PROTOCOL FACE PAGE FOR
MSK THERAPEUTIC/DIAGNOSTIC PROTOCOL

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Participating Institutions	PI's Name	Site's Role
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Please Note: AConsenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

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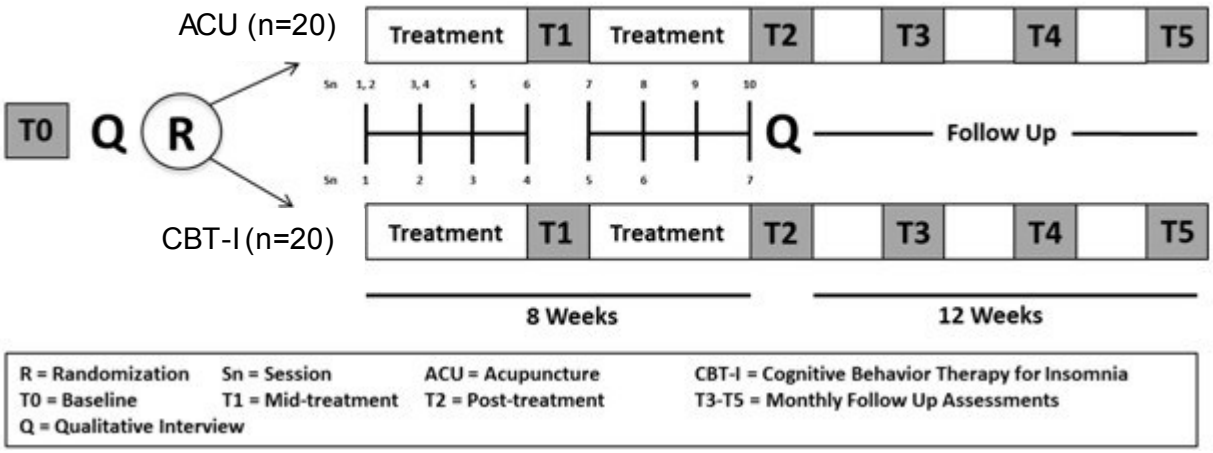
1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Table 1. Protocol Summary	
Study Title	CHoosing Options for Insomnia in Cancer Effectively (CHOICE): A Comparative Effectiveness Trial of Acupuncture and Cognitive Behavior Therapy
Primary Objective	To compare the effectiveness of acupuncture versus Cognitive Behavior Therapy for insomnia (CBT-I) and co-morbid symptoms.
Secondary Objectives	To identify patient-level demographic characteristics, clinical factors, and psychological attributes, that are associated with improved insomnia at post-intervention in acupuncture or CBT-I. To understand patients" experiences of acupuncture or CBT-I to better inform future decision-making, intervention refinement, and treatment dissemination.
Patient Population	Patients with a diagnosis of insomnia who have completed active treatment (surgery, chemotherapy, radiation) for cancer at least one month prior to study initiation with no restrictions placed on type of cancer or stage.
Number of Subjects	40
Study Design	Parallel-randomized controlled trial
Treatment	Acupuncture delivered by a licensed acupuncturist for a total of 10 treatments over the course of 8 weeks. Cognitive Behavior Therapy for Insomnia delivered by a study therapist for a total of 7 sessions over the course of 8 weeks.
Time to Completion	Patients will receive 8 weeks of treatment and be followed for 3 months post-treatment.

Figure 1. CHOICE Study Schema



This project was initially opened at the University of Pennsylvania Health System (Penn) by the principal investigator (Jun Mao, MD, MSCE). Dr. Mao has changed institutions as of December 7th, 2015; he is now at MSK. As of June 30, 2016, ninety participants were enrolled at Penn. The protocol currently open at Penn will remain open there and will continue to be administered by Penn. A separate and parallel protocol will be open at MSK upon MSK's IRB approval. Target enrollment at MSK will be 40 patients. Target enrollment at Penn will be 120 patients. At the end of the study, Penn will send deidentified data and samples to MSK. The appropriate material transfer and data transfer agreements will be executed for this transfer. The datasets will be combined for analysis. The funding agency (PCORI), Penn's IRB, and their Cancer Center support this plan. Upon MSK's IRB approval, we plan to enroll 20 patients at MSK in 2016 and another 20 in 2017.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

To determine which of the treatments (acupuncture or cognitive behavioral therapy for insomnia [CBT-I]) is more effective for insomnia (Primary outcome) and co-morbid symptoms (i.e. pain, fatigue, and psychological distress) in individuals with cancer.

- **Primary Aim:** To compare the effectiveness of acupuncture versus CBT for insomnia and co-morbid symptoms.

- **Secondary Aim 1**: To identify patient-level demographic characteristics (e.g. gender), clinical factors (e.g. pain), and psychological attributes (e.g. outcome expectancy), that are associated with a better Insomnia Severity Index (ISI) score at Week 8 (post-intervention) in acupuncture or CBT-I.

- **Secondary Aim 2:** To understand patients' experiences of acupuncture or CBT-I to better inform future decision-making, intervention refinement, and treatment dissemination.

- **Exploratory Aim 1:** To understand the potential impact of sleep disruption and insomnia treatment on memory, attention, and concentration.

- **Exploratory Aim 2:** To collect biological samples to examine potential biomarkers that are associated with sleep disturbance and/or response to insomnia treatment.

3.0 BACKGROUND AND RATIONALE

Burden of Cancer and Insomnia: Cancer is one of the leading causes of global morbidity and mortality, second only to heart disease. [1] Fortunately, with early detection and treatment advances a greater number of Americans will live longer with cancer and many will become cancer-free. [1] These improved survival rates mean that more people will require ongoing treatment for persistent side effects from cancer and its treatments. Compared with the general population, cancer survivors are at a greater risk for chronic physical and psychological symptoms. [2,3] Sleep disturbances, primarily in the form of insomnia, are an especially important, but frequently overlooked, consequence of cancer. [4,5] Several large-scale epidemiological studies demonstrate that close to 60% of people treated for cancer experience insomnia. [6,7] Unfortunately, once chronic, sleep disturbances are unrelenting if not appropriately treated, and can persist for years or even decades. [7] Sleep difficulty is one of the most frequent reasons that cancer survivors visit their general practitioners and corresponds to 7.8 fewer workdays and $2,280 in lost income per person per year. [8,9] When patients were asked about the development of their insomnia, most reported that it began with, or followed, their cancer diagnosis and that the effects of poor sleep were more overwhelming than the effects of cancer treatment. [10]

Insomnia and Co-morbid Symptoms: Cancer-related sleep disturbances are particularly pernicious because of their negative relationship to psychological health and physical well-being. More often than not, insomnia co-exists with pain, fatigue, depression, and anxiety, creating a positive feedback loop in which all symptoms are amplified and overall symptom burden is increased. In a study exploring the relationships between patient-reported pain, fatigue, depressed mood, and difficulty sleeping in 11,445 cancer patients, depressed mood significantly increased trouble sleeping, pain, and fatigue levels. [11] Independent of mood, trouble sleeping also had a direct influence on pain and fatigue levels. A more recent study also investigated the relationships between self-reported sleep difficulty, pain, and emotional distress in a sample of 2,862 cancer outpatients. [12] Individuals reporting significant pain were 2.7 times more likely to experience sleep difficulty than those without pain, whereas people with higher levels of emotional distress were 4.5 times more likely to report problems with sleep that those with low distress levels. In a prospective study of a heterogeneous sample of 828 cancer patients over an 18-month period, those patients with higher levels of insomnia, anxiety, depression, and fatigue had significant impairments in functioning and the lowest quality of life. [13] This supports the relationship between disturbed sleep, perceived physical functioning, and psychological well-being. Based on these results the use of targeted interventions to treat difficulty sleeping and depressed mood would be expected to also positively impact pain and fatigue levels.

