URCC / UNIVERSITY OF ROCHESTER
NCORP RESEARCH BASE

A Randomized Clinical Trial Comparing the Effectiveness of Yoga, Survivorship Health Education, and Cognitive Behavioral Therapy for Treating Insomnia in Cancer Survivors

URCC Protocol: URCC14040
NCT number: *NCT02613364*

Study Chair: **Karen M. Mustian, Ph. D., M.P.H.**
URCC NCORP Research Base
University of Rochester School of Medicine

Study Co-Chairs: **Michelle Janelsins, Ph.D., M.P.H.**
Luke J. Peppone, Ph.D., M.P.H.
Supriya G. Mohile, M.D., M.P.H.
Wilfred Pigeon, Ph.D.
Charles Kamen, Ph.D.
Gary R. Morrow, Ph.D., M. S.

Heather Bowles, Ph.D.
National Cancer Institute

Judith O. Hopkins, M.D.
Southeast Clinical Oncology Research Consortium

Biostatistician: **Charles E. Heckler, Ph.D., M.S.**
Eva Culakova, Ph.D., M.S.
Victor Kipnis, Ph.D.
National Cancer Institute

Participating Institutions: NCORP Community Sites Affiliated with the University of Rochester NCORP Research Base

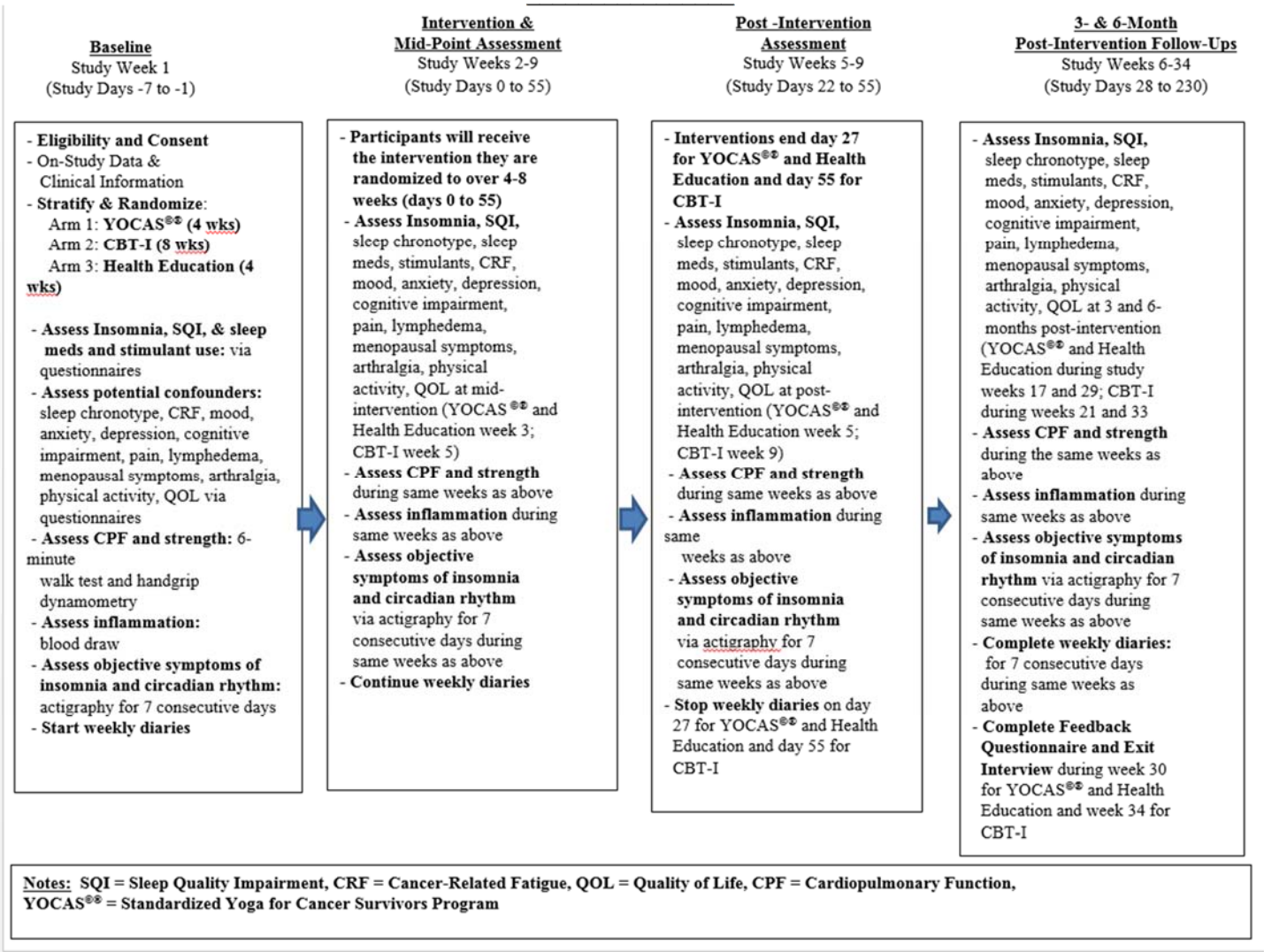
Initial Version: 24-Jun-15
Amendment 1 Version: 23-Sep-15
Amendment 2 Version: 05-Feb-16
Amendment 3 Version: 17-Mar-17
Amendment 4 Version: 12-Feb-18
Amendment 5 Version: 07-Jun-18

Protocol Resources

URCC NCORP Research Base: Saunders Research Building 265 Crittenden Blvd CU 420658 Rochester, NY 14620	phone: 585-275-1364 fax: 585-461-5601 website: http://www.urcc-ncorp.org/
Study Chair:	Karen M. Mustian, Ph.D., M.P.H. URCC NCORP Research Base
Study Co-Chairs:	Michelle Janelsins, Ph.D. M.P.H. URCC NCORP Research Base
Biostatistician:	Charles Heckler, Ph.D., M.S. URCC NCORP Research Base
Regulatory Contact:	Cathy Lesniewski 585-275-2282 cathleen_lesniewski@urmc.rochester.edu
Website/Registration Contact:	Sebastien Estaque 585-275-2044 sebastien_estaque@urmc.rochester.edu
Protocol Contact & Data Submission:	Libby Nagalski 585-275-1364 elizabeth_nagalski@urmc.rochester.edu

TABLE OF CONTENTS

Study Schema



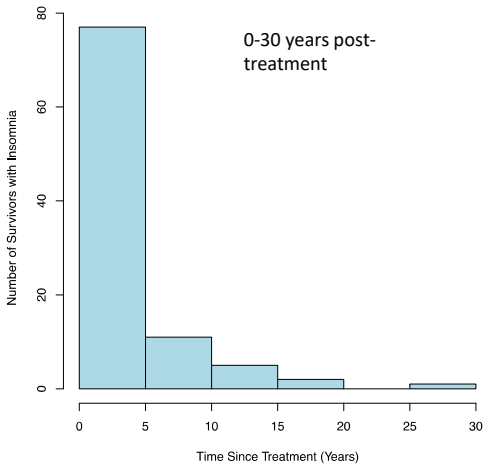
Notes: SQI = Sleep Quality Impairment, CRF = Cancer-Related Fatigue, QOL = Quality of Life, CPF = Cardiopulmonary Function, YOCAS®Ⓢ = Standardized Yoga for Cancer Survivors Program

1.0 Introduction

Sleep Problems and Cancer: The vast majority of cancer survivors, up to 90%, report some form of sleep quality impairment (SQI) post-treatment, such as excessive daytime napping, difficulty falling asleep, difficulty staying asleep, and waking up too early.[1-10] These SQI are also symptoms of insomnia, which is defined as one or more of these symptoms in severe and persistent form. Insomnia and SQI are among the most prevalent and distressing problems reported by cancer survivors and can be severe enough to increase cancer mortality.[1-11] Cancer survivors also demonstrate dysregulated circadian activity rhythms, impaired physical function (i.e., cardiopulmonary and muscular function) and chronically up-regulated inflammatory responses when their sleep is compromised. [4,5,12-48] Despite the ubiquity of insomnia and SQI, they are under-diagnosed and under-treated in cancer survivors.[1-11,48]

Previous research demonstrates that insomnia can begin before cancer treatment,[4,5] continue during treatment,[3,49] and persist for years after treatments are completed.[6,50] Approximately, two thirds of cancer patients who experience insomnia acutely while receiving treatments will develop chronic insomnia that persists for years into survivorship.[3,50] Recent data from a local randomized clinical trial led by Dr. Roscoe and investigators in our URCC NCORP Research Base shows that **80% of cancer survivors recruited for this study report experiencing persistent insomnia during the first 5 years after completion of surgery, chemotherapy and/or radiation therapy.[51-53] See Figure 1. Patients reported that insomnia began during the time they were receiving treatments for their cancer and persisted up to 30 years into survivorship.[51-53] Collectively, prior research[3-6,49,50] and our new data suggest that the insomnia we propose to study, during the first 5 years post-treatment, is related to cancer and its treatments.**

Figure 1: Number of Survivors Reporting Persistent Insomnia Post-Treatment



Data from Dr. Roscoe and colleagues also suggests that cognitive behavioral therapy for insomnia (CBT-I) is effective for treating persistent insomnia ($p < 0.05$) among these survivors and that the number of years since completing primary treatments for cancer has no impact on the efficacy of CBT-I ($p > 0.05$).[51-53] Formally intervening with a behavioral treatment for insomnia was both necessary and helpful for cancer survivors regardless of number of years since completion of primary cancer treatments.[51-53] This is supported by other research suggesting that persistent insomnia does not resolve on its own and requires formal intervention.[3,50,54,55] Finally, we note that the NCCN guidelines for cancer survivors specifically recommend formally intervening among cancer survivors to alleviate insomnia with no designated cut-off in terms of years since completion of treatment.[56]

Treatment options for insomnia include: 1) pharmaceuticals, which do not cure insomnia and can lead to toxicities, negative interactions with cancer therapeutics, dependency, and rebound impairment after discontinuation, 2) traditional exercise, which is recommended in treatment guidelines, but not widely implemented in survivorship care plans beyond the use of generalized statements in which survivors are encouraged to be physically active and exercise, and 3) psychobehavioral interventions.[1-10] Cognitive Behavioral Therapy for Insomnia (CBT-I) is the gold standard psychobehavioral treatment for insomnia for the general population, and it is efficacious for treating insomnia among cancer survivors.[57,58]

Yoga is a well-tolerated exercise intervention with promising preliminary evidence for its efficacy in improving insomnia and SQI among cancer survivors. Our research and that of others suggest that yoga may improve insomnia and SQI by regulating circadian activity rhythms, improving physical function (i.e., cardiopulmonary and muscular function) and decreasing inflammation.[14,59-73] We conducted—to our knowledge—the first multicenter, phase III, randomized, controlled trial (RCT), in 410 cancer survivors from 12 community oncology practices throughout the U.S., showing that

our standardized yoga intervention (YOCAS©®: 4 wks., 2x/wk., 75 min./session) produced significant moderate to large improvements in insomnia and SQI while also improving circadian activity rhythms. Yoga participants decreased sleep medication use, while control participants increased sleep medication use. Adherence to YOCAS©® was relatively high at 80%, and there were no study-related adverse events. All (100%) participants found the YOCAS©® program useful and would recommend it to other cancer survivors experiencing sleep problems.

In response to NCI research priorities and PA 11-260, we proposed a follow-on study that aligns with NCI research priorities to develop effective supportive care interventions for survivors. We proposed a multicenter, 3-arm, blinded, phase III RCT to fill remaining empirical gaps by comparing the effectiveness of ARM 1) our standard YOCAS©® program, ARM 2) standard CBT-I, and ARM 3) a health education intervention controlling for time and attention for improving insomnia in 720 cancer survivors 2-60 months following adjuvant treatment. We will also explore three possible mechanisms through which YOCAS©® may improve insomnia—circadian activity rhythms, physical function (i.e., cardiopulmonary and muscular function) and inflammatory immune responses—based on our biobehavioral model.

