after the informed consent is signed (including during run-in) will be recorded on the adverse event case report form (CRF) whether or not related to study agent.

The following information will be collected for all adverse events:

- AE reported date
- AE Verbatim Term
- CTCAE Term (v 4.0)
- Event onset date and event ended date
- Severity grade
- Attribution to study treatment (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments
5.5 Severity of AEs

Toxicity will be graded according to NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be found at [http://ctep.cancer.gov].

AEs will be assessed according to the CTCAE grade associated with the AE term. AEs that do not have a corresponding CTCAE term will be assessed according to their impact on the participant’s ability to perform daily activities as follows:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Severity</th>
<th>Description</th>
</tr>
</thead>
</table>
| 1     | Mild     | • Asymptomatic or mild symptoms  
        |          | • Clinical or diagnostic observations only  
        |          | • Intervention not needed |
| 2     | Moderate | • Minimal, local or non-invasive intervention indicated  
        |          | • Limiting age-appropriate instrumental activities of daily living |
| 3     | Severe   | • Medically significant but not immediately life-threatening  
        |          | • Hospitalization or prolongation of hospitalization  
        |          | • Disabling  
        |          | • Limiting self-care activities of daily living |
| 4     | Life threatening | • Life threatening consequences  
        |          | • Urgent intervention needed |
| 5     | Death    | • Death related to Adverse Event |

5.6 Assessment of Relationship of AE to Treatment

The possibility that the adverse event is related to study treatment will be classified as one of the following: not related, unlikely, possible, probable, definite.

5.7 Follow-up of AEs

All AEs, including laboratory abnormalities that in the opinion of the Investigator are clinically significant, will be followed according to good medical practices, and documented as such.

5.8 Serious Adverse Events (SAEs)

A serious adverse event is defined (by ICH Guideline E2A and Fed. Reg. 62, Oct. 7, 1997) as an event, occurring at any dose, which meets any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect

In addition, events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will be reported in the same manner.

5.9 Study Specific Adverse Event Reporting Plan

All Serious Adverse Events that are deemed related, probably related or possibly related will be reported to the IRBMED within 7 days, as per UM IRBMED guidelines ([http://med.umich.edu/irbmed/ae_orio/ae_report_standard.htm](http://med.umich.edu/irbmed/ae_orio/ae_report_standard.htm)).
All other non-serious, non-life-threatening adverse events will be reviewed by the PI and reported as per the following **Study Specific Adverse Event Reporting Plan:**

<table>
<thead>
<tr>
<th>Reportable Events</th>
<th>Timing of Report to IRBMED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unanticipated / unexpected problem involving risks to subjects or others</td>
<td>Serious - within 7 days</td>
</tr>
<tr>
<td></td>
<td>Non-Serious - with scheduled continuation review</td>
</tr>
<tr>
<td>Any physical, social, or psychological harm attributable to participation in this research study (e.g. an injury occurring during a study visit, infection at the site of a blood draw if antibiotics are required, bruising at the site of acupressure treatment)</td>
<td>Serious - within 7 days</td>
</tr>
<tr>
<td></td>
<td>Non-Serious - with scheduled continuation review</td>
</tr>
<tr>
<td>Death while on study</td>
<td>With scheduled continuation review</td>
</tr>
<tr>
<td>Loss of job or insurability due to breach or revelation of research records or participation.</td>
<td>Within 7 days of notification</td>
</tr>
</tbody>
</table>

**Non-Reportable Events**

- Pregnancy, or birth-related complications
- Hospitalizations and morbidity expected in population (e.g. surgery for removal of fibroid tumour)
- Other serious or non-serious events deemed not related or unlikely related to the research

**Scheduled continuation review** = renewal application.

### 6.0 CONCOMITANT MEDICATION, EXERCISE, DIET AND SMOKING

#### 6.1 Limitations on Medication, Exercise, Diet and Smoking

Concomitant prescribed medications are allowed except as listed in section 4.1 (Exclusion Criteria). Participants will be asked to refrain from starting or stopping any new medications or supplements for the entire duration of the study. We will allow acute medication, defined as taking a medication for < 10 days over the course of a month with the intent not to continue that medication.

Similarly participants will be asked to maintain their customary exercise, dietary and smoking habits during the screening, intervention and follow-up phase of the study.
Participants will be asked to refrain from starting or stopping any new lifestyle modifications for the entire duration of the study.