Need for Non-pharmacological Treatment: Considering the prevalence, significance, and impact of insomnia, cancer patients require information about treatment options in order to

make timely and informed decisions. At present, the treatment for cancer patients with sleep difficulties is typically pharmacological. In a sample of 219 women with breast cancer, 46% received a prescription for sleeping medication during cancer treatment.[14] Although sleep medication is only recommended for short-term use, 30% of the original sample was still using prescription sleep aids one year following treatment completion. Unfortunately, sedative medications can have substantial side effects. Long-term hypnotic use is associated with continued sleep difficulty and performance problems, memory disturbances, driving accidents, and falls in the general population.[15] As such, many patients often prefer non-pharmacological interventions to treat insomnia. In a qualitative study conducted by Drs. Mao and Barg with White and African American cancer survivors, some patients indicated their desire for natural approaches to avoid adding another "toxin" to their body after chemotherapy. Others simply wanted to avoid poly-pharmacy given that their many co-morbid conditions often require ten or greater medications already.[16] These findings support the need for rigorously evaluating the effects of, and patient preferences for, non-pharmacological therapies for insomnia and co-morbid symptoms in cancer.**Gap in Evidence:** Acupuncture and Cognitive Behavioral Therapy for Insomnia (CBT-I) are both widely available and commonly used non-pharmacological treatments for insomnia and other co-morbid symptoms. Despite a documented preference for non-pharmacological methods of treating insomnia, there is currently *a* gap in the evidence available as to the comparative effectiveness of these options. [17] Some estimates suggest that up to one-third of cancer patients use acupuncture to help manage problematic cancer-related symptoms [18] and there is increasing evidence for the use and efficacy of acupuncture for the treatment of insomnia. [19,20] Acupuncture has been shown to affect a number of neurotransmitters and hormonal factors known to be involved in sleep regulation, such as serotonin, melatonin, and gamma-aminobutyric acid (GABA). [21] A systematic review of 20 randomized controlled trials of acupuncture for insomnia suggested that traditional needle acupuncture was slightly more effective than benzodiazepines with response rates for acupuncture and benzodiazepines being 91% and 75%. [22] Similarly, acupuncture was found to be equally as effective as zolpidem for improving sleep in 33 patients with insomnia. [23] Evidence also suggests that acupuncture has the potential to repair fragmented sleep architecture and increase time spent in slow wave sleep. [24] While the evidence for the use in insomnia and comorbid symptoms is compelling, acupuncture research has also been criticized for having substantial poor methodologies such as small sample size, questionable randomization, poor reporting, and inappropriate analyses. [25-27] Our study aims to address these methodological challenges and provide reliable evidence that patients and providers can rely on.Cognitive Behavior Therapy for Insomnia (CBT-I) is a form of CBT specifically for insomnia that combines principles from stimulus control therapy (developing a learned association between the bed and sleep) and sleep restriction therapy (consolidation of sleep periods through buildup of sleep drive) with formal cognitive restructuring (reducing misconceptions about sleep) in order to target hyperarousal, dysfunctional behaviors and maladaptive thoughts, beliefs, and attitudes associated with insomnia. CBT-I is recommended by the American Association of Sleep Medicine as a first line treatment for insomnia,[28,29] is considered well established by the American Psychiatric Association,[30] and has demonstrated efficacy in many randomized controlled trials.[31-34] A review of studies with clinical samples of individuals

with primary insomnia concluded that CBT-I is a highly effective treatment for sleep disturbance and produces significant improvements in a variety of subjective sleep components.[35] In preparation for this proposal, our team completed a systematic review of eight controlled and four uncontrolled trials of CBT-I in cancer patients and concluded that CBT-I is associated

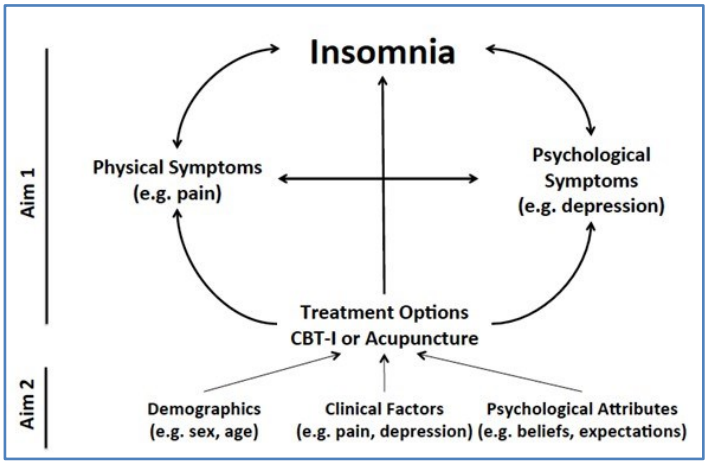


Figure 2. CHOICE STUDY MODEL

with clinically and statistically meaningful sleep improvements in cancer patients.[36] Recent evidence also suggests that CBT-I is effective in reducing clinical levels of fatigue, anxiety, and depression related to cancer treatment. Despite the evidence that CBT-I is an effective intervention, there is still a significant proportion of individuals whose insomnia does not respond or remit after treatment. In a study comparing CBT-I alone or combined with medication, 40% of those randomized to CBT-I did not experience a treatment response and 61% still experienced residual insomnia symptoms.[34] Considering that 32-89% of patients treated with CBT-I (including those with cancer) do not consistently follow treatment recommendations,[38] poor adherence may be one factor accounting for these findings. Additionally, perhaps CBT-I does not adequately, or comprehensively, address the multitude of factors that contribute to the development and maintenance of insomnia (e.g. autonomic hyperarousal).[39] There is an increasing awareness that not all treatments are effective for every person and that treatment decisions should be guided by person-level factors such as personal preference. [40] For behavioral interventions like CBT-I, which require a significant investment of time and active participation, patient preference for treatment is a particularly important contributor to patient adherence and outcomes. [41,42] Clearly, there is a need to improve and/or expand the available insomnia treatment options.

Rationale for the study:

- We chose to compare acupuncture against CBT-I because CBT-I is the current gold standard non-pharmacological intervention for insomnia. [28,29] Our patient stakeholders were clear that they preferred non-pharmacological interventions.
- We did not include a usual care or waitlist control because both acupuncture and

CBT-I have already demonstrated superiority over no-treatment control groups. Research demonstrating that insomnia is relatively stable once developed [7] reduces the potential for change due to the passage of time alone (maturation) or statistical regression towards the mean.

- We have chosen the Insomnia Severity Index [51] as the primary outcome measure because it has been validated in cancer populations with excellent reliability and validity. The ISI captures the daytime impairment and subjective distress associated with insomnia, has clinical cutoffs for symptom severity, and has established minimally important change values to ensure that the changes produced are not only significantly but also clinically significant to patients. When our patient stakeholders reviewed the available options they preferred the ISI because it is short, easy to complete, and has face validity.
- We incorporated patient-centered secondary outcomes of pain, physical and mental fatigue, anxiety, and depression because these were the areas that our advisory panel told us were impacted the most by insomnia symptoms. We also included a measure of quality of life in order to capture the potential for insomnia treatment to improve overall well-being.

In summary, the proposed study is highly significant in that it is the first rigorously designed comparative effectiveness study ever to examine the relative benefits of acupuncture and CBT-I. As summarized in the background section, with the help of our patient partners, we have built a conceptual model that is grounded in the current scientific understanding of acupuncture, CBT-I, and insomnia. It is also the first study to incorporate carefully selected social-demographic, clinical, and psychological factors to examine the predictors and moderators of treatment effect of both acupuncture and CBT-I. The results of the proposed study have the potential to improve healthcare and outcomes by helping cancer survivors and their caregivers make informed and evidence-based decisions and leading to patient-centered and individualized care for cancer survivors with insomnia.