Innovation: This study is innovative because it is the first multi-center, phase III, blinded, RCT to test: 1) the effectiveness of YOCAS©® compared to CBT-I and a health education control for improving insomnia and SQI, 2) the 3- and 6-month sustainability of insomnia benefits from YOCAS©®, and 3) the role of possible functional and biological mediators in the efficacy of YOCAS©®. CBT-I is an effective gold standard treatment for the general population—this trial will provide pivotal scientific data to determine if YOCAS©® should be considered a gold standard treatment option for insomnia in cancer survivors. In addition, this is the first study to examine the associations between both 24- and 12-hour circadian activity rhythms using a multi-oscillating model, physical function, cytokines, yoga and sleep in cancer survivors. We are not aware of any other group doing this work.

2.0 Background

If YOCAS©® is shown to be as effective as or more effective than CBT-I and more effective than health education and if insomnia improvements are sustained 3 and 6 months later from the yoga intervention, the benefits for cancer survivors would include: 1) an additional evidence-based, safe, non-pharmacological, effective, low-cost, enjoyable treatment for insomnia—possibly a new gold standard treatment option; 2) a standardized yoga therapy that can be explicitly prescribed and reproducibly disseminated in communities as part of survivorship care plans for the treatment of insomnia; and 3) a better understanding of the functional and biological pathways through which YOCAS©® works to improve insomnia in order to further refine its effective use and applicability in various cancer populations.

Yoga—A Holistic Mind-Body Mode of Exercise: The many different styles and types of yoga are based on Eastern traditions from India (e.g., Classical, Advaita Vedanta, Tantra), Tibet (e.g., Tibetan), and China (e.g., Chi Kung, Tai Chi).[61,74,75] The word yoga is derived from its Sanskrit root "yuj," which literally means "to yoke" or join together. In this case, yoga refers to joining the mind and the body.[61,74,75] The earliest forms of yoga were firmly rooted in physical and mindful (breathing and meditative) practices and led to what is known today as classical yoga which forms the basis for most of the yoga currently taught in the U.S.[74]

Yoga, Sleep Quality Impairment and Insomnia: The existing evidence suggests that yoga is effective for improving SQI, but we were unable to find published studies that specifically addressed the effects of yoga on insomnia in cancer survivors. In addition, no studies in cancer compared the effects of yoga on SQI to a proven effective gold-standard treatment for insomnia or SQI, examined the long-term durability of effects, or examined potential mechanisms of action through which yoga may improve insomnia or SQI.[14,59-61,64,65,71,73,76]

Yoga Program Evaluations: Four evaluations of community yoga programs for cancer patients and survivors suggest that yoga may improve SQI.[62,63,69,70] These yoga programs were based in cancer centers or community-based yoga studios and offered yoga classes specifically for cancer patients receiving treatment and survivors who had completed treatments. The yoga classes included a wide variety of postures and mindfulness exercises from different types of yoga, and they were offered 1-2 times a week for 60-90 minutes. Participants in two of these programs also attributed improvements in strength, physical function, and physical fitness to their yoga practice.[62,70] However, these

reports utilized convenience samples and did not use research methods designed to answer specific scientific questions about the effects of yoga on SQI. These programs also did not use standardized yoga interventions that can be accurately and consistently replicated for dissemination and use in the treatment of insomnia or SQI. **Therefore, this study will be a confirmatory phase III RCT and will use our standardized yoga intervention, YOCAS©®.**

Phase I and II Pilot Studies: One phase I and five phase II studies provide preliminary support for the safety, feasibility and efficacy of yoga for improving SQI among cancer patients and survivors (See Table 1).[59,61,71,73,76] These studies assessed a range of yoga doses from 1-2 sessions/week with classes lasting 50-120 minutes using a variety of different types of yoga over 4-12 weeks. The interventions included a variety of postures and mindfulness exercises. The interventions were deemed safe and feasible for cancer patients receiving treatment and survivors. Participants enjoyed the yoga interventions and in four studies reported improvements in SQI; two studies showed no changes in SQI.[60,76] Three of the phase II RCTs compared yoga to a waitlist control, one to a support therapy control condition and one to a health education control condition.[59-61,73,76] The latter two studies suggest that yoga may be more effective for improving SQI than counseling, health education, time and attention. Using YOCAS©® we conducted the first—to our knowledge--phase III RCT demonstrating the efficacy of yoga for improving insomnia, SQI, and circadian activity rhythms among 410 cancer survivors. [See preliminary study 1.] **This follow-on study compares the efficacy of YOCAS©® to CBT-I and a health education control, examines the durability of insomnia benefits, and explores possible mechanisms (circadian, physical and immune function). This RCT compares yoga to a health education control for time and attention.**

Table 1: Summary of Phase I, II & III Yoga Studies Examining Sleep Among Cancer Patients and Survivors

Phase I	Trial Design	Sample	Treatment Status	Type of Yoga	Dose of Yoga	Outcomes
Ulger et al., 2010	1-Arm	Breast Cancer (N=20)	Post-Adjuvant Treatment	Classical	2x's/week 60 min/sess 4 weeks	Sleep ⬆ * QOL ⬆ CRF NA
Phase II	**Trial Design**	**Sample**	**Treatment Status**	**Type of Yoga**	**Dose of Yoga**	**Outcomes**
Cohen et al., 2004	2-Arm RCT w/ SC Waitlist	Lymphoma (N=39)	Mixed receiving active treatment and within 12 months post-adjuvant treatment	Tibetan	1x's/week NA min/sess 7 weeks	Sleep ⬆ * Meds ⬆ *
Carson et al., 2009	2-Arm RCT w/ SC Waitlist	Breast Cancer (N=37)	Survivors post-adjuvant treatment	Yoga of Awareness	1x's/week 120 min/sess 8 weeks	Sleep ⬆ *
Vidiraja et al., 2009	2-Arm RCT w/ SC + Support Therapy	Breast Cancer (N=88)	During adjuvant radiotherapy	Integrated	3x"s/week 50 min/sess 6 weeks	Sleep ⬆ *
Chandwani et al., 2010	2-Arm RCT w/ SC Waitlist	Breast Cancer (N=61)	During adjuvant radiotherapy	Patanjali from VYASA	2x's/week 60 min/sess 6 weeks	Sleep NC
Bower et al., 2011	2-Arm RCT w/ SC + Health Education	Breast Cancer (N=31)	Survivors post-adjuvant treatment	Iyengar	2x's/week 90 min/sess 12 weeks	Sleep NC
Phase III	**Trial Design**	**Sample**	**Treatment Status**	**Type of Yoga**	**Dose of Yoga**	**Outcomes**
Mustian et al., 2013, 2011, 2010b, 2010a	2-Arm RCT w/ SC Waitlist	Mixed Cancer Survivors (N=410)	Survivors post-adjuvant treatment	YOCAS©®	2x's/week 75 min/sess 4-weeks	Sleep ⬆ * Insomnia⬆* Meds ⬆ * Circadian Activity⬆* Rhythms

Notes: An arrow with an asterisk pointing upward indicates a statistically significant improvement in study outcome (i.e., improved sleep quality, less insomnia and reductions in sleep medication use).
RCT = Randomized, Controlled Trial. NC = No Change, SC = Standard Care

Why We Developed YOCAS©®: While yoga is increasingly popular in the U.S. and there are many books and DVDs as well as cancer center and community programs marketed toward cancer survivors (e.g., "Gentle Yoga for Cancer

Patients," "Yoga for Breast Cancer Patients and Survivors," and "Healing Yoga"), there is little, if any, evidence as to the efficacy of these programs for improving insomnia or SQI among cancer survivors. These yoga programs are not regulated, and there is significant variability in what is offered. For example, some yoga programs focus on very gentle, low-intensity, meditative practices (e.g., Restorative, Integral, Svaroopa), while others focus on vigorous practices (e.g., Power, Ashtanga), and yet others focus on both (e.g., Hatha, Iyengar, Kundalini).[77] Some programs modify the yoga environment by using heaters and humidifiers (e.g., Bikram) or props such as straps, blocks, ropes and chairs (e.g., Iyengar).[77] Class structure varies considerably; some classes include only physical postures and no mindfulness exercises, while others include only mindfulness exercises and no physical postures. The small number of studies examining the safety and effectiveness of only limited types of yoga for improving SQI among survivors coupled with the lack of regulation and wide variability of yoga course offerings substantially increases the chance that survivors may spend a sizeable amount of time, energy and money participating in yoga programs that may not be safe or effective. For example, yoga in a room heated to over 100 degrees may be contraindicated for some survivors, and vigorous yoga may result in excessive muscle soreness and joint pain, increasing insomnia.

We developed Yoga for Cancer Survivors (YOCAS©®) as a standardized program of yoga that can be easily and consistently replicated for research, and ultimately, dissemination and used in the treatment of insomnia and SQI. YOCAS©® is a standardized yoga program designed by Dr. Mustian and her research team specifically for use by cancer patients and survivors. The YOCAS©® program is a low to moderate intensity mode of exercise that draws from two basic types of yoga: gentle Hatha and Restorative yoga. The program includes 16 specific physical postures (asanas) and mindfulness exercises focused on breathing (pranayama) and meditation (dhyana). The program is designed to be delivered by Registered Yoga Alliance instructors in community settings, two times a week for 75 minutes over four weeks—an explicit yoga prescription for the treatment of insomnia and SQI. [See the detailed clinical protocol.] We also developed a training program for yoga instructors, including a written manual and two DVDs. The training materials provide precise instructions for all posture, breathing and meditation exercises with appropriate modifications if necessary. **We successfully trained 18 yoga instructors and used the YOCAS©® program in our first multicenter study. We will train additional instructors and use YOCAS©® again in the current study.**

Limitations of Previous Phase I-III Studies: None of the phase I-II studies was a definitive phase III RCT that was planned and powered a priori to test the effects of yoga on insomnia or SQI as a primary outcome. The sample sizes were small, ranging from 20-88. They did not screen for or require a specific level of insomnia or SQI as part of participant eligibility. The studies did not blind participants with the exception of the Bower study.[76] Yoga interventions were not standardized and were highly variable in content, type, intensity, and duration of yoga, making it impossible to determine the actual dose of yoga needed to improve insomnia or SQI. The yoga interventions were not described in great detail, making repeatability and standardized dissemination impossible. While general comments suggested the interventions were safe and that participants enjoyed them, no specific details were provided on the rate of adverse events. Information on participant attendance, compliance and attrition, details of the prescribed yoga dose versus the actual dose achieved (e.g., mode, frequency, intensity, duration), and information on sustainability of improvements in SQI stemming from yoga were limited. Furthermore, no studies, including our previous phase III trial, compared yoga to a gold-standard treatment for insomnia or SQI such as CBT-I—a required next step in clinical research if yoga is to be determined a gold-standard treatment option for insomnia. Moreover, no studies, with the exception of ours, examined possible biological mechanisms through which yoga may improve insomnia or SQI. **This phase III RCT capitalizes on the positive aspects of our prior phase III RCT and addresses most of the remaining limitations by blinding participants, comparing YOCAS©® to CBT-I and a health education time and attention control, examining the durability of effects on insomnia and investigating biological mechanisms whereby YOCAS©® may improve insomnia.**