6.2 Documentation of Medication, Exercise, Diet and Smoking

All chronic medications (prescription or OTC used for at least 14 days continuously), dietary supplements and/or herbal preparations taken by the participant during the run-in period and/or study period will be documented on a CRF with information including:

- Start and stop dates of drugs, supplements or herbs (if available)
- Dose and route of administration (if available)
- Purpose for taking the medication, supplements or herbs (if available)

Smoking habits ("Current Smoker", "Past Smoker" or Non-Smoker": with a smoker defined as someone who has smoked more than 100 cigarettes in their lifetime) will be recorded along with length of smoking (years), number of packs smoked per day, and length of time since smoked, as appropriate.

General dietary and exercise habits will be noted including:

- Type of exercise, duration and intensity
- Dietary pattern (e.g., standard American diet, Mediterranean, vegetarian, vegan, macrobiotic)

7.0 OFF-STUDY CRITERIA

7.1 Study Termination

The study will be terminated for an individual when a participant completes the full study, as defined in section 4.0.

The Principal Investigator can decide to terminate a participant’s participation in the study at any time. This decision could be based on factors such as unacceptable adverse events or for safety concerns. The reason for termination shall be documented in the case report form.

7.2 Premature Removal of a Participant

7.2.1 Personal reason

A participant may withdraw from the study at any time.

7.2.2 Lost to follow-up

Diligent attempts must be made by telephone and letter to determine the circumstances for loss to follow-up, since such loss may be related to the study intervention.

7.2.3 New illness or Medication

Participants who are diagnosed with a new chronic illness, start a new prescribed chronic medication (taking medication continuously for longer than 10 days) or have an increase in medication dose during the study period, e.g. increase in pain medication will be withdrawn from the study and replaced by another participant. Participants who experience an acute illness (less than 2 weeks) e.g., a cold or receive acute medications will have these documented but will remain in the study.

7.2.4 Death

Participants who die while on study will be replaced by another new patient.
8.0 DATA MANAGEMENT

8.1 Case Report Form Set

The CRF, a set of forms for each participant, provides a record of data generated according to protocol. These forms are to be completed on an ongoing basis during the study. The research chart is the source of verification of data. During the study, CRFs will be monitored for completeness, accuracy, legibility and attention to detail. The CRFs will be retained for review.

8.2 Data Entry, Data Management and Quality Control

Hard copies of the data are kept in folders in the project coordinator’s office, where it will be available for the project coordinator to evaluate whenever overall protocol assessment is wanted or needed. The coded list of participants on the study is maintained in a locked cabinet by the PIs. Confidentiality will be maintained and information kept on each participant will be made available only to the project coordinator and identified investigators.

8.3 Additional Reporting Requirements

8.3.1 Protocol revisions and amendments

- The IRBMED must be notified of proposed protocol amendments to assess impact on trial safety and management of regulatory submission.
- A full copy of the amended protocol must be submitted to the IRBMED for review and approval prior to initiating the amended protocol.
- The revised or amended protocol document must be accompanied by a cover sheet detailing the protocol changes, rationale for change, impact on other areas of the protocol, and specific reference to the changed protocol sections.
- The protocol shall be clearly marked with the protocol version number or amendment number.
- All protocol amendments must be approved by the IRBMED prior to activation.

9.0 STATISTICAL METHODS

9.1 Primary and Secondary Aims

Primary Aim: The primary aim of this study is to investigate the differential effects of different modes of acupressure on fatigue in breast cancer survivors. For this, we shall focus on three fatigue outcomes, namely, BFI, which will be administered weekly, a measure of average daily physical activity as well as a self-reported fatigue score, both based on Actiwatch-S data. BFI is collected weekly and provides a measure of average degree of fatigue, a score that ranges between 0 and 10, with higher numbers indicating more fatigue. We shall break up the observation period in three phases. The first phase BFI obtained by averaging week-1-week2 measures indicate the status midway through the treatment phase (mid-treatment). The second phase comprising of week 3-week 6 measures will indicate the status in the second half of the treatment phase (end-treatment). The final phase comprises of week 7-week 10 that indicates the washout phase (washout). In order to investigate the difference in BFI between the three study arms, we shall use mixed-effects regression analysis with average BFI in the three phases as outcome, phase as the within-subjects factor and group (RA, SA, standard of care) as the primary between-subjects factor. We shall carry out two separate analyses, one with phase restricted only to the treatment period (mid-treatment and end-treatment), and the other with the phase variable with only end-treatment and washout as the only levels. The purpose of investigating the first model is to identify group differences during the treatment period whereas
the second model will compare the differences between the treatment and washout period across groups (phase-group interaction).