Role of Patient and Stakeholder Advisory Panel

Our patient advisory panel consists of eight patients, one caregiver, and two representatives of cancer support organizations. The panel is diverse in terms of cancer type, stage, age, race, sex, educational level and occupational status. The panel helped generate the research question, choose the comparison groups, develop patient-centered inclusion and exclusion criteria, refine the research protocol, choose the most appropriate outcomes, and decide on specific measurement tools. Our patient partners will help to ensure that our research is able to engage participants from a diverse audience. We have created four committees consisting of researchers and patient partners with oversight of key research components: recruitment, outcomes, interpretation, and dissemination. The research team and patient partners will attend bi-annual meetings to review the research progress, develop or revise recruitment and engagement strategies, and plan for dissemination efforts.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

We will conduct a parallel-randomized controlled trial to compare the effectiveness of

acupuncture and CBT-I for insomnia and co-morbid symptoms in a heterogeneous sample of cancer survivors who have finished primary treatment. Forty patients will be enrolled in this study at MSK. A parallel study is being conducted at Penn. Deidentified data from the 120 patients enrolled at Penn will be combined with the MSK data for analysis. Eligible patients will be randomly assigned to acupuncture or CBT-I. In the acupuncture group, patients will receive ten treatments of acupuncture over eight weeks. In the CBT-I group, patients will receive seven sessions of CBT-I over eight weeks. Patients will complete validated patient-reported outcome (PRO) measures of sleep and co-morbid symptoms at baseline, mid-treatment, post-treatment, and at monthly intervals for 3 months to assess durability of effect. For the Penn study, to understand patient experience, semi-structured interviews will be conducted among 60 patients pre- and post-intervention to elicit their experience of their insomnia and cancer, their attitudes, beliefs, and preferences for a specific intervention prior to the intervention, as well as explore what influences their decision to choose a particular treatment. Structured interviews will not be done as part of the MSK protocol. At the end of intervention, we will elicit both expected and unexpected benefits and side effects of treatments, assess changes in patient attitudes/beliefs/preferences, and gather recommendations for how to disseminate our findings. In keeping with standards for transparent reporting of clinical trials, we will follow the CONSORT guidelines for reporting of non-pharmacological treatment interventions [43] and the Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA). [44] In designing the current study we relied heavily on the Effectiveness Guidance Document for conducting comparative effectiveness research of acupuncture interventions. [45]

4.2 Intervention

Acupuncture: After the acupuncture evaluation, the acupuncture procedure will be carefully explained to each subject. The patient will be positioned in a comfortable position, either in a massage chair or lying on an exam table depending upon patient comfort and need for access to appropriate acupuncture points. Each acupuncture session lasts approximately 30 minutes. Licensed acupuncturists will administer acupuncture following the acupuncture protocol and procedure (Appendix 1) twice per week for two weeks, then weekly for six more weeks, for a total of ten treatments over eight weeks. The first visit to an acupuncturist often involves a more detailed history and an examination that takes an additional 30 minutes so the total contact time is about 330 minutes.

The FDA classifies acupuncture needles as a Class II medical device for "general acupuncture use" by licensed, registered or certified practitioners. The acupuncture groups at each site have performed many clinical trials in acupuncture without significant adverse events.

Cognitive Behavior Therapy for Insomnia (CBT-I): CBT-I is a multi-component intervention that includes sleep restriction, stimulus control, cognitive restructuring, relaxation training, and sleep hygiene (See Appendix 2). Sleep restriction is designed to restrict time spent in bed to closely match the time actually spent sleeping. A sleep efficiency percentage (the amount of time spent sleeping divided by the amount of time spent in bed) is calculated and when the individual is able to achieve 90% sleep efficiency their sleep time is increased. This process continues until the person can achieve a restful night"s sleep with few or no

disturbances. Stimulus control is based on the theory that the body eventually becomes conditioned to associate the sleep time and setting with arousal (e.g. only go to bed when sleepy and refrain from lying awake in bed). This technique is designed to break the perpetuating behaviors and re-associate the bed with positive sleep experiences. Cognitive restructuring addresses the dysfunctional thoughts and beliefs that serve to maintain and exacerbate insomnia. Individuals are taught to monitor these thoughts and beliefs, challenge their validity, and replace them with adaptive cognitions conducive to the sleep process. Relaxation training targets the physiological and cognitive arousal that accompanies insomnia and sleep hygiene promotes healthy sleep behaviors and environmental conditions. Study therapists will deliver six weekly sessions of CBT-I for six weeks followed by one session two weeks later, for a total of seven sessions over eight weeks. The first CBT-I session lasts 60 minutes and the remaining sessions last 30 minutes, bringing the total contact time to 240 minutes.

Selection of study therapists and their intensive training and supervision have been carefully considered. The manualized research intervention for this protocol is highly structured, and the session interventionist is provided with an outline of content for all study modules. Study therapists will have received specialized training in CBT-I prior to delivery in this study.

Study therapists will at minimum be a doctoral student in Clinical Psychology or have a Masters degree in Mental Health Counseling, Social Work, or Psychology to qualify for consideration as an interventionist on this study. Clinicians with greater experience and more advanced skills will also be considered for the interventionist role. We will largely draw from our existing pool of experienced therapists (mental health counselors, psychologists, psychiatrists, social workers, and advanced psychologist trainees) already trained for our ongoing trials.

Supervision and training for CBT-I interventionists will be conducted by Dr. Katherine Duhamel and/or Dr. Allison Applebaum, both of whom have extensive training and supervision experience in these approaches, and will include both didactic and experiential training. At study start-up, intensive training workshops in the delivery of CBT-I will be provided, with a focus on the unique issues of cancer survivors. These trainings will focus on the acquisition of skills in the conduct of the sessions. All interventionists will be provided with a copy of the manual, describing in detail the philosophy, format, and techniques involved in the approach. Drs. Duhamel and Applebaum will lead weekly supervision sessions for the different providers. Interventionists will receive intensive supervision, and their competency in the approach will be continually assessed.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

The FDA classifies acupuncture needles as a Class II medical device for “general hospital and personal use” by licensed, registered or certified practitioners.

Acupuncture Needles Seirin acupuncture needles will be used in this study. The needles are purchased and distributed from Seirin® in the United States

(http://www.seirinamerica.com). Seirin acupuncture needles are approved by the FDA (http://www.accessdata.fda.gov/cdrh_docs/pdf/K962809.pdf).

The acupuncture needles will be inserted 0.5 inch into the skin and will remain in the skin for 30 minutes at the points noted in Appendix 1.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

- English-speaking, age ≥ 18 years old
- A diagnosis of cancer with no restrictions placed on type of cancer or stage. Eligibility criteria are not be restricted to MSK confirmed biopsy/diagnosis. Participating institution"s testing is sufficient for other study sites.
- Completed active treatment (surgery, chemotherapy, and/or radiotherapy) at least one month prior to study initiation (patients on continued hormone treatment or maintenance targeted therapies will not be excluded).
- A score >7 on our primary outcome (the Insomnia Severity Index)
- A diagnosis of insomnia disorder as defined by the Diagnostic and Statistical Manual of Mental disorders, 5th Edition (DSM-5), per the diagnostic interview. According to this nosology, insomnia is defined as dissatisfaction with sleep quality or quantity characterized by difficulty initiating sleep, maintaining sleep, or early morning awakenings that cause significant distress or impairment in daytime functioning and occur at least three nights per week for at least three months despite adequate opportunity for sleep.
- Patients using psychotropic medication (e.g. antidepressants) will remain eligible for study participation provided that the dose was not recently altered (stable over the previous 6-weeks).
- Patients using hypnotics or sedatives will be eligible for study participation. Considering the high use of benzodiazepines within the oncology population, past research has included participants who met diagnostic criteria for insomnia, despite the use of benzodiazepines, and included monitoring of medication use.

6.2 Subject Exclusion Criteria

- Another sleep disorder, other than sleep apnea, that is not adequately treated.
- Previous experience with CBT or acupuncture to treat insomnia
- Currently participating in another acupuncture trial or a trial to treat insomnia
- The presence of another Axis I disorder not in remission
- Employment in a job requiring shift work that would impair the ability to establish a regular sleep schedule
- Patients who are currently taking oral (not including oral sprays/inhalers) or intravenous corticosteroids as part of treatment for cancer or any other condition will be excluded because of the potential of these drugs to induce insomnia

7.0 RECRUITMENT PLAN

Recruitment Plan (with Limited waiver of Authorization)

No restrictions are placed on cancer type or stage so all patients with a diagnosis of cancer, who completed active treatment, have a diagnosis of insomnia, and meet the remaining eligibility criteria will be eligible for participation in the study. There will be no restrictions regarding Service or Clinic. Potential patients who meet basic eligibility criteria will be identified via querying of Dataline at MSK and sent a recruitment letter (See Appendix 6). The recruitment letter introduces the study to patients and states that we are conducting a study to compare the effectiveness of two non-medication based insomnia treatments for individuals diagnosed with cancer and if interested in learning more about the study, the patient should contact the research study assistant. The letter provides patients with an opt-out phone number and study e-mail address to contact if they do not wish to participate or be contacted further. We have successfully used this recruitment method for similar studies. A Dataline query for MSK patients who meet basic eligibility criteria, including having an ICD-9 coded diagnosis of insomnia after their last treatment date, yielded over 500 patients per year for each of the three years queried. In addition to patients who have been formally diagnosed with insomnia, we expect that there will be patients who are experiencing insomnia that have not yet been diagnosed and that we will be able to meet our target accrual goal of 40 patients at MSK. We will also be identifying patients that meet basic eligibility criteria and report sleep difficulties on the MSK Engage symptom questionnaire through a dataline query.