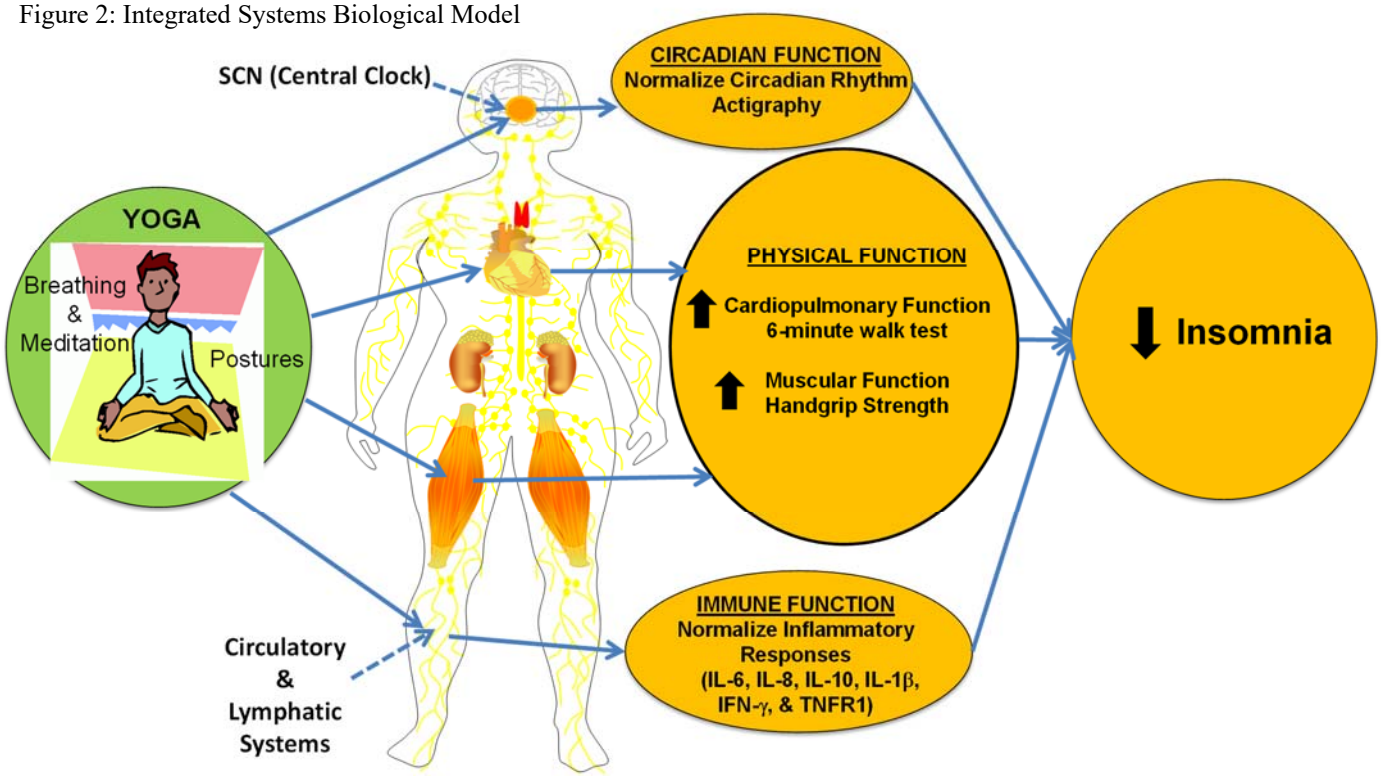
Yoga Summary: Further research is warranted because, despite their limitations, these phase I-III studies collectively suggest that: 1) cancer patients can safely participate in yoga during and after cancer treatments, 2) yoga interventions are feasible in a variety of cancer centers and community-based yoga studios, 3) cancer survivors participating in these yoga programs enjoy them and find them beneficial, and 4) yoga participation ranging from 1-2 sessions/week for 50-120 minutes per session over a period of 4-12 weeks may lead to improvements in insomnia and SQI.

Pathophysiology of Insomnia and SQI: The pathophysiology of insomnia and SQI and their relationships with cancer and its treatments are largely unexplained.[25,48,78] Research suggests that sleep problems may arise through multiple pathophysiologic pathways including dysregulated hypothalamic-pituitary-adrenal axis (HPA axis) function stemming

from abnormal sleep/wake homeostasis, hyperarousal, disruptive cognitive and behavioral factors and impaired circadian, physical (i.e., cardiopulmonary and muscular) and immune function. [Note: We acknowledge our model does not include ALL potential biopsychosocial mechanisms (e.g., relaxation pathways); it's not possible to investigate them ALL in a single clinical trial.] Our working model is based on our research and that of others showing that cancer survivors with compromised sleep demonstrate dysregulated circadian function (i.e., flattened diurnal rhythms, suppressed morning peaks, elevated evening nadirs, and delayed acrophases), impaired physical function (decreased cardiopulmonary and muscular function) and dysregulated immune responses (chronically up-regulated pro-inflammatory responses).[4,5,12-2425-47] **Based on these data, we theorize that yoga will elicit positive changes in circadian activity rhythms, physical function and inflammation that will, in turn, mediate the effect of yoga on insomnia. We developed a theoretical model to serve as a framework to guide our research on these putative mechanisms whereby yoga may improve insomnia.** All components of the full biobehavioral model will not be statistically evaluated, as that is beyond the scope of any single study, but we will statistically evaluate the direct effects of yoga on circadian activity rhythms, physical function (i.e., cardiopulmonary [6-minute walk] and muscular [strength]) and inflammatory responses, as well as, the mediating effects of these plausible mechanisms on insomnia.

<u>Integrated Behavioral and Biological Systems Model (See Figure 2):</u> Our theory is that cancer and its treatments directly and negatively influence circadian, physical (i.e., cardiopulmonary and muscular) and immune function; in turn, diminished function in these systems leads to insomnia. Cancer and its treatments also lead to a reduction

Figure 2: Integrated Systems Biological Model



in physical activity/exercise that elicits physical deconditioning responses which, in turn, lead to diminished function in these same systems, further impairing sleep. Yoga, a form of exercise, is capable of positively influencing each of these systems and improving circadian, physical and immune function and, consequently, improving insomnia as described below.

<u>Yoga and The Circadian Clock System:</u> Yoga is a form of exercise that may regulate circadian function by acting as an exogenous behavioral non-photosensitizer for the circadian system that normalizes dysregulated circadian activity rhythms stemming from cancer and its treatments, thereby improving insomnia. The circadian clock system consists of a central component—the suprachiasmatic nucleus (SCN) of the hypothalamus known as the body's "master clock"—and peripheral components involving multiple organ- and tissue-specific "clocks." These peripheral clocks are synchronized through humoral and neural connections throughout the body that, in turn, affect behavioral and physiological output rhythms (i.e., diurnal fluctuations in sleep, physical activity, heart rate, strength, and cytokines).[79-81]

The master clock, however, has its own intrinsic rhythm which is entrained—synchronized to a 24-hour cycle--by exogenous photo- and non-photosensitizers. The strongest photosensitizer is light; one of the strongest non-photosensitizers is exercise (e.g., yoga).[81] Our prior study suggests that yoga favorably alters circadian activity rhythms.[14] **We will assess circadian activity rhythms using actigraphy as in preliminary study 1 described below.**

Yoga and The Immune System—Inflammatory Responses: Yoga may regulate immune function in the same way as other modes of exercise, by dampening the chronically up-regulated pro-inflammatory responses exhibited in cancer survivors as a result of their disease and its treatments; this dampening, in turn, may normalize overall inflammatory responses and improve insomnia. Exercise reduces low-grade inflammation by triggering the immediate but transient release of IL-6.[82] IL-6 is released from skeletal muscle in proportion to exercise intensity and duration; the proportion of muscle mass used during an exercise bout, and training status.[82] In this environment IL-6 functions as an anti-inflammatory molecule by triggering the release of TNFr□, IL-10, and IL-1r□ which, consequently, inhibits the production of TNFα, IL-8, IL-1β and IFNg and regulates overall inflammatory responses.[82] Research suggests that yoga may improve inflammatory immune responses in cancer survivors with SQI.[66,67,72] **We will assess inflammation with appropriate standardized high-sensitivity multiplexed cytokine/chemokine assay kits under GLP compliance as in preliminary studies 2 through 5 below.**

Yoga and Physical Function in the Cardiopulmonary and Muscular Systems: Yoga may improve physical function (i.e., cardiopulmonary and muscular function) in the same way as other modes of exercise, by eliciting a physiological conditioning response. This physical conditioning response may improve the reduced physical function exhibited by cancer survivors as a result of their disease and its treatment, consequently improving insomnia. It is well documented that traditional modes of exercise performed frequently at high enough intensities for a sufficient duration improve cardiopulmonary and muscular function as part of a desirable physical conditioning response,[83,84] and that regular exercise, using traditional modes, which improves physical function (cardiopulmonary and muscular), results in medium to large improvements in total sleep time, slow wave or "deep" sleep, nighttime wakefulness, sleep onset latency and insufficient sleep.[85-88] Research suggests that participation in yoga improves cardiopulmonary and muscular function in healthy individuals and those with other diseases,[68,77,89-92] but we could find no studies showing this in a cancer population. **We will assess physical function with a 6-minute walk test and a handgrip dynamometry test as in Dr. Mustian's preliminary studies 2 through 5.**

PRELIMINARY STUDIES BY THE PI AND RESEARCH TEAM

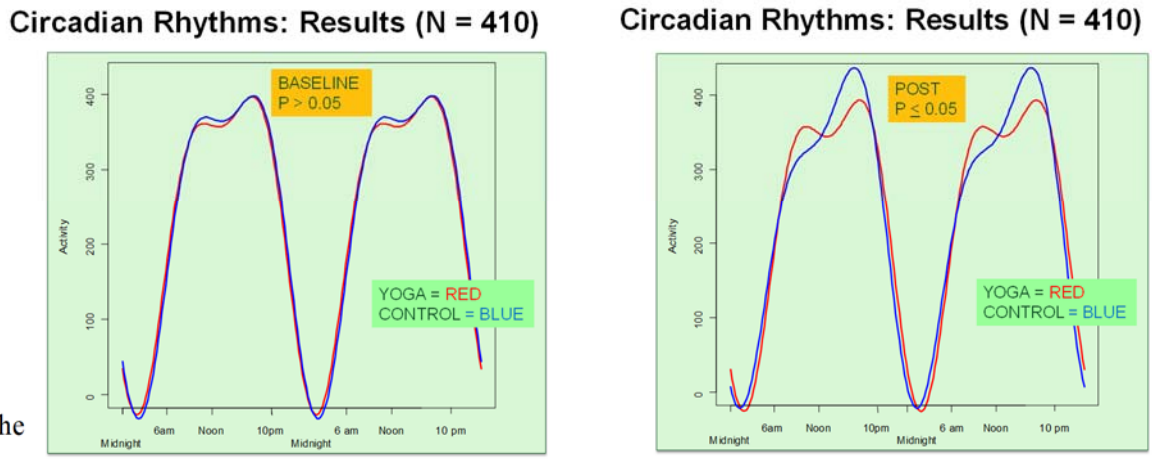
YOCAS©® Multicenter Phase III RCT (URCC04-01/U3905) --Study 1: Dr. Mustian[14,64,65] and her research team completed a nationwide, multicenter, phase III RCT examining the effectiveness of a standardized 4-week yoga program (YOCAS©®--Yoga for Cancer Survivors) for improving SQI in 410 cancer survivors. Insomnia, wake after sleep onset, sleep efficiency and circadian activity rhythms were also assessed as secondary endpoints. Study participants were recruited through the University of Rochester Cancer Center Community Clinical Oncology Program (URCC CCOP) Research Base in Rochester, NY and 9 affiliated Community Clinical Oncology Programs (CCOPs; 12 total community oncology practices) across the U.S. —a consortium of oncology researchers and practicing community oncologists with over 30 years of success conducting large, multicenter, phase III RCTs to test new treatments for the side effects stemming from cancer and its treatments. The study was highly successful and accrued all 410 cancer survivors through 12 community oncology practices in 12 different cities across the U.S. in 32 months; 321 participants (79%) provided evaluable data.

Table 2: Sleep Quality Impairment, Insomnia, and Sleep Medication Use in YOCAS Trial

Outcome Mean (SEM)	Yoga (N = 168)		Control (N= 153)		Between Group P-value
	Pre	Post	Pre	Post	
Sleep Quality	9.20 (0.25)	7.23 (0.26)	8.96 (0.28)	7.89 (0.26)	0.009
Insomnia	22.9 (1.62)	13.4 (1.55)	22.9 (1.76)	20.2 (1.64)	< 0.001
Sleep Medication Use	1.01 (0.10)	0.80 (0.10)	0.81 (0.10)	0.84 (0.10)	0.018

Results (See Table 2 and Figure 3): Our standardized yoga intervention (YOCAS©®; 4 wks., 2x/wk., 75 min. /session; 600 total min.) significantly improved SQI, insomnia, and circadian activity rhythms among 410 cancer survivors.[14,64,65,93] The YOCAS©® intervention not only significantly improved SQI and secondarily, insomnia, wake after sleep onset, and sleep efficiency, but the yoga participants decreased their sleep medication use during the intervention, while the control participants increased sleep medication use.