In either model, the baseline BFI level will be used as a covariate. We shall further adjust the model for key demographic variables such as age and ethnicity, as well as the baseline HADS score. A subject random-effect will be used to account for the clustering effect within the three measurements on the same subject. Also of interest is the group*phase interaction (to be included in the model), significance of which will indicate differences in extent of decrease between the arms. Model diagnostics will be carried out to confirm the distributional assumptions and appropriate corrective actions (e.g. transformation) will be performed as needed.

Two types of fatigue-related measures will be collected from the Actiwatch-S. The first is a daytime activity count per minute, which is calculated by dividing the total daily activity counts by the total daytime minutes. For each phase as defined above we shall use the corresponding 21-day (or 28-day) average as appropriate. The second type of measure is obtained from the four self-reported fatigue readings of the Actiwatch-S. The daily averages are obtained from the non-missing entries each day, and are then combined to provide the phase average the same way as the daytime activity count. The analytical framework is identical to that for BFI, albeit with the changed outcome.

A secondary analysis with BFI will also be carried out which investigates the difference in proportion of severely fatigued subjects (BFI ≥ 6) across the three study arms. The analytical framework will be that of a mixed-effects logistic regression model with severe BFI (yes/no) being the dichotomous outcome. Apart from group, phase, and group*phase interaction as primary covariates, the model will also be adjusted for baseline status of severity. Remaining covariates in the model are identical to those in the continuous BFI model. The clustering effect due to subject will be accounted for using a generalized estimating equations approach.

In order to assess the extent of association between the improvement in FACT-B and improvement in fatigue measure (specific aim #1 letter D), we shall create the change-scores (week 6 – baseline, week 10 – baseline) for FACT-B (both total and component scores), and BFI. Then we shall fit a linear mixed model similar to that for the original BFI analysis, with BFI change-score as outcome, and the FACT-B change-score as a time-varying covariate. There will not be any phase or week variable in the model. We shall restrict this analysis to the SA and RA arms only so that the group variable will consist of two levels. A group*FACT-B interaction in the model will investigate any differential association across the arms between the change-scores. The model will include as additional covariates age, ethnicity, and baseline HADS score. The clustering effect due to subject will be accounted for using a random subject effect.

Secondary Aims:

1. Assessing difference across study arms with respect to sleep parameters

One of the most widely used sleep measures is the PSQI, which shall be administered at screening, week 6 and week 10. We shall follow the scoring convention followed for PSQI which constructs scores for seven components, namely sleep quality; sleep latency; sleep duration; habitual sleep efficiency; sleep disturbances; use of sleep-promoting medication; and daytime dysfunction, all derived from the original PSQI. The component scores are summed to obtain a total score, the primary outcome for the proposed study. The modeling framework and subsequent analysis will be similar to that for BFI with the phase variable replaced by a week variable with the levels 6 and 10.

Since PSQI score larger than 7 is considered an indicator of poor sleep quality in BC survivors, we shall also carry out a logistic regression analysis with a dichotomous outcome indicating whether PSQI > 7 is satisfied or not. This will compare the proportions (longitudinally) of subjects with poor sleep quality across the study arms. The analytical framework will be very similar to that for testing equality of proportions of subjects that are severely fatigued (BFI ≥ 6).
A second sleep outcome that will be used in our analysis is the daily sleep diary. The analytical framework will be very similar to that of BFI with group, phase and group*phase interactions being the primary covariates.

A number of secondary sleep outcomes will be obtained using a conjunction of the Actiwatch-S data and sleep diary. These will allow us to compare across the study arms summary measures such as total sleep time (minutes spent asleep each night) and sleep efficiency (total sleep time/time in bed* 100). These can all be analyzed using the models and methods described above within the mixed linear or logistic regression modeling framework as appropriate.

A change-score analysis between LTQL and PSQI will be carried out in a manner similar to that between LTQL and BFI, which will address Aim 2D.

2. Assessing differences in time to onset and time to relapse (after treatment ends) across the acupressure arms

Time to onset of the acupressure effect is investigated by studying the treatment subgroups, namely RA and SA. For fatigue, we shall use the daily average values of the Actiwatch-S. Time to onset will be calculated as the first time (in days) the fatigue rating falls down by 3 points in comparison to the baseline. We shall restrict this analyses to subjects whose baseline Actiwatch-S fatigue rating is at least 3. From our prior experience, this will be the case with most, if not all of the subjects. A proportional hazards regression model will be employed to analyze the time to onset data. Treatment arm (RA vs. SA) will be used as the primary covariate in the analysis. Independent variables used in the earlier regression analyses for the primary and secondary aim 1 will be used as additional covariates.