In addition to sending recruitment letters, patients also can be identified and referred to the study RSA for accrual and consent by a member of the patient's treatment team or by protocol investigators. The study PI and other members of the research team will reach out to colleagues about the study and present at Service meetings, including Breast Medicine, GI, Prostate, Head and Neck Services and Psychiatry and Behavioral Sciences to introduce the study. Colleagues in Survivorship will be informed about the study and recruitment materials will be provided to them. In addition to Integrative Medicine physicians, other Integrative Medicine therapists can also refer patients to the study. Study investigators and interested colleagues will be provided with study flyers and/or rack cards to provide to patients (See Appendix 7 and 8 for a study flyer and rack card). Patients may also be self-referred or referred by a clinician from other hospitals. Information about the protocol will appear in lay language on MSK"s web site and on clinicaltrials.gov. Printed material will be posted in clinic areas where we have successfully posted study materials for other Integrative Medicine studies before (e.g., the Breast and Imaging Center, the Main Hospital, Kimmel, and the Rockefeller Outpatient Pavilion). Permission from the clinic sites will be obtained before posting in any location. Materials will also be distributed to potential referral sources who we have worked with on other research studies. All study recruitment materials will be submitted to, and approved, by the Institutional Review Board. We have used these recruitment strategies successfully to recruit participants to similar studies.

Participants will receive $20 at the first, second, and third evaluation time points with an additional $40 for completion of the final assessment (total of $100 per participant). Compensation will be in the form of gift cards.

Initial contact with prospective subjects typically will be made by a member of the study team. The recruitment process presents no more than minimal risk to patient privacy, and minimal PHI will be maintained on screening logs. For these reasons, we seek a (partial) limited waiver of authorization to: (1) review medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) converse with

patients regarding possible enrollment; (3) handle PHI contained in those records and provided by potential subjects; and (4) maintain minimal PHI information in a screening log of patients approached.

8.0 PRETREATMENT EVALUATION

Initial Screening: All potential participants will undergo an initial screening with a research study assistant (RSA) in person or over the telephone. At this initial contact, the study goals and procedures will be explained and the research study assistant will ensure that participants meet basic eligibility criteria, including having an insomnia severity score greater than 7.

Diagnostic Phone Interview: Interested participants will be scheduled to be interviewed by telephone by a trained member of the research staff to complete a diagnostic interview for insomnia and confirm inclusion/exclusion requirements. Research staff conducting the diagnostic interview will review with a study investigator, and the study investigator will approve the patient's insomnia diagnosis per the diagnostic interview conducted with research staff.

Confirmed eligible patients will then be scheduled to meet with a trained member of the research staff to obtain informed consent and complete the baseline assessment.

Sleep Apnea Screening Protocol: Interested patients will be screened for possible obstructive sleep apnea using the Multivariable Apnea Prediction (MAP) form (Appendix 3). The Multivariable Apnea Prediction (MAP) Index and computing tools were developed by the Human Assessment and Biostatistics Core of the Center for Sleep and Respiratory Biology, University of Pennsylvania Medical Center. A cut off score of 0.50 or greater warrants a referral for formal assessment.

Patients with scores of 0.50 or greater will be told that they have symptoms suggestive of sleep apnea. We will provide them with a copy of their answers and suggest that they discuss it with their family physician. We will recommend that they pursue this first to treat their sleep difficulty. If, after treatment, the patient continues to have residual insomnia symptoms they will be welcome to participate in the trial. Should the patient not want to speak with their doctor about their potential sleep apnea, they will still be able to enroll. We will use their MAP score to determine whether it is significantly related to treatment outcome.

Baseline Assessment: After consenting, the patients will complete the baseline assessment which includes questionnaires and a blood draw. Please refer to Table 2 for questionnaires collected at baseline. Patients who endorsed difficulties with attention, concentration and/or memory will also complete the supplementary cognitive measures. Identification of patients who have difficulties with attention, concentration and/or memory is by self report in response to the question " Have you experienced any difficulty with attention, concentration and/or memory as a result of your cancer treatment and/or insomnia?" At this time, we will assess beliefs about insomnia and pre-randomization treatment expectancy using validated

measures. Treatment preference will be elicited using the Treatment Acceptance and Preference (TAP) instrument with two sequential questions. The first item asks participants to indicate whether they have a preference for one of the two treatment options (yes or no). The second question asks participants with a preference to indicate which option is the preferred choice. The participant will be informed that there are two treatment options under investigation and there is an interest in learning about his or her perception of each treatment. A verbal description of the first treatment option will be read aloud in a slow, clear, and unbiased manner and the participant will be asked to respond to the TAP items measuring treatment acceptability and preference in relation to the option presented. This process will be repeated for the other treatment. The presentation of the treatment options will be alternated to prevent sequencing effects. All participants will then receive the details of their treatment group allocation. The RSA will provide participants with two weeks of sleep diaries to complete at home.

Blood Draw: In preparation of a future grant submission, blood samples will be collected at baseline, at the end of the intervention, and at the final follow up assessment to be banked for future correlative studies related to the intervention should we identify any literature during the conduct of the trial demonstrating that specific biomarkers are associated with symptoms or treatment responses. Patients will be able to opt out of the blood draw or provide a saliva sample if desired. Saliva samples are collected once at baseline. Samples will be stored at -80°C until ready for processing. (See Appendix 5 for details). If there is anything left over, it will be banked for future use under 06-107.

Table 2. Schedule of Assessments and Outcome Measures

Instrument	Baseline T0 Week 0	Mid-treatment T1 Week 4[4]	Post-treatment T2 Week 8[4]	Follow-up T3 Week 12[1, 4]	Follow-up T4 Week 16[1, 4]	Follow-up T5 Week 20[4]
DEM[3]	X[3]					X[3]
TAP	X					
TES	X					
CAM-I	X					
HAS	X					
BSR[2]	X		X			X
BADDS[2]	X		X			X
NYU-PR[2]	X		X			X
ISI	X	X	X	X	X	X
Sleep Diaries	X	X	X			X
PSQI	X	X	X			X
BPI	X	X	X			X
HADS	X	X	X			X
MFSI-SF	X	X	X			X
PROMIS	X	X	X	X	X	X

Blood Draw	**X**		**X**			**X**
Time to Complete	**45-60 min**	**15-20 min**	**30-45 min**	**5-10 min**	**5-10 min**	**30-45 min**

(BADDS)-Brown Attention Deficit Disorder Scale; (BPI)-Brief Pain Inventory; (BSR)-Buschke Selective Reminding Task; (CAM-I)-Causal Attributions of my Insomnia questionnaire; (DEM)-Patient Demographics Form (HAS)-Hyperarousal Scale; (HADS)-Hospital Anxiety and Depression Scale; (ISI)-Insomnia Severity Index; (MFSI-SF)-Multidimensional Fatigue Symptom Inventory-Short Form; (NYU-PR)- New York University Paragraph Recall Test; (PSQI)-Pittsburgh Sleep Quality Index; (PROMIS)-Patient Reported Outcomes Measurement Information System; (TAP)-Treatment Acceptability and Preference questionnaire; (TES)-Treatment Expectancy Scale

1. Can be conducted over the phone
2. These measures will only be administered with those patients who report difficulty with memory, attention, and/or concentration at baseline, and consent to cognitive testing.
3. DEM form includes patient's height and weight. At week 20 patient's weight will be re-assessed, patient will not be asked to repeat filling out the demographic form.
4. (+/-) 3 day window

9.0 TREATMENT/INTERVENTION PLAN

Acupuncture: Licensed acupuncturists will administer acupuncture twice per week for two weeks, then weekly for six more weeks, for a total of ten treatments over eight weeks. The first visit to an acupuncturist often involves a more detailed history and an examination that takes an additional 30 minutes so the total contact time is about 330 minutes. A window of +/- 3 days will be allowed for these treatment appointments. Refer to Appendix 1 for acupuncture protocol.