Figure 3: Circadian Rhythms at Pre- and Post-Intervention



Multi-oscillator modeling revealed a 12-hour, ultradian rhythm model fit the circadian activity rhythms better than a single-oscillator, 24-hour model and demonstrated significant rhythm differences between groups post-intervention ($p<0.05$) with a delayed 12-hour acrophase in the yoga group ($p<0.05$). The yoga group demonstrated higher physical activity during the morning (first 12 hours of the day) and stabilized physical activity throughout the afternoon and evening (second 12 hours of the day); whereas, the standard care control group showed a lower physical activity pattern in the morning and a higher peak in physical activity in the afternoon and evening. Blunted morning circadian rhythms (low physical activity) and excessive peaks (high physical activity) in circadian rhythms during the afternoon and evening are associated with SQI.[4,5,12-24]

Adherence and Adverse Events: Survivors assigned to the yoga arm attended an average of 6.5 of the 8 prescribed sessions for a total of 480 minutes of the prescribed 600 minutes during the 4-week intervention period. Survivors in the yoga arm also reported extra yoga practice outside of the two required yoga sessions, resulting in a total average of 182 minutes each week over 3 days with a rating of perceived exertion of 3.4 (moderate intensity). Contamination in the control condition was very low; 7 participants reported an average of 20 minutes of yoga one time each week with a rating of perceived exertion of 1.0 (very weak) during the intervention period. There were no study-related adverse events. Survivors liked the yoga intervention; 100% found it useful for improving their sleep and would recommend it to other cancer survivors.

Yoga Intervention: We used the YOCAS©® program previously described in the background section and fully detailed in the manual. To ensure intervention quality, fidelity across study sites and instructors, and to prevent drift over the course of the study, Dr. Mustian and her team developed a specialized training program for instructors that included a set of two DVDs, a written manual, and a 2-hour web-based teleconference training workshop. Training updates were provided on a regular basis—minimally every six months. An independent and random observation of class instruction was also made during each 4-week YOCAS©® intervention by research staff to assess the quality and fidelity of intervention delivery by instructors.

Measures: Measures included: SQI and Sleep Medication Use (Pittsburgh Sleep Quality Index; PSQI),[94] Insomnia (Insomnia Severity Index; ISI).[95,96] Wake after sleep onset, sleep efficiency and circadian activity rhythms were assessed by actigraphy.[20,24,97]

Summary: Results suggest that YOCAS©® can improve insomnia, SQI, and circadian activity rhythms among cancer survivors and that survivors like the YOCAS©® intervention, will attend it, will practice yoga on their own, and will

recommend it to others. These data also suggest that altering circadian activity rhythms is a plausible mechanism whereby yoga may lead to improvements in insomnia.

Changes in Physical Function and Inflammation Are Possible Mechanisms Whereby Yoga May Improve Insomnia—Studies 2 through 4:

Study 2: Dr. Mustian and her team conducted a phase II RCT comparing the influence of a Tai Chi Chuan (a Chinese form of yoga) intervention (3x/week, 60 minutes/session, 12 weeks) on physical function and inflammation to a psychosocial support therapy intervention among breast cancer survivors (N=21) between 2 weeks and 24 months post-adjuvant therapy. **Results showed better cardiopulmonary function (6-minute walk test) and muscular function (handgrip test) as well as more favorable inflammatory responses in the tai chi group compared to the support therapy group post intervention. Participants liked the intervention and attended 72% of the sessions with no adverse events.**[36,38,41-43,45,47]

Study 3: Dr. Mustian and her research team also conducted a phase II RCT examining the influence of a low to moderate intensity aerobic and resistance exercise intervention (Exercise for Cancer Patients—EXCAP©®) on SQI, physical function (i.e., cardiopulmonary function and muscular function) and inflammatory responses among breast and prostate cancer patients (N=38) beginning radiation therapy. Participants were randomized to 4 weeks of exercise or no exercise. Cytokines and receptors were measured using appropriate ELISAs. **Exercise participants exhibited less SQI, better physical function (i.e., cardiopulmonary function via 6-minute walk test and muscular function via handgrip dynamometer test) and reduced inflammatory responses post intervention compared to participants in the control group. Higher levels of IL-6 and lower levels of TNFR1 were associated with increased SQI.**[35,46]

Study 4: We also recently completed a phase II RCT examining the influence of the EXCAP©® intervention over 6 weeks on SQI and physical function (cardiopulmonary and muscular function) in 53 prostate cancer patients. **EXCAP©® participants demonstrated improvements in cardiopulmonary function (VO_2max) and strength (repetition maximal testing), and these improvements were inversely correlated with SQI (all $p<0.05$). These changes in cardiopulmonary and muscular function significantly predicted changes in SQI ($p<0.05$, $r=0.120$) and, collectively, accounted for approximately 17% of the variance in SQI.**

Successful Experience and Expertise in Collecting Actigraphy, 6-Minute Walk, Handgrip Dynamometry and Cytokine Data in a Large Multicenter Research Base Study:

Study 5: In addition to successfully completing the previously mentioned multicenter RCT examining the influence of yoga on insomnia, SQI and circadian activity rhythms (via actigraphy), Dr. Mustian and colleagues are currently conducting a nationwide, multicenter, phase III RCT examining the influence of EXCAP©® over 6 weeks on SQI, cardiopulmonary (6-minute walk) and muscular (handgrip dynamometry) function, inflammation (cytokines in serum), and energy expenditure (actigraphy) among cancer patients receiving chemotherapy. This study has accrued > 600 participants in 36 months. **Dr. Mustian and her team have trained 256 CCOP (now NCORP) staff members at 19 CCOPs affiliated with the Research Base to obtain actigraphy data, administer the 6-minute walk and handgrip tests, and acquire and process blood samples for cytokine analyses. The same methods used to collect data in those two RCTs will be used in this multicenter RCT. We will measure the same cytokines in our follow-on RCT as in our previous studies because our preliminary data are positive.**

Successful Experience and Expertise in Delivering Group-Based Psychotherapy and CBT-I in a Large Multicenter Research Base Study:

Studies 6 and 7: The URCC Research Base is currently conducting a study testing the efficacy of a modified version of standard CBT-I for improving insomnia, sleep quality, circadian activity rhythms and heart rate variability among cancer patients receiving chemotherapy (URCC12048). The URCC Research Base previously successfully conducted a phase III RCT testing the effectiveness of group-based psychosocial support therapy for improving quality of life and other symptoms among 326 men receiving treatment for prostate cancer through the Research Base (U9994). **The same procedures used successfully to implement these group-based psychotherapies will be used in this RCT.**

Preliminary Studies Summary: These seven preliminary studies: 1) suggest that YOCAS©® may be effective for improving insomnia, SQI and circadian activity rhythms, 2) provide support for testing our theory that YOCAS©® may improve insomnia by improving circadian activity rhythms, cardiopulmonary function, muscular function and inflammation, 3) demonstrate our expertise and ability to successfully conduct nationwide, multicenter, phase III RCTs, 4) demonstrate our abilities to deliver group-based yoga and psychotherapies and to collect objective physical function, sleep and circadian activity rhythms data in large multicenter clinical trials, and 5) demonstrate our ability to work with the Research Base and NCORP Affiliates.

3.0 Objectives

3.1 **Primary Aim:**

1. To determine if YOCAS©® is effective for improving patient-reported insomnia (Insomnia Severity Index) compared to CBT-I and a health education control immediately post intervention.

3.2 **Secondary Aims:**

1. To examine if YOCAS©® is effective for improving objective symptoms of insomnia (sleep latency, sleep efficiency, wake after sleep onset, sleep duration, and daytime napping via actigraphy) and global sleep quality impairment (Pittsburg Sleep Quality Index) compared to CBT-I and a health education control.

2. To examine if YOCAS©® and CBT-I are effective for maintaining improvements in insomnia (Insomnia Severity Index) 3 and 6 months post intervention compared to a health education control.

3.3 **Exploratory Aims:**

1. To explore whether YOCAS©® is effective for improving circadian activity rhythms (24 and 12 hour amplitudes and acrophases measured via actigraphy), physical function (i.e., cardiopulmonary [6-min. walk] and muscular function [dynamometry]), and inflammation (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFR1 via standardized ELISAs) compared to CBT-I and a health education control.

2. To explore whether changes in circadian activity rhythms, physical function and inflammation mediate the effect of YOCAS©® on insomnia.

3. To explore the time-varying nature of physical activity behavior after cancer treatment and develop a new methodological approach to jointly model longitudinally measured exposures and outcomes subject to measurement error and modification by personal characteristics in a physical activity intervention study.

4.0 Participant Eligibility

Eligibility criteria for all study participants must be confirmed using the Eligibility Checklist. The Eligibility Checklist must be signed by an NCORP physician or the physician's designee prior to enrollment on this study.

Inclusion Criteria: Study participants must:

4.1 Have a confirmed diagnosis of cancer

4.2 Have received surgery, chemotherapy, and/or radiation therapy

4.3 Have completed all surgery, chemotherapy and/or radiation therapy within the last 2-60 months

4.4 Meet DSM-V criteria for insomnia and score ≥10 on the Insomnia Severity Index. (See the screening teleforms package for screening criteria forms)

4.5 Be at least 18 years of age

4.6 Be able to read and understand English

4.7 Be able to provide written informed consent

Exclusion Criteria: Study participants must not:

4.8 Have contraindications to functional testing or yoga participation according to the physician or the physician's designee.

4.9 Have practiced yoga ≥ 1 day a week within the 3 months prior to enrolling in the study

4.10 Be planning to start yoga on their own during the time they are enrolled in the study

4.11 Have a confirmed diagnosis of sleep apnea or restless leg syndrome

4.12 Be receiving any form of treatment for cancer with the exception of hormonal or biologic therapy

4.13 Have distant metastases

5.0 Registration, Enrollment & Randomization

5.1 CTEP Requirements. As this study is using the CTSU Regulatory Support System, the CTSU requires the following:

5.1.1 CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

5.1.2 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

5.1.3 CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval:

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org.

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.

Checking Your Site's Registration Status:

- You can verify your site registration status on the members' section of the CTSU website. Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

5.2 To enroll a cohort of participants who meet the inclusion/exclusion criteria and who have signed the informed consent document, log on to the URCC NCORP Research Base website at http://urcc-ncorp.org/, enter your

NCORP's username and password and enter the information outlined in the section below. If you are unable to log on, call 585.275.1364, between 8:30 AM and 4:30 PM (Eastern Time); Monday through Friday.

5.3 The following information will be requested:

5.3.1 NCORP site

5.3.2 Most recent IRB approval date (either initial or annual-not an amendment date)

5.3.3 Name and telephone number of coordinator following the study participant

5.3.4 Treating component or subcomponent CTEP institution code

5.3.4.1 Enrolling physician CTEP Investigator ID

5.3.5 Confirmation that participant meets all inclusion/exclusion criteria requirements listed in Section 4.0 including

5.3.5.1 Documentation of eligibility screening score of $\geq$10 on the Insomnia Severity Index Screening Form.
5.3.5.2 Documentation of meeting DSM-V Insomnia diagnosis criteria on the DSM-V Screening Form.
5.3.5.3 Documentation of meeting all eligibility requirements on the Eligibility Checklist.

5.3.6 Confirmation that the consent form has been signed

5.3.7 Participant's identification

5.3.7.1 Screening ID# from the Screening Log
5.3.7.2 First and last initials
5.3.7.3 Birth date (MM/DD/YYYY)
5.3.7.4 Gender
5.3.7.5 Race and ethnicity
5.3.7.6 Five-digit zip code
5.3.7.7 Payment code
5.3.7.8 Stratification: ISI severity screening score and current hormone therapy status (yes/no)

5.4 An email confirmation of registration will be sent from the URCC NCORP Research Base.

5.5 Registration and randomization of participants will occur when an entire cohort has been consented. A cohort consists of a yoga group, a CBT-I group and a health education group at a single NCORP location. All participants are registered at the same time. The minimum number of participants to comprise a cohort is 15 and the maximum is 30. The NCORP must notify the URCC when the final participant in a cohort is being consented, and provide the total number of participants enrolled to that cohort, the institution's CTEP ID, and the date of the first day of the baseline week. The Research Base requires a 24-hour turn-around time to open the registration site. The NCORP site must then register the entire cohort of participants within 24 hours and will receive the randomization assignment for each participant at that time. **NCORP coordinators will know the randomization assignments; however participants are not to be notified of their randomization assignments until they have completed all baseline assessments.** The participants randomized to each of the three conditions will all participate in the intervention they are assigned together as a group and the sessions will only contain study participants. (Note: The URCC has successfully used this method of randomization in previous studies including U3905 (the prior yoga study), U2991 and U9994 where cohorts were randomized to treatments delivered using group formats.) Participant cohorts will be recruited at each NCORP and then randomized; this will allow for statistical analyses by site.