For sleep, we shall use the Actiwatch-S sleep patterns measure to carry out our time to onset analysis. As in the case of fatigue, a 3-point drop from baseline in the Actiwatch-S sleep patterns for the first time will be considered as onset. Since the Actiwatch-S sleep pattern measures are weekly, we shall employ a discrete survival analysis technique to analyze this data. A discrete survival model is a logistic regression model of the discrete-time hazards, and is easily implemented in most standard statistical softwares. As in the case for the Actiwatch-S fatigue rating, this analysis will be confined to subjects with a baseline Actiwatch-S sleep pattern score of 3 or more.

We would analyze similarly the time to relapse since the end of treatment, which is defined as the first time a 3-point increase (Actiwatch-S fatigue rating or Actiwatch-S sleep patterns) from the six-week value occurs. This part of the analysis will be restricted to subjects for whom an onset has occurred.

Handling Missing Data. The linear mixed-effects framework is an intent-to-treat framework in the sense that it uses all available data at all time-points. So if there are missing outcome values in any phase due to patient dropout, the usual analysis will still be valid. If the proportion of dropouts is substantial (20% or more) in either arm, then we shall also perform a weighted analysis with weights equal to the inverse of the probability of dropout. On the other hand, missing covariate values for the subject-level information will be imputed using multiple imputation methods. All missing values will be imputed using the chained equation method.(77) The advantage of using this technique is its flexibility in allowing different types of variables (categorical and continuous) to be imputed together without requiring any multivariate joint distributional assumption. In this method, the missing values are sequentially updated using bootstrap or Markov Chain Monte Carlo based on multiple regression models with other variables as covariates. This procedure will be carried out for a number of repetitions or cycles, thereby constructing an 'imputed' dataset. Ten such 'imputed' datasets will be used for the final analysis, a number which is considered adequate for most applications. Finally we shall combine the results from the ten regressions with the imputed data using Rubin’s formula.(78)
The multiple imputation method uses the assumption that the missing-ness conforms to a *missing at random* pattern which allows missing-ness in a variable X to depend on other covariates but does not allow it to depend on X itself. All analyses will be carried out in the statistical software SAS version 9.2.

### 9.2 Sample Size Justification

Our power analysis is based on our primary aim “To examine the effect of 6 weeks of RA compared to a regime of SA or standard of care on fatigue as assessed weekly by self-report using the BFI.”

We compute the power via simulation using a mixed effects model with a between-subject factor group (3 levels), a within-subject factor phase (2 levels), group*phase interaction and a random subject effect. The mean BFI values at mid-treatment were assumed to be 4, 3, 3, respectively for standard care, SA and RA arms whereas the means were taken to be 4, 3, 2 at the end-treatment point in the same arms. The between-subject variance is assumed to be 4 at all time-points whereas the variance of the random subject component is taken to be 4 also (yielding an intra-class correlation of 0.5). These assumed values are estimates based on our pilot data. For this configuration, the power for detecting the difference between groups is more than 0.95 and the power for detecting a significant phase*group interaction is 0.82 with a sample size of 100 per treatment arm and a 5% level of significance. In the second model discussed in the analysis section with phase comprising of end-treatment and washout, if we assume the washout point BFI values to be 5, 4, 3, in the standard care, SA, and RA arms, respectively, the power for detecting either the phase effect or group effect are both around 99%.

We also want to power the study to allow us to observe differences in sleep parameters. The extent of overlap between fatigue and sleep disturbances in BC survivors is currently unknown. Research indicates that 51% of BC survivors experience sleep disruptions and 19% meet diagnostic criteria for insomnia. (23) While fatigued women are most likely enriched with individuals experiencing sleep disturbances we will conservatively assume that roughly 51% women will have some significant sleep disturbances and 19% will have insomnia per treatment arm. As such, with 100 women per treatment group we will be overpowered for detecting a difference in fatigue and sufficiently powered to detect changes in key sleep measures. For example, using the PSQI as a basis for powering differences in sleep quality from previous studies the mean PSQI in BC patients ranges from 6.84 ± 0.376 to 7.16 ± 0.325.(60,74) A 1 point decrease in the PSQI from ~7 to ~6 is considered clinically significant in this population.(60) The mean PSQI values at mid-treatment are assumed to be 7, 6, 6, respectively in standard care, SA and RA arms whereas the means are taken to be 7, 6, 5 at the end-treatment point in the same arms. Assuming an intra-subject correlation of 0.5, we have powers above 99% to detect any of the group, phase, and group*phase interaction effects with a sample size of 100 per treatment arm and a 5% level of significance.