Cognitive Behavioral Therapy for Insomnia (CBT-I): Study therapists will deliver six weekly sessions of CBT-I for six weeks followed by one session two weeks later, for a total of seven sessions over eight weeks. The first CBT-I session lasts 60 minutes and the remaining sessions last 30 minutes, bringing the total contact time to 240 minutes. A window of +/- 3 days will be allowed for these treatment appointments. Refer to Appendix 2 for CBT-I protocol.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

The study schema and study schedule were presented in Section 1.0, Figure 1, and Section 8.0, Table 2, respectively. The following questionnaires (Appendix 4) will be collected according to the study schedule table.

Primary Outcome - Insomnia Severity Index (ISI): We will use patient-reported insomnia severity as measured by the Insomnia Severity Index (ISI) as the primary study outcome. The ISI is one of the few well-validated patient-reported outcome measures designed to specifically assess the impact on daytime functioning and the amount of associated distress.[47] The ISI includes 7 items that are scored on a five-point scale ranging from 0 to 4 with higher scores representing more severe insomnia symptoms. The optimal cutoff scores are 0-7 (no clinically significant sleep difficulties, 8-14

(sleep difficulties warrant further investigation) and 15+ (presence of clinically significant insomnia).[47] The ISI has demonstrated internal consistency, reliability, construct validity, specificity and sensitivity in a representative sample of 1670 cancer patients.[46] The ISI has established minimally important change values to ensure that the change is not only statistically, but also clinically, meaningful to patients.[48] A reduction of eight points has been deemed to be clinically significant improvement.[48] The ISI has been used in several insomnia trials in cancer survivors and has demonstrated sensitivity to change in response to intervention as well as discriminating effects between interventions.

Secondary Sleep Outcomes: The Pittsburgh Sleep Quality Index (PSQI) was specifically designed for use in clinical populations to assess seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) and a global score. It consists of 19 self-rated questions that are scored on a 0 to 3 scale over a period of one month. It has sensitivity and specificity in distinguishing good and poor sleepers. Acceptable measures of internal homogeneity, consistency (test-retest reliability), and validity have been demonstrated.[50,51]

The Consensus Sleep Diary (CSD) provides a night-by-night, self-report of sleep duration, disruption, and perceived quality and will be used to capture more subtle variations in sleep. The sleep diary will be used to calculate sleep efficiency, sleep-onset latency, wake after sleep onset, total sleep time, time in bed, number of awakenings, sleep quality, and terminal wakefulness. Sleep diaries are considered a reliable and valid patient report of nightly insomnia symptoms.[52] Participants will complete the sleep diary daily throughout treatment.

Secondary Comorbid Symptom Outcomes:
Brief Pain Inventory (BPI): An 11-item pain assessment tool for use with cancer patients.[53] The BPI measures both the intensity of pain (sensory dimension) and interference of pain in the patient's life (reactive dimension). It also queries the patient about pain relief, pain quality, and patient perception of the cause of pain. The BPI has a total score and two subscales, pain severity and pain interference. The psychometrics of the BPI is well-established with Cronbach"s alpha ranging from 0.77 to 0.91.

Hospital Anxiety and Depression Scale (HADS): A 14-item, self-rated instrument for anxiety (7 items) and depression (7 items) symptoms in the past week and has been extensively used in people with cancer.[54] Established cutoffs for the depression and anxiety scales are independent and are: 0–7 not significant; 8–10 subclinical; and 11-21 clinically significant depression/anxiety.

Multidimensional Fatigue Inventory-Short Form (MFSI-SF): A 30 item self-report measure comprised of five subscales (general, emotional, physical, mental, vigor) and a total fatigue score. Internal consistency ranges from 0.87 to 0.92 with test-retest reliabilities ranging from 0.51 to 0.70. The MFSI-SF has demonstrated appropriate convergent and discriminant validity.[55] We chose MFSI-SF over the Brief Fatigue Inventory[56] based on feedback from our patient partner advisory panel that mental fatigue was a unique and important consequence on insomnia that was not adequately captured by the other measurement tools.

Patient Reported Outcomes Measurement Information System – Global Health Scale (PROMIS-GHS): The 10-item Patient-Reported Outcomes Measurement Information System Global Health Scale (PROMIS® Global 10) was used to assess key HRQOL domains including pain, fatigue, mental health, physical health, social health, and overall health. Prior psychometric work suggests the presence of two 4-item factors: global physical health (overall physical health, physical functioning, pain, and fatigue) and global mental health (quality of life, mental health, satisfaction with social activities, and emotional problems)[57]. The physical and mental health summary scores will be scored according to PROMIS® instructions and transformed to T-score distributions with a mean of 50 and SD of 10. The PROMIS® T-score metric was set on the basis of a sample that is representative of the U.S. adult population. Higher PROMIS® scores represent better[58]

Assessment of Potential Mediators of Outcome

Treatment Acceptability and Preference (TAP): This measures patient acceptability and preference for treatment and is based on the methodology used by Sidani et al.[59] The specific attributes included in the TAP are: (a) appropriateness (i.e. the treatment option seems logical for addressing insomnia); (b) suitability to individual lifestyle; (c) effectiveness in managing insomnia; and (d) convenience, operationalized as willingness to apply and adhere to the treatment. Each of the four attributes are rated on a 5-point scale ranging from „not at all" (0) to „very much" (5), with higher scores indicating that the treatment option is perceived as appropriate, suitable, and effective, and that the participant would be willing to adhere to it. A total score is computed as the mean of the four items" scores to reflect overall acceptability. This method of eliciting treatment acceptability and preferences was well received by patients and has established internal consistency reliability and factorial validity.[59] An outcomes panel of the patient advisory group has agreed to assist researchers to generate a brief description of the treatment"s purpose, components and specific activities, role of provider, schedule (number of sessions, frequency, and mode of delivery), benefits, and risk of discomfort to ensure that the information is presented in a non-technical, clear and simple to understand manner at a 6th grade reading level.

Causal Attributions of my Insomnia Questionnaire (CAM-I): This is a 12 item self-report measure that presents 12 domains often attributed to contribute to insomnia.[60] These include: sleep related thoughts, hormonal factors, bodily arousal, genetic factors, lifestyle factors, thinking patterns, biochemical factors, environmental factors, scheduling, sleep-related emotions, other emotions, and developmental factors. The questions are rated on a 7-point Likert scale with three anchors, „very likely," „neither likely nor unlikely," and „very unlikely." Responses on the CAM-I have been associated with preference for psychological or biological treatment options. This measure will be particularly important to determine the relative importance or impact of patient beliefs about insomnia on treatment outcome. Each item is assessed separately.

Treatment Expectancy Scale (TES): A 4-item instrument developed by Mao (PI) et al. Outcome expectancy has long been considered an important predictor of treatment outcomes[61] and has gained important consideration in acupuncture in recent years.[62] It has demonstrated reliability (Cronbach"s α of 0.82) and validity and is positively correlated with patient self-reported efficacy and satisfaction.[63] The TES has also been validated in breast cancer survivors and is sensitive to change over time in response to acupuncture treatment.[64] In our previous study, we found expectancy was stable overtime in the waitlist control group.[65] Baseline expectancy predicted

treatment outcomes of acupuncture. We will modify the TES for CBT by changing the word "acupuncture" to "Cognitive Behavioral Therapy." A single total score is calculated.

Hyperarousal Scale (HAS): A 26 item measure of self-reported behaviors commonly exhibited in individuals with insomnia and has been validated against objective measures of EEG arousal. [66] Items are rated on a four point Likert scale ranging from „0-not at all" to „3-extremely." Considering that insomnia is characterized by 24 hour hyperarousal in which perceived stress can initiate and maintain sleep difficulty in patients with pre-existing levels of elevated emotional, cognitive, and physiological arousal,[67,68] it is relevant to determine how levels of hyperarousal may impact treatment outcomes. A single total score is provided.