5.6 A total enrollment of 720 participants (accounting for 30% of participants providing non-evaluable data) is planned as follows:

Group	***N***	***Evaluable***
YOCAS	*240*	*168*
CBT-I	*240*	*168*
Health Education	*240*	*168*

5.7 Randomization will be stratified by ISI severity score obtained during the screening process (ISI score of 10-18 = "moderate" and 19-28 = "severe") and hormone therapy (two levels: yes/no). In addition, participant cohorts will be recruited at each NCORP and then randomized; this will, in turn, allow for statistical analyses by site.

5.8 The three study arms are as follows:

Arm 1 = The standard YOCAS©® intervention
Arm 2 = The standard CBT-I intervention
Arm 3 = The health education control intervention which is equally matched to YOCAS©® on time and attention.

5.9 The randomization will assign participants to the three arms in the ratio of 1:1:1 using random block sizes of 3 or 6 and will be administered at the URCC NCORP Research Base by means of a computer generated random numbers table provided by the biostatistician.

6.0 Research Protocol

6.1 **Overview and Intervention Groups:** 720 cancer survivors 2-60 months post-primary (i.e., surgery, chemotherapy, and/or radiation) treatment will be randomized to YOCAS, CBT-I, or the Health Education group.

6.2 **Blinding:** As part of the consenting process, participants will be blinded to study hypotheses and the true nature of the health education control condition (which is not expected in any way to improve insomnia; it is there to provide a time and attention control condition for the yoga arm). In the beginning of the study they will be told that we are comparing three different interventions for improving sleep, specifically insomnia. Participants will be fully briefed about the nature of the study, the hypotheses we tested, and the true nature of the health education control condition upon completing the study during the exit interview.

6.3 **YOCAS©® Group:** This is the standardized YOCAS©® yoga intervention which is a low to moderate intensity mode of exercise that draws from two basic types of yoga; gentle Hatha and Restorative yoga. The program includes 18 specific physical postures and mindfulness exercises focused on breathing and meditation. Instructors will be allowed to modify the yoga postures to meet the specific needs of participants and participants will be allowed to use yoga props. (See the YOCAS©® manual, "Yoga for Cancer Survivors".) The program is delivered by Registered Yoga Alliance and/or International Association of Yoga Therapists (IAYT) instructors in community settings, 2 times a week for 75-minute sessions over 4 weeks. Yoga instructor qualifications are documented in a resume or CV and submitted to the Research Base along with a copy of their Yoga Alliance and/or International Association of Yoga Therapists (IAYT) credentials for approval.

6.4 **CBT-I Group:** This is standard Cognitive Behavioral Therapy for Insomnia (CBT-I). CBT-I is a standardized structured, multi-component cognitive behavioral intervention (sleep education, sleep hygiene, sleep restriction, stimulus control, cognitive therapy, and relapse prevention). (See the CBT-I workbook, "Cognitive Behavioral Therapy for Insomnia".) CBT-I is delivered by health professionals who are trained (e.g., clinical psychologists, licensed clinical social workers, licensed counselors, nurses, etc.) to deliver CBT. The intervention is delivered

once a week for 90 minutes over an 8 week period. CBT-I instructor qualifications are documented in a resume or CV and submitted to the Research Base for approval.

6.5 **Health Education Control Group:** This group will receive a survivorship health education intervention (equally matched to YOCAS©® for time and attention) which is based on the American Society of Clinical Oncology cancer survivorship educational recommendations and a booklet entitled "Cancer Survivorship Next Steps for Patients and Their Families." (See the health education booklet.) The intervention is delivered by community health educators with a minimum of a Bachelor's degree in a health-related field or Registered Nurse certification, and a year of experience working in a clinical oncology setting with patients. This intervention is delivered 2 times a week for 75 minutes per session over 4 weeks. Health professional qualifications are documented in a resume or CV and submitted to the Research Base for approval.

6.6 The participants will all participate in the treatment they are assigned together as a group (1 group for each study arm condition) and the treatment sessions will only contain study participants. Participants will not be charged for any of the treatment sessions.

6.6.1 Each participating NCORP will be responsible for finding suitable yoga, CBT-I and health education instructors.

The study PI, Dr. Karen Mustian, along with members of the research team, will be available to assist NCORPs in selecting appropriate instructors. Each instructor will be required to provide the following:

- copy of his/her resume or curriculum vitae
- documentation of his/her Yoga Alliance or International Association of Yoga Therapists (IAYT) instructor training and certification status, CBT instructor training/experience, or health educator instructor training/experience in a clinical oncology setting.
- personal liability insurance information
- in order to be paid as a study consultant, the instructor will complete
    - an IRS W-9 form
    - a University of Rochester Acceptance form to follow the terms and conditions of working with the University

Additionally, the instructors will sign an Adherence Statement promising to follow the yoga, CBT-I and health education interventions exactly as outlined in the clinical protocols provided.

The NCORP site will submit these materials to the Research Base (elizabeth_nagalski@urmc.rochester.edu) for review by Dr. Mustian and members of the research team to approve the yoga, CBT-I and health education instructor for consultation and for teaching the interventions.

Each instructor will also be required to complete a training session with Research Base staff under the direction of Dr. Mustian, prior to final approval as a study instructor.

A decision regarding approval of the instructor will be made within two weeks of providing all the necessary materials and fully completing training.

All instructors will be paid directly as consultants by the URCC NCORP Research Base. Instructors must submit an invoice to the Research Base within 7 calendar days of completing the series of 8 intervention sessions for processing. Instructors will be paid a flat fee of $1200.00 per cohort to teach all 8 sessions and includes all preparation and travel time. Instructor invoices should be sent to: Libby Nagalski at Elizabeth_nagalski@urmc.rochester.edu.

6.6.2 Details and logistics on where the yoga, CBT-I and health education sessions will be conducted, obtaining props, meeting rooms and specifics regarding participant transportation will be individualized by each NCORP site.

6.7 **Instructor Training:** Dr. Mustian and her team developed a training program for yoga instructors, including a written manual and 2 DVDs, one for instructors and one for participants. The training materials provide precise instructions for all posture, breathing and meditation exercises with appropriate modifications if necessary. We successfully trained 18 yoga instructors and used the YOCAS©® program in our previous yoga study, U3905. We will train additional instructors and use YOCAS©® again in the current study. Dr. Pigeon and his team have developed a CBT-I training program for health professionals that includes a manual and PowerPoint presentation. The training materials provide precise instructions for all CBT-I components. He has successfully trained instructors to deliver CBT-I for the University of Rochester Medical Center and the Veteran's Administration. We will use this same training program to train the CBT-I instructors for this study. Dr. Mustian and her team also developed a training program for health educators, including a manual and PowerPoint presentation. The training materials provide precise instructions on the content to be covered in each of the health education sessions. We will use this program to train the health education instructors for this study. Each study instructor must successfully complete all training sessions prior to final approval to serve as an instructor in this study. Training sessions take approximately 1 hour. NCORPs cannot hire and use instructors that are not trained and approved by Dr. Mustian and her team.

6.8 **Intervention Quality:** The exact same procedures used to ensure quality and fidelity and to prevent drift that were used in the previous yoga study, U3905, will be used in this trial, except we will use videotaping to ensure proper class content rather than independent observations. The interventions will be delivered by professionally qualified instructors hired and vetted by Dr. Mustian and members of the research team. All instructors will receive extensive training regarding the information to be taught. Training updates will be provided minimally every year for instructors and NCORP site staff. Dr. Mustian and her staff will be available to answer questions at all times. Coordinators will be required to videotape the third class in each condition and send the videotape to the URCC NCORP Research Base by the end of the next business day. Tapes will be reviewed within 3 business days of receipt by qualified staff under the direction of Dr. Mustian. Immediate feedback will be provided to the instructor and NCORP site staff so that corrections can be made if necessary. If at any time a coordinator or staff member realizes the intervention protocols are not being followed properly, the Research Base and study P.I. (Dr. Mustian) must be notified immediately. Video recordings will be uploaded via the research base's secure encrypted Box data upload system. Once URCC has reviewed the video recordings and given authorization, the sites must destroy them.

6.8.1 Assessment Data Quality: The coordinators must submit all baseline data from one individual in each of the three arms by the 3rd work day post baseline. This includes paperwork, fitness assessments, and actigraphy. Data are either uploaded or emailed to URCC. The Research Base will review and give the sites feedback so that corrections can be made if necessary. Once the site has downloaded the actigraph data they must immediately give the actigraphs back to the appropriate participants so they have them before the mid-intervention assessment.

6.9 All instructors will complete an Attendance Log for each session to assist in documenting intervention compliance by instructors and participants. They will return these logs to the study coordinator. The Coordinator will darken the participants names; leaving only the initials visible. They will in turn submit attendance logs for each of the three study arms to the Research Base. One attendance log is to be submitted at the end of the intervention for each intervention session for all 3 study arms. The names should be darkened to leave just participant initials visible.

6.10 **Coordinator Training:** All NCORP coordinators and staff must complete mandatory training conducted by Research Base staff and PEAK Lab staff for this study. The training includes study orientation, actigraphy, handgrip testing, 6-minute walk test, and blood drawing, processing, storage and shipping. The training lasts approximately 2 hours.

6.11 **Screening:** Cancer survivors 2-60 months post-primary (i.e., surgery, chemotherapy, radiation) treatments, who have been treated at NCORP communities affiliated with the URCC NCORP Research Base will be screened. A screening consent form will be used by the coordinators when approaching potential study participants either over the phone or face to face. If the person declines participation in the study, the screening consent form will be destroyed. If the person agrees to discuss the study, a screening consent form will be completed and submitted to the Research Base. At screening, the DSM-V and ISI screening forms will be used to determine eligibility for the study. All persons presented with this study will be entered on a REDCap screening log found on the Research Base website.

6.12 **Consent, Collection and Handling of Sensitive Data:** If the person meets all eligibility criteria, the coordinator will go over the study in detail using the full study consent form. Both parties must sign the study consent form if the person agrees to be on study. Participants are asked to provide their medical insurance ID number and their social security number in the consent form to follow them as part of future research in the Medicare and Medicaid Beneficiary databases and the URCC NCORP Research Base Distributed Research Network (DRN). Information will not be obtained from individuals who do not give us permission to track them for future research in these databases. Permission to follow a participant is voluntary. They will be able to decline giving this information and still participate in the study.

6.12.1 The URCC NCORP Research Base DRN enables investigators to collaborate with each other in the use of electronic health data, while also safeguarding protected health information and proprietary data. It supports both single- and multisite research programs. The Network's querying capabilities reduce the need to share confidential or proprietary data by enabling authorized researchers to send queries to collaborators holding data (i.e., data partners). In some cases, queries can take the form of computer programs that a data partner can execute on a preexisting dataset. The data partner can return the query result, typically aggregated (count) data, rather than the data itself. This form of remote querying reduces legal, regulatory, privacy, proprietary, and technical barriers associated with data sharing for research. This form of querying also provides added protection for research participants.

The network seeks to build strong and trusted collaborations to support the research that will lead to improved health for millions of people around the world.

6.12.2 The data will be collected in a web-based; encrypted electronic REDCap YOCAS Insurance Information form created by URCC NCORP Research Base. The REDCap system is a secure, web-based application that is flexible enough and has an intuitive interface for users to enter data and real time validation rules (with automated data type and range checks) at the time of data entry. NCORP site study staff will meet with each participant in a private and secure setting to fill out this form. The staff member will confirm that the subject has consented to giving this information by checking the consent form signed by the subject. Only participants that consent to giving this information will fill out a REDCap electronic Insurance Information form. The form must be completely filled out during this session with the subject. The study staff will NOT be allowed to save this information in any other form, whether paper or electronic, etc. to be uploaded later. Once the form is complete the sites will no longer have access to it. Each REDCap form has a unique ID# for tracking purposes. It will be sent directly to University of Rochester's server in a local data center. The database is secured behind a firewall. Only the PI, Lead coordinator of this study, URCC Research Base IT analyst, and the REDCap Administrator will have access to the database. There will also be limited access for two Research Base staff members who will be auditing this information. Once all data for the study have been collected, the file will be transferred to a URCC NCORP DRN secured database separate from the study database. At this point only the data custodian (PI of the study), the Lead Coordinator, and Lead URCC IT staff member will have access to it.