### 10.0 ETHICAL AND REGULATORY CONSIDERATIONS

#### 10.1 Institutional Review Board (IRB) Approval

Prior to initiating the study, the PI must obtain written approval to conduct the study from the appropriate IRB. Should changes to study protocol become necessary, protocol amendments will be submitted electronically by the PI to the IRB for approval prior to implementation.

#### 10.2 Informed Consent

All potential candidates for the study will be given a copy of the study informed consent to read. The investigator or their designee, will explain all aspects of the study in lay
language and answer all the candidate's questions regarding the study. If the candidate decides to participate in the study, he/she will be asked to sign the informed consent document. Participants who refuse to participate or who withdraw from the study will be treated without prejudice.

The informed consent document must be reviewed and approved by the IRB prior to study initiation. Any subsequent changes to the informed consent must be approved by the IRB for approval prior to implementation.

10.3 Data and Safety Monitoring

10.3.1 Guidelines

The purpose of the data and safety monitoring plan is to insure the safety of participants, the validity of data, and the appropriate termination of studies for which significant benefits or risks have been uncovered or when it appears that the trial cannot be concluded successfully. Risks associated with participation in research must be minimized to the extent practical, and the method and degree of monitoring should be commensurate with risk. The essential elements of the Data and Safety Monitoring Plan include:

- Monitoring the progress of trials and the safety of participants
- Plans for assuring compliance with requirements regarding the reporting of adverse events (AE)
- Plans for assuring data accuracy and protocol compliance.

10.3.2 Study-specific DSMP

The PIs will review study progress weekly with study staff, and problems with or pertaining to study subjects will be communicated immediately. The entire research team will meet monthly to review progress and any problems encountered. This team includes one physician, a PhD trained nurse and trained acupuncturist who are highly experienced with cancer control trials. The PIs will be notified when an AE occurs and will determine the attribution and relatedness of each adverse event. All AE must be given to the PI within 48 hours if involving a death or life threatening event, or within one week, if serious (not-life threatening/death) or non-serious. Lastly, we will work with the UM Prevention Research Base DSMB which meets monthly by means of regularly scheduled meetings.

Composition of the UM Prevention Research Base DSMB: the principal investigator is present in an open session portion of the meeting and absent in a closed session. All DSMB official subjects in the review of confidential data and discussions regarding continuance or stoppage of a study have no conflict of interest and no financial stake in the research outcome. The current UM Prevention research base Data and Safety Monitoring Committee is Chaired by the Dr. Mack Ruffin and comprised of Faculty members from the departments of gastroenterology, Family Medicine, Hematology/Oncology. At least 3 faculty members, not including the study PI, must be present to have quorum. If the DSMB cannot meet face-to-face, a conference call is acceptable. Prior to each meeting, the UM Prevention Research Base clinical research associate distributes a standard summary report detailing accrual, biomarker modulations data, new publications or presentations relevant to the ongoing project, quality control audit information, any ethical concerns, patient-subject complaints and adverse events or serious adverse events of all prevention protocols. The DSMB will begin meeting in mid-year of year 2, and monthly after that. The DSMB will also report its findings of any adverse events or decisions regarding modification of the protocol to the University of Michigan IRB committee.
10.4 Record Retention

Clinical records for all participants studied, including CRFs, history and physical findings, laboratory data, and results of consultations, will be maintained by the Investigator in a secure storage facility and stored for at least five years after the study is closed.

11.0 REFERENCES


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115. Hawks RA. The blood-brain barrier and glutamate. Am J Clin Nutr 2009;90:867S-74S.


123. Ford JM, Mathalon DH. Neural synchrony in schizophrenia. Schizophr Bull 2008;34:904-6.


140. Statistical Parametric Mapping (SPM). In.

Section 12.0 Appendices – Acupressure Point Locations

Figure 2.0: Relaxation Points

- Yin Tang*
- Anmian
- Ht 7
- Liv 3
- Sp 6
Figure 3.0 Stimulating Points

- **Si Shen Chong**
- **CV 6**
- **St 36**
- **Sp 6**
- **LI 4**
- **K 3**

* = bilateral