Cognitive Measures:

Brown Attention Deficit Disorder Scale (BADDS): The BADDS is a 40-item scale that measures a range of symptoms related to attention. The items are scored on a 4-point scale (0 = never, 1 = once a week or less, 2 = twice a week, 3 = almost daily) and are grouped into five subscales: 1 (Organizing and Activating to work), 2 (Sustaining Attention and Concentration), 3 (Sustaining Energy and Effort), 4 (Managing Affective Interference), and 5 (Utilizing Working Memory and Accessing Recall). A total score is also calculated. The BADDS has been used to assess attention in peri- and post-menopausal women and has demonstrated sensitivity to change. [69]

Buschke Selective Reminding Test (BSR): The BSR is a validated measure of memory retention and retrieval. Subjects are read a list of 16 words and asked to recall as many as possible in a total of 6 trials immediate recall) and 20 minutes after completion of the sixth trial (delayed recall). Words are substituted from a standard set so that each word list is completely different each assessment time. The Total Recall is the sum of Short-term Recall and Long-term Recall. Performance on the Buschke was previously found to vary by age and impairment status. [70,71]

New York University Paragraph Recall (NYU-PR): The NYU-PR test is a verbal memory measure that is one component of the Guild Memory Test. [72] It consists of a short paragraph presented verbally and measures encoding of contextual information. Participants are asked to recall the paragraph verbatim following immediate and 30-minute delays. No credit is given for gist responses. Scores range from 0–21 on both immediate and delayed portions of the test. Alternate forms are used to avoid practice effects on re-testing. [73]

Blood Samples: Samples will be labeled with the subject's study ID, the date that the sample was drawn and type of the blood sample. The laboratory technicians will keep a log with the specimen information, conditions, processing, and storage information.

11.0 TOXICITIES/SIDE EFFECTS

Potential Risks: Patients will be monitored for side effects at each visit. Adverse effects related to the administration of acupuncture or CBT-I will be collected each week before and after each treatment by the acupuncturist/therapist or research study assistant.

Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. It will be further explained that while some risks are not predictable, every precaution consistent with the best medical practice to protect the health and safety of subjects will be taken. We will document all adverse events and report any related serious adverse events promptly to the IRB.

Risk of Acupuncture and CBT-I: The risks associated with acupuncture and CBT-I are minor, and there are very few serious side effects. The most common side effects of acupuncture are mild pain on insertion of the needle, occurring at rates twice that of the placebo group. There is a possibility of a small amount of bleeding or bruising and very rarely infections at the site of insertion. Every effort will be made to ensure the safety and comfort of the research subjects, including wiping the needling site with alcohol before the procedure and wiping the needling site with sterile gauze. The most common side effects of CBT-I are short-term (less than 2 weeks) increases in daytime sleepiness and mood disturbance. The acupuncture and CBT-I will be delivered by experienced professionals under the supervision of senior faculty psychologists. Every effort will be made to ensure the safety and comfort of the research subjects. Adverse events will be recorded during each clinical visit. Any SAEs will be reported to the IRB within 5 calendar days of the event.

Risk of Blood Draw: A small number of people find blood draws very uncomfortable. Risks and discomforts involved in having blood drawn are pain and bruising where the needle enters the skin and the possibility of infection or fainting. Standard of care procedures will be followed to minimize these risks.

Confidentiality Risks: Information about study subjects will be kept confidential and managed according to the requirements of the Health Information Portability and Accountability Act (HIPAA). The paper data files will be kept in locked cabinets and electronic files will be kept in password protected computers. The data will be disclosed to the IRB upon request for regulatory and data safety monitoring. Secondary use of the data will not be attempted after the study ends without subsequent IRB approval.

Risk of psychological distress: It is possible that subjects may be upset to find out that they are randomized to their non-preferred arm of the study. With appropriate consent and the debriefing process, such risks are minimized. Subjects will be informed that they are participating in an experimental study to determine the comparative effectiveness of acupuncture or CBT for insomnia. They have the chance to be randomized to either intervention. At the end of the study, subjects will be offered the opportunity to discuss the findings with the PI. In addition, some of the questions in the questionnaire may elicit distress among subjects. At the baseline examination, patients will be screened for any elevated anxiety and depression or suicidal ideation/plan. If the subject demonstrates clinically significant distress, she/he will be referred to the psychosocial counseling services at each study site. During the study period, if the research staff identifies any patients who are psychologically distressed they will notify the study PI immediately to facilitate appropriate evaluation and treatment.

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Our primary outcome measure is the Insomnia Severity Index (ISI), which will be measured at baseline, mid-treatment, post-treatment, 1-month, 2-month and 3-month follow-up visits. Our hypothesis is that between Acupuncture and CBT, one treatment will result in greater overall reduction in insomnia measured by the ISI. Our secondary outcomes will be measured by Brief Pain Inventory (BPI), Brief Fatigue Inventory (BFI), Hospital Anxiety and Depression Scale (HADS) (see Section 10.0), etc. Our hypothesis is that between Acupuncture and CBT-I, one intervention will result in greater improvement in pain, fatigue, and psychological distress than the other intervention for patients reporting insomnia.

13.0 CRITERIA FOR REMOVAL FROM STUDY

Any subjects experiencing a serious adverse event felt to be related to study intervention will be withdrawn from the study. Subjects will be withdrawn if they miss two consecutive acupuncture or CBT-I visits without notification of study staff, or if discontinuation from the study is deemed by the principal investigator to be in their best interest. Sometimes, cancer patients have unexpected medical visits or family events, if they miss two visits, but let study staff/PI know, we can reschedule their visits. Based on our experience doing these types of interventions, as long as patients get adequate sessions of treatments, their therapeutic outcomes should be optimal. Any subject withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study. Subjects discontinued from the clinical trial will be scheduled for a final evaluation and given appropriate treatment referrals. For the final visit, subjects will receive all assessments that were scheduled for the end of study visit.

Subjects will be informed at the consent session that treatment may be discontinued due to:

1) Intolerable side effects (side effects felt by the patient, therapist, acupuncturist or physician to be of greater severity than the potential benefit from treatment);
2) Failure to attend 2 consecutive acupuncture or CBT-I visits without notification of study staff;
3) Failure to complete questionnaires.

If patients fail to attend sessions with notification, every effort will be made to reschedule the patient such that they can receive the maximum number of treatments.

Reasons why subjects are discontinued from the clinical trial will be documented on the Study Termination Form, along with any referrals that are made. Every effort will be made to continue to collect data on every subject for the entire study duration regardless of whether or not the subject continues to adhere to the study interventions, assuming the subject has not withdrawn his/her authorization to obtain such information.

14.0 BIOSTATISTICS

Quantitative Data Analysis Plan

De-Identified data and biospecimens from the University of Pennsylvania study will be submitted to MSKCC to combine databases for our final dataset.

Descriptive Statistics: Standard descriptive statistics will be used to report baseline participant characteristics. Summary statistics such as means, medians, standard deviations, and ranges will be produced for measured variables. Frequencies will be tabulated for categorical and ordinal variables. Graphical methods will be used extensively to examine distributions, identify potentially influential points, and guide data transformations if warranted. For continuous variables with markedly non-normal or skewed distributions, appropriate transformations may be required, such as natural logarithms, and will be applied as necessary and appropriate. In the sections below, we will assume, when discussing particular outcomes, that the appropriately transformed variables will be used. We will perform analysis according to the intention-to-treat (ITT) principle (i.e. participants will be analyzed according to the treatment group to which they will be randomly allocated regardless of drop-out or treatment adherence status).

Primary Aim Hypothesis Testing: To evaluate the comparative effectiveness of acupuncture vs. CBT-I for insomnia and comorbid symptoms. *Primary Hypothesis:* Between Acupuncture and CBT-I, one treatment will result in greater overall reduction in insomnia measured by the Insomnia Severity Index (ISI). The primary endpoint is ISI at week 8. The primary comparison will be ISA difference between groups at week 8. We will use mixed-effects models and will include ISI measures at all time points to address this primary hypothesis. Time by treatment interaction will be included in the mixed-effects models in order to obtain the between group difference of ISI at week 8. *Secondary Hypothesis*: Between acupuncture and CBT, one intervention will result in greater improvement in pain, fatigue, and psychological distress than the other intervention for patients reporting insomnia. Since our primary outcome (ISI) will be repeated over time, we will use mixed-effects models to examine the primary hypothesis. [74] This statistical procedure takes into account within-subject correlations from repeated measurements in the same subjects and allows estimation of between-group difference without necessitating last observation carried forward or exclusion of participants with missing data. Tests of ITT differences between intervention arms with respect to change of ISI will be based on time-intervention interactions in the mixed-effects models. Although randomization theoretically balances the potential confounders between treatment groups, occasional unequal distribution can be seen. Should this happen, we will perform sensitivity analyses to evaluate the effect of confounding by including the potential confounders as co-variates in the models. [75] For secondary and exploratory hypotheses, we will use similar analytical strategies co-morbid symptoms (pain, fatigue, anxiety and depression), QOL, and cognitive dysfunction.