6.12.3 The information collected will allow us to be able to follow the participant's progress concerning their cancer or any new cancers that may arise for up to a 30 year period post their study completion. In order to allow us access to future medical claims it is necessary to collect social security numbers along with Insurance ID information.

6.12.4 All study personnel must follow the NCORP Clinical Trial site specific policy on Collection of Social Security and Insurance ID numbers. This Policy should cover privacy regulations regarding the collection and transmission of Social security numbers and Insurance ID information. Each NCI NCORP community affiliate site should have a Privacy Policy and an official who will work with the URCC NCORP Research Base. Study sites must document that staff members have read and will follow their local policy. This information must be retained with study regulatory files for URCC NCORP auditing purposes.

6.12.5 Any breach must be reported promptly, within 5 calendar days, to the Research Base (Libby Nagalski and Ann_Colasurdo@urmc.rochester.edu) and Study PI (Dr. Mustian). They in turn will notify the URMC Privacy officer and Security official. They may be required to complete follow-up information regarding exactly what the breach was and what steps were taken to prevent further breaches. A breach of privacy must be reported to the University of Rochester IRB as well as the NCORP site's IRB.

6.12.6 The disclosure of social security numbers, Medicaid and Medicare and Insurance ID numbers by potential subjects is optional. Potential participants can still take part in this study if they decide not to disclose this information.

6.13 **Procedure Overview:** Participants in all three groups will complete a battery of assessments including questionnaires, a weekly diary, a 6 minute walk test, a handgrip dynamometer test, actigraphy monitoring, and a fasting blood draw. Within the informed consent process, the coordinator or other study personnel will explain to the participants that there will be five assessment periods. These assessments are completed at: 1) baseline, 2) mid-intervention, 3) post-intervention, 4) 3 months after post-intervention, and 5) 6 months after post-intervention. Reminder phone calls will be made to participants regarding study appointments, wearing the actigraphs, and completing questionnaires. Permission will be obtained to leave messages; however, coordinators must make every effort to speak with the study participant for these calls to be considered complete. Documentation of permission to leave a message should be recorded in coordinator notes. Special arrangements are made to retrieve study materials via courier on a case by case basis via each NCORP community if necessary.

Each assessment will include 1) questionnaires on sleep (ISI, PSQI, MEQ-SA), mood (POMS), anxiety (STAI), depression (CES-D), pain (BPI and VAS), fatigue (MFSI, BFI, FACIT-F), cognitive problems (FACIT-COG), exercise (Godin), symptoms (Symptom Inventory), sleep medications and stimulant use (medication and CAM Use forms), and quality of life (FACIT), 2) a daily diary for assessing sleep patterns and specific symptoms, 3) one week of actigraphy 4) physical function tests (6-minute walk and handgrip tests), 5) and a fasting blood draw. The actigraphs are small, water-resistant devices; one is worn around the wrist for 7 consecutive days to gather data on sleep and circadian rhythm. The other is worn on the waist for the same 7 consecutive days to determine physical activity. Participants will complete their questionnaires at the time of their assessments or at home.

6.14 **Requesting Actigraphs, Blood Draw Kits and Other Study Materials:** Study initiation materials will be shipped to the NCORP after the entire cohort is registered. These materials are comprised of 1) the coordinator's kit (including equipment for conducting the 6-minute walk test and handgrip test), 2) the video recorder, 3) actigraphs, 4) yoga kits, and 5) blood supplies. The study supplies will be shipped from the Research Base via FedEx for delivery within 2-3 business days.

6.15 **Baseline Assessments:** Baseline assessments will occur on Study Days -7 to -1, or during study week 1. The coordinator will charge and initialize the actigraphs. The actigraphs should be initialized no earlier than the Wednesday prior to baseline week to ensure adequate data storage. The coordinator will also instruct all participants on how to put each actigraph on and give them written instructions. An actigraph manual along with videos and training sessions are provided for coordinators by the Research Base. The coordinator will reinforce with the participant to wear their actigraphs for 7 consecutive days and to begin filling out their daily diaries on day -7. Only NCORP site staff who have completed the URCC YOCAS©® study actigraphy training can instruct participants on how to wear them and give them to participants.

All participants will be asked to complete on study data and clinical information forms as well as a series of questionnaires to evaluate insomnia, their emotional state, and their physical health. The questionnaires will take

approximately 35 minutes to complete and participants are asked to complete them as close to the end of the baseline week as possible. Treatment notes including all cancer-related treatment should be submitted with this assessment. A 6 minute walk and handgrip test will be conducted to measure strength, and a fasting (minimum of 8 hours) blood draw of approximately 3 tablespoons, will be completed to assess inflammation. Coordinators will call participants to remind them to wear the actigraphs and complete study assessments on the Thursday or Friday prior to the start of the baseline assessment. At the end of the baseline week, a second call is made to remind participants to complete study assessments and to inform them of their study randomization assignment. Alternatively, these reminders can be made in person at the baseline assessment visit. Study coordinators are to inform participants of their study randomization after fitness testing, fasting blood draw and case report forms have been completed. Only NCORP site staff who have completed the URCC Research Base training on functional assessment and blood draw and processing are allowed to perform these assessments and process the blood specimens.

6.16 **Intervention:** Participants will begin the intervention immediately after baseline assessments are complete. Participant adherence will be monitored by attendance records, daily diaries, and actigraphy.

6.16.1 Participants in the YOCAS©® and health education groups will partake in the intervention twice a week for 75 minutes over a 4 week period (study days 0-27 or study weeks 2-5).
6.16.2 Participants in the CBT-I group will complete one session a week for 90 minutes over an 8 week period (study days 0-55 or study weeks 2-9).

6.17 **Mid-Point Assessment:** Half-way through the intervention, participants will again complete study questionnaires (as detailed in section 6.13 above) as well as the 6 minute walk and handgrip tests, fasting blood draw, 7 more consecutive days of wearing the actigraphs, and continue recording in their daily diaries. The coordinator will call and remind the participants to wear their actigraphs for 7 consecutive days, to continue filling out their daily diaries, and to complete all study assessments.

6.17.1 For participants in the YOCAS©® and health education groups, the mid-point assessment will be done during study days 7-13 or study week 3.
6.17.2 For participants in the CBT-I group, the mid-point assessment will be done during study days 21-27 or study week 5.

6.18 **Post-Intervention:** At the end of the intervention period, participants will complete all study procedures as outlined above and stop entering data in their daily diaries after this assessment. The coordinator will call participants and remind them to wear the actigraphs, complete forms and diaries, and to complete all study assessments.

6.18.1 For participants in the YOCAS©® and health education groups, the post assessment will be done during study days 21-27 or study week 5.
6.18.2 For participants in the CBT-I group, the post assessment will be done during study days 49-55 or study week 9.

6.19 **3-Month Post Intervention Follow Up:** At this assessment, participants will again be asked to fill out questionnaires, complete a 6 minute walk and a handgrip test, a fasting blood draw, 7 consecutive days wearing the actigraphs, and filling out daily diaries for that time. The coordinator will complete a scheduling and reminder call during the week prior to the follow-up visit.

6.19.1 For participants in the YOCAS©® and health education groups, the 3-month post assessment will be done during study week 17.
6.19.2 For participants in the CBT-I group, the 3-month post assessment will be done during study week 21.

6.20 **6-Month Post Intervention Follow Up:** At this assessment, participants will again be asked to fill out questionnaires, complete a 6 minute walk, and a handgrip test, a fasting blood draw, 7 consecutive days wearing the actigraphs, and filling out daily diaries for that time. Additionally, participants will complete a feedback form

and a 15-minute qualitative exit interview at the end of the 6-month post-intervention assessment period. All participants will be debriefed and the 3 study arms will be explained. The coordinator completes a scheduling and reminder call during the week prior to the follow-up visit.

6.20.1 For participants in the YOCAS©® and health education groups, the 6-month post assessment will be given during study week 29.

6.20.2 For participants in the CBT-I group, the 6-month post assessment will be given during study week 33.

6.21 **Management of actigraphy:** Actigraphy will be handled by the PEAK Laboratory at the Research Base.

6.21.1 Each NCORP site will be responsible for designating someone on the research staff to be responsible for receiving the actigraphs and an alternate person to cover in case of vacation or illness. The staff member will verify identification numbers on the actigraphs and log all equipment onto the Investigational Device Accountability Record. This form will be used to track actigraphs arriving from the URCC, actigraphs given to participants, actigraphs returned from participants, and actigraphs returned to the URCC. Recording the identification codes on the devices as assigned to each participant will ensure that the same actigraphs are used for each participant.

6.21.2 When the NCORP site notifies the Research Base that the entire cohort has been registered, the actigraphs will be shipped from URCC fully charged. The coordinator will recharge them and initialize each actigraph. The actigraphs should be initialized no earlier than the Wednesday prior to baseline week to ensure adequate data storage The coordinator will instruct each participant on how to put the actigraphs on, care for them and charge them. The coordinator will also give them written instructions developed by URCC, and successfully used in prior studies to aid in proper data acquisition.

6.21.3 The Research Base PEAK Lab staff will ensure that the actigraphs are in good working order before shipping the units to the NCORP site. The NCORP site staff will distribute the actigraphs, actigraph chargers and actigraph instructions to each participant at the baseline assessment. The participants must have the actigraphs and must be able to start wearing them when they get up on the morning of Study Day -7 (Sunday morning). Participants will wear a wrist actigraph 24 hours a day for 7 consecutive days, and a second actigraph will be worn around the participant's waist 24 hours a day for the same 7 consecutive days. The coordinator will instruct the participant when to remove the actigraphs (the following Sunday). Both will be worn during the baseline assessment, the mid-point assessment, the post-intervention assessment, the 3-month post intervention follow-up, and the 6-month post intervention follow up. As the actigraphs are water resistant but not waterproof, participants will take the actigraphs off only when they shower, bathe, swim or do anything where the actigraphs would be submerged in water. Otherwise, they should wear them as described above during each assessment period.

6.21.3.1 NCORP research staff will explain to participants the procedures for wearing the actigraphs and reinforce the importance of wearing them through the night.

6.21.3.2 All study participants will keep both actigraphs from baseline throughout study week 5 (this is the post-intervention assessment period for yoga and health education groups, and mid-point for CBT-I group). All actigraphs will then need to be retrieved from participants during study week 6. All data needs to be downloaded and sent to URCC. DO NOT RE-INITIALIZE ANY ACTIGRAPHS UNTIL CONFIRMATION IS RECEIVED THAT URCC HAS THE DATA. Once it is confirmed the data has been properly downloaded the actigraphs can be reinitialized.

The coordinator will need to make arrangements within 3 business days following baseline assessments to meet one participant in each arm and download their actigraph data to be submitted to URCC for the data quality audit at the beginning of the cohort and return the actigraphs to the 3 participants prior to the mid-point assessment.

The coordinator will need to re-initialize and return the actigraphs to participants in the CBT-I group only, during study week 8, so they can wear them for post-intervention assessments during study week 9.

The coordinator will need to re-initialize and return the actigraphs to participants in all three study groups for both the 3-month and 6-month follow-up assessments. Actigraphs need to be sent to participants during the week prior to the scheduled 3- and 6-month follow-ups.

When not wearing the actigraphs, participants are instructed to plug them into the wall chargers and keep them charging. Every attempt will be made to send the same actigraphs to participants for all assessments.

6.21.3.3 The NCORP research staff will download the data from the actigraphs within 3-4 business days of receiving them from the participants and upload them to the URCC NCORP Research Base secure website. DO NOT RE-INITIALIZE ANY ACTIGRAPHS UNTIL CONFIRMATION IS RECEIVED THAT URCC HAS THE DATA. The electronic data file will be saved in a privacy-secure electronic file at the Research Base and PEAK Human Performance Laboratory. In the event the supply of actigraphs is ample, the Research Base may allow the NCORP to keep devices between the post-intervention and the 2 follow-up assessments. This will be determined on a case by case basis.