Missing Data: As the only certain way to avoid biases from missing data is to collect complete data,[76] our first line of defense will be to minimize the occurrence of missing observations, using well-constructed study design with patient input, well-trained research staff and acceptable subject burden,[77] as demonstrated by our preliminary data. [78] We have and will continue to engage our patient partners to help us understand the clinical trial experience from the patient perspective and decrease the barriers to recruitment/retention by providing treatment at convenient time for the patient. Next, we will ask those who would potentially withdraw from intervention to continue to provide data and reimburse them for completing the evaluation. Lastly, for those who voluntarily withdraw from the study, we will record their reasons for withdrawing and use this information in the sensitivity analyses. Because missing data is inevitable in a prospective study like this, our second line of defense is to apply data analysis strategies that are as robust as possible to data losses. No

universal method exists for handling missing data in clinical trials. [76] We will perform sensitivity analyses to evaluate the robustness of our results. Initially, we will perform compete-case analysis (participants with missing data are simply excluded from the analysis). We will then apply single imputation methods such as last-observation and baseline carry forward analyses. Lastly, we will perform multiple imputation analyses. When estimating models by maximum likelihood, inferences retain their validity under the assumption of missing at random (MAR), which asserts that the probability an observation is missing, given all the observed data items, does not depend on the value of the potentially missing data item. This is a weaker assumption than missing completely at random (MCAR), which is the broadest general sufficient condition for validity of inferences in frequentist analysis methods. While it is generally impossible to test whether MAR is a valid assumption, one can readily assess the sensitivity of maximum likelihood estimates to departures from MAR using the Index of Sensitivity to Nonignorability (ISNI), a class of methods developed by Heitjan et al. [79,80] These sensitivity analyses will not replace the primary findings of ITT, but will enhance the understanding/interpretation of our data. Patient partners will be engaged as we present our primary and secondary analyses to ensure our interpretation of data remains patient-centered.

Secondary Aim: Heterogeneity of treatment effect (HTE): We will conduct HTE analyses to identify patient-level demographic characteristics (e.g. sex[81]), clinical factors (e.g. pain,[82] time since diagnosis, time since cancer therapy completion), and psychological attributes (e.g. preference and expectancy[41]) that are associated with improved ISI scores at Week 8 in acupuncture or CBT-I. To be specific, factors that predict better outcomes regardless of treatment assignments are considered predictive factors. Factors that predict outcomes for one treatment (e.g. acupuncture), but not the other (e.g. CBT-I) are considered prognostic factors.[83] In a clinical trial such as ours, continuous outcomes provide the greatest statistical power to detect an effect, especially potential effect modification between baseline characteristics and treatment groups; however, our patient partners suggested that this may not be as patient centered or as clinically meaningful as using a dichotomous outcome of treatment response. In reviewing the literature[34] and, consulting with patient partners, we will define treatment responders as those patients with an ISI change score compared to baseline of >8 points. We will consider participants to be remitted from their insomnia if their absolute ISI score is <8. We intend to approach the evaluation of HTE based on existing literature and patient/clinician input as well as important knowledge gained from the qualitative study. Our current focus of evaluating and reporting HTE will be based on the approach proposed by Kent et al.[84] Based on the conceptual model, past literature, and patient input, we are going to select four actionable variables as primary subgroup analyses. These variables are gender, presence of pain at four or greater, outcome expectancy, and preference score. The rest of the sub-group analyses will be exploratory and these will include socio-demographic (e.g. age, race/ethnicity, education, and marital/partner status), clinical (time since diagnosis, time since cancer therapy completion, insomnia severity, depression, anxiety, fatigue, and sleep apnea symptoms), and psychological (insomnia beliefs, hyperarousal) factors.

We will carefully examine the data descriptively stratified by sub-groups using tables and appropriate graphs. Logistic regression will be used to examine predictors of treatment response. We will initially examine the main effect of key patient characteristics associated with the dependent outcome. Then we will test whether specific characteristics will interact with treatment groups (acupuncture vs. CBT)

in impacting outcomes by adding an interaction term. Once we have done preliminary analyses, we will bring in patient partners for a data analyses and interpretation meetings to maximally incorporate their perspective as we interpret the statistical outputs. Subgroup analyses and HTE is an area of uncertainty in clinical research [85,86] without clear guidelines. [87] However, by pre-specifying primary subgroup analyses and using multivariate regression modeling with interaction terms, we will minimize the possibility of false positive results. [84,88,89] As we publish our results, we will caution readers/patients that these are exploratory and require caution in interpretation. With that acknowledged, the HTE is probably the most patient-centered given that patient will have a more nuanced perspective whether for his/her type of person, one treatment will be more effective than the other. As we conduct this research, we will learn together with our patient-partners to develop more matured methodologies to guide future patient-centered outcomes comparative effectiveness research.

Sample Size Considerations: Our sample size is based on our primary hypothesis and primary outcome of Insomnia Severity Index (ISI). Since the ISI is a continuous outcome, we powered our trial using independent t-test for score at the end of Week 8. This is a conservative way to estimate sample size since the longitudinal analysis using the mixed-effects model specified in the analysis plan will provide higher power than a t-test. Based on our preliminary research with CBT-I in cancer, ISI score decreased from baseline 17.8 to 8.3 with SD of 3.7 at end of CBT-I treatment. [90] If we hypothesize that the post-treatment effect difference between acupuncture and CBT-I is 1.85 (0.5 SD of observed ISI in CBT-I group), this will provide a Cohen"s *d* of 0.5 (moderate effect size). We estimated that the difference between the two treatments would be half of the effect observed for CBT-I alone which would provide adequate strength to detect a difference between the two groups. Sample size was not based on what has been considered a clinically meaningful change within groups (e.g. and 8 point reduction). With power of 0.8 and two-sided alpha of 0.05, we will need 64 participants per treatment group and 128 in total to detect this effect size of 0.5. Accounting for a 20% potential attrition, we will need to enroll 160 participants to reach our recruitment target. We accounted for attrition in sample size calculations because our sample size calculation was based on complete data and was a conservative estimate. In the actual analysis, we will use all patient data including patients without complete data according to ITT principle. Based on discussion with our patient partners, insomnia and co-morbid symptoms are highly subjective and patient preference plays a key role in choosing what therapies they would like. We feel that a moderate effect would be required to influence patients" pre-treatment preference of acupuncture or CBT-I. If acupuncture is only slightly better than CBT-I with very small effect size, it is unlikely a patient would choose acupuncture over CBT-I even knowing that acupuncture will produce a small benefit if a patient"s prior preference is CBT-I. With that stated, our research might miss detecting small effects between acupuncture and CBT-I. For our secondary aim, since the sample size is fixed, the effect size of sub-group analyses will be determined by the distribution of predictors and outcomes from the trial. Before approaching sub-group analyses, we will perform effect size estimations. These analyses will be conducted in conjunction with the stratified qualitative data interpretation to explore important sub-group differences that can guide future research, clinical innovation, and personalized care.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.2 Randomization

Randomization for the full sample size (n=160) was already prepared by the University of Pennsylvania with a randomization list for 200 treatment assignments if necessary. MSKCC participants will be taking the 40 randomization slots (121-160) and will be allocated as per those 40 slots (20 acupuncture slots and 20 CBT-I slots are identified in these randomizations). Patients will be blinded to randomization until completion of baseline questionnaires.

16.0 DATA MANAGEMENT ISSUES

The Research Study Assistant will be responsible for project compliance, data collection, abstraction and entry, data reporting, regulatory and quality control monitoring, problem identification and prioritization. Coordination of study team activities will be the responsibility of our Research Supervisor and/or Research Manager.

All data and forms gathered for this study will be collected and stored in a secure location in the facilities of the Integrative Medicine Service. The data collected for this study will be entered into a secure database (CRDB), a study Excel database and into study Access Databases. Source documentation will be available to support the computerized patient data. The confidentiality of patient information will be carefully protected. Following data entry by Integrative Medicine Service research staff, data will be maintained in a secure location in the Integrative Medicine offices.

The questionnaires that patients fill out for this protocol will not be IRB stamped documents. The questionnaires will not be changed from their IRB stamped counterparts, but in order to use these questionnaires, we need to have them in Microsoft Word format. The software (AutoData Scannable Office) we will use takes these Microsoft Word documents, and prints them with a patient specific barcode at the bottom. After the patient fills it out, the original questionnaire can be scanned into this software, and the software reads and records the patients answers in a Microsoft Access database, where the data will ultimately be stored.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://cancertrials.nci.nih.gov/researchers/dsm/index.html. The DSM Plans at MSK were established and are monitored by the Office of Clinical Research. The MSK Data and Safety Monitoring Plans can be found on the MSK Intranet at: *http://mskweb2.mskcc.orglirb/index.htm*

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

In addition to MSK‟s DSM, this study also has an independent Data and Safety Monitoring Board (DSMB) which was required by the funding agency PCORI. This DSM will monitor the Penn site. In order to assess possible changes in risk/benefit ratio to study subjects and to obtain independent oversight of the study conduct (including review of the consent form, protocol, subject requirement and retention, AE reporting, SAE reporting, procedures for handling patients who have symptom worsening), external safety monitors will be invited to oversee the progress of the study: (1) Roger Cohen, MD, Professor of Medicine, Division of Hematology-Oncology, Department of Medicine, Perelman School of Medicine, University of Pennsylvania, (2) Tavis Campbell, PhD, Professor of Psychology, Department of Psychology, University of Calgary, and, (3) Sarah Ratcliffe, PhD, Associate Professor of Biostatistics, Center for Clinical Epidemiology & Biostatistics at the University

of Pennsylvania. These DSMB members will review and monitor the study procedures, study risks, risk/benefit ratio, patient enrollment, and any study-related SAEs. All SAEs will be reviewed by the DSMB members in order to determine whether additional safety measures should be initiated, or whether there is a change in the risk / benefit ratio for study subjects. External DSMB oversight and study review will be conducted at 6-month intervals between the PI and DSMB members by direct meetings or by regular teleconferencing and e-mail correspondence. It is expected that the DSMB experts will be available to the PI and other study personnel regarding emergency issues, changes in research design, and for other regulatory and clinical questions.

17.0 PROTECTION OF HUMAN SUBJECTS

Potential Risks and Protection against Risks (See Section 11.0 Toxicity/Side Effects):

Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in an informed consent form, and will also be fully discussed with each subject prior to enrollment. We will also explain to each subject that in the unlikely event of physical injury directly resulting from the research procedures, every effort will be made to make available the facilities and professional skills of MSK. It will be further explained that while some risks are not predictable, every precaution consistent with the best medical practice to protect the health and safety of subjects will be taken. We will document all adverse events and report any serious adverse event promptly to IRB and DSMB.

Risk of Acupuncture and CBT-I: The risks associated with acupuncture and CBT-I are minor, and there are very few serious side effects. The most common side effects of acupuncture are mild pain on insertion of the needle, occurring at rates twice that of the placebo group. There is a possibility of a small amount of bleeding or bruising and very rarely infections at the site of insertion. Every effort will be made to ensure the safety and comfort of the research subjects, including wiping the needling site with alcohol before the procedure and wiping the needling site with sterile gauze. The most common side effects of CBT-I are short-term (less than 2 weeks) increases in daytime sleepiness and mood disturbance. The acupuncture and CBT-I will be delivered by licensed and experienced professionals. Every effort will be made to ensure the safety and comfort of the research subjects. Adverse events will be recorded during each clinical visit. Any related SAEs will be reported to the IRB.

Confidentiality Risks: Every effort will be made to maintain confidentiality of the study subjects. Research and hospital records are confidential. Subject's names or any other personally identifying information will not be used in reports or publications resulting from this study. Authorized agencies (e.g., qualified monitors from PCORI etc.), and appropriate personnel may review subject's records as required. All forms are kept in a locked file cabinet when not in use. Clinical data will be kept in a centralized database with restricted access to study personnel. Data will be entered into MSK's clinical research database (CRDB), a study excel file, and study Access Databases on a secure MSK shared drive. Individual identifying information will be omitted from figures used in publications resulting from this research.

Risk of psychological distress: It is possible that subjects may be upset to find out that they are randomized to their non-preferred arm of the study. With appropriate consent and the debriefing process, such risks are minimized. Subjects will be informed that they are participating in an experimental study to determine the comparative effectiveness of acupuncture or CBT for insomnia. They have the chance to be randomized to either intervention. At the end of the study subjects will be offered the opportunity to discuss the findings with the PI. In addition, some of the questions in the questionnaire may elicit distress among subjects. At the baseline examination, patients will be screened for any elevated anxiety and depression or suicidal ideation/plan. If the subject demonstrates clinically significant distress, she/he will be referred to the psychosocial counseling. During the study period, if the research staff identifies any patients who are psychologically distressed they will notify the study PI immediately to facilitate appropriate evaluation and treatment.

Costs: Study related procedures and visits will be provided to the subjects at no cost. To encourage adherence to the study procedures, we will provide $20 at the first, second, and third evaluation time points with an additional $40 for completion of the final assessment (total of $100 per participant). Compensation will be in the form of gift cards.

Potential Benefits:

Subjects who receive acupuncture or CBT-I may experience an improvement in their insomnia and/or other cancer-related co-morbidities (e.g. pain, fatigue, mood disturbance). Improving insomnia and other problematic symptoms often leads to an improvement in overall physical and emotional well-being.

Alternatives to Participation:

If patients do not enroll in this study, they may contact their personal physicians to discuss other treatments for insomnia.

Risk/Benefit Ratio:

The potential benefits of this study far outweigh the potential risks. Insomnia is a common and debilitating symptom that is experienced by many cancer survivors. The results of the proposed study will have an immediate impact to help cancer survivors and their caregivers make informed and evidence-based decisions about how to most effectively address cancer-related insomnia and co-occurring symptoms. Thus, this study has the potential to improve symptom burden and wellbeing for millions of individuals whose life is impacted by cancer. This research also has the potential to generalize to other chronic conditions and the population at large. We will carefully monitor any adverse events related to acupuncture and CBT-I, and minimize the risks for research subjects.

17.1 Privacy

MSK"s Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health

information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is considered serious if it results in ANY of the following outcomes:

- Death
- A life-threatening adverse event
- An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect
- Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition

Note: Hospital admission for a planned procedure/disease treatment is not considered an SAE.

SAE reporting is required as soon as the participant signs consent. SAE reporting is required for 30-days after the participant's last investigational treatment or intervention. Any events that occur after the 30-day period and that are at least possibly related to protocol treatment must be reported.

If an SAE requires submission to the IRB office per IRB SOP RR-408 „Reporting of Serious Adverse Events", the SAE report must be sent to the IRB within 5 calendar days of the event. SAE's classified as unrelated to the study intervention (per section 11.0) will not be considered reportable to the IRB and will not have a corresponding Clinical Research Database (CRDB) SAE report generated. The IRB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office as follows:

For IND/IDE trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to saemskind@mskcc.org.

For all other trials: Reports that include a Grade 5 SAE should be sent to saegrade5@mskcc.org. All other reports should be sent to sae@mskcc.org.

The report should contain the following information:

Fields populated from CRDB:

- Subject's initials
- Medical record number
- Disease/histology (if applicable)

- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- The grade of the event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
    - A explanation of how the AE was handled
    - A description of the subject"s condition
    - Indication if the subject remains on the study
- If an amendment will need to be made to the protocol and/or consent form
- If the SAE is an Unanticipated Problem

The PI's signature and the date it was signed are required on the completed report.

For IND/IDE protocols:
The CRDB SAE report should be completed as per above instructions. If appropriate, the report will be forwarded to the FDA by the SAE staff through the IND Office

17.2.1 Not Applicable

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In

addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

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20.0 APPENDICES

Appendix 1: Acupuncture protocol

Appendix 2: CBT-I protocol

Appendix 3: Multivariable Apnea Prediction (MAPS) Index

Appendix 4: Patient Reported Outcome Measures

Appendix 5: Blood Processing and Shipping

Appendix 6: Recruitment Letter

Appendix 7: Recruitment Flyer

Appendix 8: Recruitment Rack Card

Appendix 9: Tips for Healthy Sleep