6.21.4 **Assessment Training and Adherence to Assessment Protocols:** The University of Rochester PEAK Human Performance Laboratory, a URMC CTSI Clinical Research Core Lab, provides services to aid investigators in effectively implementing behavioral interventions and assessing clinical outcomes that involve physical activity and function. The PEAK Lab has been instrumental in standardizing the procedures for the collection of actigraphy, handgrip, and 6-minute walk data to ensure adherence to protocol. The staff is also adept at training NCORP site staff to properly collect, process, store and ship blood for NCORP studies. Study Chair, Dr. Karen Mustian, directs the PEAK Lab which has been closely involved in URCC Research Base studies since its inception. PEAK Lab staff have designed support materials and trained NCORP site staff to administer the behavioral interventions and outcome assessments for the URCC studies involving yoga (U3905), EXCAP intervention (UCCO08106) and many other URCC Research Base studies. The PEAK lab staff are adept at managing and analyzing actigraph data and all functional data for NCORP Research Base studies as well as biological samples.

The URCC also requires each NCORP staff member to go through training programs which includes, overall protocol information, functional and clinical assessments, actigraphy, blood collection and processing, videotaping, proper forms completion, and quality control checks. Refresher training will be provided as needed.

Adherence will be monitored throughout the study as the information is received at the URCC. We have specifically implemented an extra quality assurance check after baseline, as well as having the NCORPs videotape the 3rd intervention class to monitor instructor adherence to the specific program they are to teach.

6.22 **Participant Reimbursement:** Participants will receive a $50.00 reimbursement for their time and effort to complete each study assessment for a total reimbursement of $250.00. Participants are only reimbursed for the study assessments they actually complete. Each NCORP will be responsible for dispersing the reimbursements to study participants using methods appropriate for their sites. Each NCORP will invoice the URCC Research Base monthly for reimbursement expenses. URCC will only reimburse for the cash value of $50.00 per assessment; no gift card or other fees will be reimbursed if NCORPs choose to use methods of reimbursement that incur extra fees in lieu of cash. Send invoices to: Christine Bryce, 265 Crittenden Blvd., Box 420658, Rochester, NY 14642 Christine_bryce@urmc.rochester.edu

6.23 **Adverse Events:**

6.23.1 Risks from participating in this research:

- YOCAS©® may result in muscle soreness, strains, and/or joint pain.
- CBT-I may result in temporary increases in daytime fatigue, sleepiness, and memory and concentration difficulties.
- Participants may feel upset or worried when filling out the questionnaires.
- Drawing blood may cause pain and bruising at the site where the blood is taken, and sometimes, may cause people to feel light-headed or even to faint. Rarely, you might get an infection at the site of the needle stick.

6.23.2 Adverse events will be reported using the URCC Adverse Event form. This form can be found on the URCC NCORP Research Base website.

	Grade 1	Grade 2			Grade 3				Grade 4		Grade 5	
	Unexpected and Expected	Unexpected		Expected	Unexpected		Expected		Unexpected	Expected	Unexpected	Expected
		with hospital-ization	without hospital-ization		with hospital-ization	without hospital-ization	with hospital-ization	without hospital-ization				
Unrelated Unlikely	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	Not Required	10 Calendar Days	10 Calendar Days	Not Required	Not Required	24-Hour; 5 Calendar Days	10 Calendar Days	24-Hour; 5 Calendar Days	10 Calendar Days

Hospitalization is defined as initial hospitalization or prolongation of hospitalization for ≥ 24 hours, due to adverse event.

6.23.3 Submit written adverse event reports in one of the following ways:

(1) PDF by email:	Cathleen_lesniewski@urmc.rochester.edu
(2) By mail:	Cathleen Lesniewski URCC NCORP Research Base Saunders Research Building 265 Crittenden Blvd CU 420658 Rochester, NY 14642
(3) By fax:	Cathleen Lesniewski 585-461-5601

6.23.4 CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized until March 31, 2018 for AE reporting. CTCAE version 5.0 will be utilized for AE reporting beginning April 1, 2018. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.23.5 An *unexpected* adverse event is defined as any adverse experience, the specificity or severity of which is not consistent with the risk information described in section 6.23.1.

6.23.6 A serious event refers to any event in which the outcome results in any of the following: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability, incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.23.7 Adverse events should be reported to the local IRB as per its requirements.

6.24 **Data Safety and Monitoring:**

6.24.1 All adverse events requiring reporting will be submitted to Cathy Lesniewski as described above. Adverse events that are *serious* AND *unexpected* AND *related* will be forwarded to the study chair and the URCC Data Safety and Monitoring Committee (DSMC) chair immediately upon receipt at URCC. Additional information may be requested upon their review.

6.24.2 All adverse events reported to URCC are entered into a protocol-specific spreadsheet. Adverse event rates are monitored utilizing the spreadsheet. If a serious adverse event is being reported frequently, the study chair will conduct a detailed review. The DSMC chair will be notified and will determine if further action is required.

6.24.3 The URCC Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events at annual meetings. An overall assessment of accrual and adverse events will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure.

6.24.4 The URCC will notify the NCORPs immediately of any serious safety concerns identified by the DSMC. DSMC reports will be available for download on the Research Base website.

7.0 Patient Reported and Functional Measures

7.1 The **On Study Data/Participant Record** and **Clinical Record Information** forms are used to record demographic and clinical information. Diagnostic, treatment and other clinical information will be abstracted from the participant's chart and recorded on these forms. These data will be used for descriptive purposes, to aid in participant monitoring, for moderator analyses and for exploratory analyses.

7.2 The two **Medication and CAM Usage** forms will track the participant's use of prescription and non-prescription sleep and stimulant medication, as well as any other sleep and stimulant aids used during each assessment conducted during the study. These forms will also specifically ask participants to report the use of any CAM modalities for any reason.

7.3 **Insomnia and Sleep Assessments:**

7.3.1 **Insomnia** will be measured by the Insomnia Severity Index (ISI), which is a well-validated self-report measure of insomnia.[98-100] The measure consists of seven questions on a 5-point Likert Scale with a total score ranging from 0-28. Reliability and validity of this measure have been established.[98-100] Total score will be used.

7.3.2 **Sleep quality** will be assessed by the Pittsburgh Sleep Quality Inventory (PSQI),[101,102] a commonly used, 24-item psychometrically sound measure scored for both global severity and subscale scores. The PSQI will assess sleep initiation and maintenance problems and possible etiologic factors (e.g., pain,

nightmares, and hot flashes). Total score will be used. This measure takes less than 5 minutes to complete.

7.3.3 **Number of hours of sleep and intended sleep period** will be calculated from the Daily Diary. For each day of the study period when sleep is assessed, participants will indicate time to bed at night and time arose in the morning.

7.3.4 **Sleep Chronotype** will be measured by the Morningness-Eveningness Questionnaire Self-Assessment (MEQ-SA).[103] This is a 19-item self-report instrument that characterizes the sleep chronotype of an individual.

7.4 **Objective Insomnia Symptoms** will be measured via actigraphy. Participants will have their sleep-wake exposure monitored through the use of a wrist-worn actigraphy-based data logger, the Actigraph GT3X manufactured by ActiGraph LLC, Pensacola, FL. The Actigraph GT3X features a variable epoch length that can be set, and has 16MB of non-volatile memory. "Non-volatile" means that even if the battery, which can log 21 days of runtime before needing to be recharged, becomes exhausted, the data remain intact. The motion data will be analyzed using the ActiLife Analysis Software. The program uses a validated sleep algorithm to provide an assessment of sleep by delineating the "in bed" and "out of bed" portions of the day. The software and algorithms calculate the percent of sleep during these two portions of the day. The actigraphy, in conjunction with the sleep/wake diaries, can be used to approximate the timing of both daytime and nighttime sleep. While daily sleep diaries are a common method used to examine patterns of sleep and wakefulness, we will internally validate the at-home monitoring by comparing actigraphy data collected during baseline and follow-up to the daily questionnaires. This measurement strategy allows for an assessment of sleep problems (sleep latency, WASO, sleep efficiency, daytime sleep) which is free from either subjective or observer bias and requires minimal subject compliance, allows for the detection of periods of wakefulness as brief as 30 seconds in duration.

7.5 **Circadian Activity Rhythm** will be assessed using actigraphy. The exact actigraphs used to objectively assess sleep described in section 7.4 will be used. A two-oscillator cosinor model (12 and 24 hours) will be calculated using nonlinear regression methods on the log (activity counts). This model was found to fit the data for cancer survivors (Study 3) better than a single-oscillator model. Mesor (overall), Amplitude, and Acrophase for the 12- and 24-hour cycles will be calculated.

7.6 **Cardiopulmonary Function** (aerobic capacity) will be assessed using the 6-Minute Walk Test, which is a sub-maximal measurement using a 6-minute walk protocol. A recent systematic review has concluded that this method possesses excellent measurement properties, was better tolerated, and was more reflective of activities of daily living than any other walk test in use.[99] Participants are directed to a specific area designated for walking. Participants walk for a total of 6-minutes and cover as much distance as they can during this time. The walk test is optimally performed in a flat, well lit area that allows for a minimum of 100 feet of walking before the participant needs to make a turning motion. For example, the test may be conducted in a hallway (walking back and forth) or a larger room that allows for a circular/square walking pattern. Upon completion of the test, the total distance walked (in feet), exercise heart rate (in beats per minute), and exercise rate of perceived exertion (using the ACSM revised rating of exertion scale) are recorded. This test was easy to implement, and well received in a busy clinical setting in the pilot study of the proposed exercise intervention. The total distance walked in six minutes can be used to estimate gross VO_2 (oxygen consumption).[87] Gross VO_2 = Resting VO_2 + Exercise (or net) VO_2. The formula used to estimate gross VO_2 is

VO_2 (mL *kg^{-1} * min^{-1}) = [0.1 mL *kg^{-1} * $meter^{-1}$ * S (m * min^{-1})] + [1.8 mL * kg^{-1} * $meter^{-1}$ * S (m * min^{-1}) * G] + 3.5 mL *kg^{-1} * min^{-1}

Where S is speed in meters per minute and G is the percent grade expressed as a fraction. [87]

7.7 **Muscular Function** (strength) will be assessed using The Handgrip Dynamometer Test, which is a grip strength test used to assess the maximal voluntary contraction generated by the arm muscles. The test is administered with the participant standing in anatomical position, the elbow joint angle will be held constant at 180 degrees. Trials

will be performed in an alternating bilateral sequence for a total of six attempts (three with each arm). A fourth test will be performed if any of the values vary by ≥3 Kg. The average score of the three trials will be used for right and left limbs to calculate static strength. The surgically involved arm(s) for breast cancer participants will be noted for data analysis.[87] This test was also easy to implement and well received in the clinic in the pilot study of the proposed intervention.

7.8 Because many symptoms including cancer-related fatigue (CRF), depression, anxiety, mood disruption, cognitive problems and impaired QOL are often present with insomnia, measures of CRF, depression, anxiety, mood, sleep and cognitive problems have been carefully selected to minimize potential confounding and enable assessment of possible confounds between these concepts.

7.8.1 **General Symptomatology** will be measured with the Symptom Inventory (SI), a list of 20 symptoms modified from measures created at M.D. Anderson and Memorial Sloan-Kettering Cancer Centers.[104] It is a series of uniscales where the severity of each symptom is indicated by filling in the appropriate circle on an 11-point scale, anchored by 0 = "Not Present" and 10 = "As Bad as You Can Imagine." An additional eight questions assess the degree that the symptoms interfere with the participant's quality of life, with 0 = "Did not interfere" and 10 = "Interfered completely." Ten additional questions assess the degree to which the participant uses specific mind-body techniques to manage symptoms. Medical oncologists at our Cancer Center use this measure as part of clinical care, and we have used it in numerous studies. It will serve as a concurrent self-report measure of symptoms that will be used in exploratory analyses.

7.8.2 **Cancer-Related Fatigue (CRF)** will be assessed subjectively via the revised Brief Fatigue Inventory (BFI),[105,106] which is a 9-item, patient-report instrument with established reliability and validity that we have used in previous studies.[92] The BFI allows for the rapid assessment of fatigue level and its interference with daily activities in cancer patients, and identifies those patients with severe fatigue. The reliability and validity of the BFI were demonstrated in a study of 305 cancer patients and 290 community-dwelling adults. An internal consistency coefficient (Cronbach's alpha) of 0.96 was demonstrated when the BFI was administered to 305 patients with cancer.[93] This measure was used in the previously mentioned pilot study of the proposed exercise intervention.

7.8.3 **CRF** will also be assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue Subscale (FACIT-F). The FACIT-F subscale is a 13 item scale that asks questions directly related to the impact of CRF on daily activities.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies. The basic measure has shown very good test/retest reliability as well as validity.[94,95] It has become one of the most commonly used measures in oncology, and we have used this scale in our previous studies including the pilot study designed for this protocol.

7.8.4 In addition, **CRF** will be assessed subjectively via the Multidimensional Fatigue Symptom Inventory (MFSI).[107] The MFSI is a multidimensional 30-item fatigue scale developed specifically for documenting CRF. In addition to a fatigue total score, the instrument includes subscales for assessing general, physical, emotional, mental and vigor domains of fatigue. The self-report instrument was psychometrically validated among a sample of 304 cancer patients and has been shown to have good fit via confirmatory factor analysis, reliability and validity.[96-98]

7.8.5 **Depressive Symptoms** will be measured with the Center for Epidemiological Studies Depression Scale (CES-D)**.** The CES-D[56] is a 20-item depression scale developed and validated for use with a variety of populations. It is in a format similar to that of the Beck Depression Inventory, but with less emphasis on physical symptoms of depression that may be confounded with disease symptoms or treatment side effects. It has been shown to reliably and validly measure depression in cancer populations,[102] and we have successfully used this measure in previous studies.

7.8.6 **Anxiety** will be measured using the Spielberger State/Trait Anxiety Inventory (STAI). In order to reduce the overall patient burden, we will use only the state portion of the questionnaire. This one-page, self-

administered questionnaire consists of 20 short statements which people may use to describe their feelings. Participants are asked to indicate the degree to which they generally experience each particular feeling, ranging from 1 = "Not at all" to 4 = "Very much so" at that time. It is one of the most widely-used assessments of anxiety. Internal consistency coefficients > 0.90 have been shown, along with test/retest reliability coefficients > 0.70. Concurrent, construct, convergent and divergent validity have also been demonstrated.[103,104] We have successfully implemented this measure in previous studies.

7.8.7 **General Mood** will be assessed using the short form of the Profile of Mood States (POMS). The POMS consists of 30 adjectives in 6 subscales (e.g., anxiety, depression), which subjects rate on a five-point scale with "1" = "Not at all" and "5" = "Extremely" to describe their moods over the past week. The POMS has been used extensively in research with cancer patients and has demonstrated reliability and validity.[105,106]

7.8.8 **Cognitive Problems** will be assessed using the Functional Assessment of Chronic Illness Therapy-Cognitive Well-being Subscale (FACIT-Cog).[108] The FACIT-Cog subscale is a 50-item scale that asks questions directly related to cognition.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies. The basic measure has shown very good test/retest reliability as well as validity.[90,94,95] It has become one of the most commonly used measures in oncology, and we have used this instrument in our previous studies (e.g., the pilot study designed for this protocol).

7.8.9 **Quality of Life** (QOL) will be assessed subjectively via the Functional Assessment of Chronic Illness Therapy (FACIT; FACT-F). The FACIT; FACT-F is a 27-item QOL scale developed specifically for use in cancer clinical trials.[90] It was developed by Cella and his group through extensive interviews with oncology professionals and patients experiencing symptoms of cancer, and it has been validated in a series of studies of 542 cancer patients. The basic measure has shown very good test/retest reliability as well as validity.[90,94,95] Along with a total score representing QOL, there are psychometrically validated subscales of physical, functional, social, and cognitive-emotional status. It is one of the most commonly used measures in oncology, and we have used this instrument in our previous studies, including the pilot study designed for this protocol.

7.8.10 **Pain** will be assessed via the Brief Pain Inventory (BPI) and the Visual Analog Scale (VAS) to evaluate the severity and quality of pain experienced. The Brief Pain Inventory (BPI) has become one of the most widely used measurement tools for assessing clinical pain.[109] The BPI allows patients to rate the severity of their pain and the degree to which their pain interferes with common dimensions of feeling and function. Initially developed to assess pain related to cancer, the BPI has been shown to be an appropriate measure for pain caused by a wide range of clinical conditions. The BPI has been used in hundreds of studies. In some ways, the BPI is a "legacy" instrument—a self-report measure that has, over time, become a standard for the assessment of pain and its impact. The Visual Analog Scale (VAS) is a measurement instrument that measures joint pain across a continuum of pictures of faces with values from 0 (no pain) to 10 (pain as bad as you can imagine). The question associated with the VAS reads as follows: ''Please score the intensity of the pain you feel in your peripheral joints (knee, wrist, fingers/toes, elbow, shoulder, etc.), excluding spine/back pain and pain at the operated area.''

7.9 **Physical Exercise/Activity** will be assessed subjectively using the Godin Leisure Time Exercise Questionnaire and a Daily Diary**.**

7.9.1 The amount of leisure time spent in physical activity will be assessed using the Godin Leisure Time Exercise Questionnaire (Godin).[110] The Godin consists of two questions designed to assess the frequency within a typical 7 day week of mild, moderate, and strenuous exercise performed for a duration of at least 15 minutes during a participant's free time. The measure is easily administered and brief, with a retest coefficient of .62, a concurrent coefficient of .32 and an objective validity coefficient of .56 compared with CALTRAC accelerometry, estimated VO_2 max and body composition (via hydrostatic weight).[111] The Godin has also been used successfully in populations of adult cancer patients.[112-115]

7.9.2 The Daily Diary is designed to track compliance and participation in the exercise intervention and additional daily activities. The participant will be asked to take 1-2 minutes and complete the journal each morning upon wakening and each evening immediately prior to sleeping. This daily diary was used in the piloted version of the proposed study, and participants completed the forms without any problems.

7.9.3 As an objective measure of physical activity, a GT3X+ actigraph will be worn around the waist. The GT3X+ actigraph provides calculated energy expenditure values for Active Energy Expenditure (AEE) in kilocalories and total energy expenditure in Metabolic Equivalents per Time (METs) in kilocalories/min/kg. The GT3X+ actigraph features a variable sample rate which can be set between non-volatile memory. "Non-volatile" means that even if the battery, which can log 31 days of data, becomes exhausted, the data remain intact. The GT3X+ actigraph AEE Algorithm is based on validation studies, copies of which are available upon request. Software supplied by the manufacturer will be used to determine bouts of activity during each assessment period.

7.10 **Participant Feedback** regarding their views on the experimental treatment they received will be assessed via completion of a feedback questionnaire by all participants and open-ended qualitative interviews at the conclusion of the study. The information in the feedback questionnaire and interviews will allow us, for future studies, to obtain information needed to alter aspects of the interventions with which participants were displeased and to determine participants' reactions to the intervention.

8.0 Blood Analysis

8.1 **Cytokines** (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1) will be assessed in the blood at all five assessment time points. A fasting blood draw (minimum of 8 hours) will be performed on all participants at all five assessment time points. The standard URCC NCORP Research Base blood collection protocol will be used. Six tubes of blood (approximately 50ml) will be collected including: two red top tubes for serum, two purple top EDTA-heparin tubes (1 for plasma and 1 for DNA) and 2 Paxgene tubes for RNA. Cytokines will be analyzed and any remaining blood samples including serum, plasma and whole blood for DNA and RNA analyses will be used by Dr. Mustian and members of her research team for additional exploratory analyses. The remaining blood samples are not banked or made available for use by investigators outside of Dr. Mustian's research team. All NCORPs will handle all human biological materials and disposal of biohazard waste in accordance with biosafety level II guidelines at their respective institutions for blood collection, handling, disposal, storage and shipping. All NCORP personnel handling human biological materials and laboratories used by NCORPs must have received appropriate biosafety certifications and meet routine inspection guidelines according to their facility guidelines.

8.1.1 All requisitions, blood tubes, microfuge tubes, freezer boxes, pipettes, and labels for blood draws are provided by the Research Base in the form of barcoded and pre-labeled patient kits. All patient kits are study specific.

DO NOT MIX REQUISITIONS, BLOOD TUBES, MICROFUGE TUBES OR PIPETTES ACROSS PATIENT BLOOD DRAW KITS EVEN IN THE SAME STUDY BECAUSE THE BARCODES AND LABELS ARE KIT SPECIFIC.

DO NOT MIX THE FREEZER BOXES, LABELS OR EXTRA SUPPLIES PROVIDED ACROSS STUDIES EVEN URCC RESEARCH BASE STUDIES, BECAUSE THEY ARE STUDY SPECIFIC.

All coordinators will fill in the appropriate patient information on the requisition form in each kit when it is assigned to the patient. Every time a patient blood draw is performed a separate new patient kit is used

and assigned to the study participant. Each NCORP is responsible for designating an individual that is certified and a lab or facility that meets the biosafety level II criteria to perform the blood draws and to handle, dispose, store and ship the blood samples appropriately. The individual designated to perform the blood draws, handle, dispose, store and ship the samples must participate in the training provided by the URCC NCORP Research Base, previously described in section 6.0, and be approved by the study PI (or PI's designee) prior to any blood collection at each NCORP site.

8.1.2 Serum will be extracted from the two red top tubes for estimation of cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1). Plasma will be extracted from one of the purple top EDTA-heparin tubes for estimation of cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1). To extract the serum and plasma, the tubes will first sit upright for 30 minutes at room temperature after blood collection. Second, the tubes will then be put into a centrifuge (note temp) and spun for 15 minutes at 1600 x g. After 15 minutes, there should be a clear separation of the serum or plasma (yellowish liquid on top) from the other cells. If this is not evident, then centrifuge for 15 additional minutes. The upper layer of serum (red top tubes) and plasma (purple top tube) is then gently aliquotted into the 2.0 ml microfuge tubes provided in each URCC NCORP patient blood draw kit. Serum from the red top blood tubes is to be placed into the pre-labeled pink microfuge tubes. Plasma from the purple top tube is to be placed in the pre-labeled purple microfuge tubes. All microfuge tubes are then placed in the pre-labeled freezer boxes provided by the URCC Research Base and the freezer box is then placed in either a -20 C or a -80 C degree freezer (-80 C is preferred if available but not required) for storage until shipped to URCC Research Base. Cytokines (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFr1) will be assessed using Multiplex and ELISA methods as appropriate. The remaining serum and plasma will be stored, as part of study participation, for use in future research by Dr. Mustian, the study PI, and her research team at the URCC Research Base.

8.1.3 One purple top EDTA-heparin tube and two Paxgene tubes will be prepared and stored for future DNA and RNA extraction. The EDTA-heparin tube will be rocked 10 times and then placed upright in a -20 C freezer for a minimum of 24 hours. After 24 hours, the EDTA-heparin tube can then be transferred to a -80 C freezer if available. The two Paxgene tubes will be rocked 10 times, stored upright for minimum of 2 hours and a maximum of 24 hours at room temp and then placed upright in a -20 C freezer for a minimum of 72 hours. After 72 hours, the Paxgene tubes can be transferred to a -80 C freezer if available. After the tubes have been frozen upright for their designated time above, they can then be placed on their side in the pre-labeled freezer boxes provided by the Research Base. (Storage in a -80 C freezer after 4 days is preferred if available but not required.) The whole blood in these tubes will be stored, as part of study participation, for use in future research by Dr. Mustian, the study PI, and her research team at the URCC. See the Blood Procedures Manual found on the URCC Research Base website for complete blood processing instructions.

8.1.4 **Shipping Supplies to NCORPs and Inventory Tracking:** Upon notification of the Research Base that a NCORP has registered a cohort for this study, a starter blood drawing package and an initial supply of barcoded and pre-labeled blood draw kits will be shipped to the NCORP for distribution and use.

Each NCORP site will be responsible for designating someone on the research staff to be responsible for receiving the blood draw supplies and kits. The staff member will verify that the shipment contains the correct number of supplies and kits and that the supplies and kits are in good condition. The identification numbers need to be verified for accuracy and recorded. The Investigational Device Accountability Record (DARF) will be used to track supplies and kits arriving from the Research Base, kits given to participants, samples stored, and samples shipped to the URCC NCORP Research Base.

8.1.5 **Shipping Frozen Blood Samples to URCC Research Base:**

PRIOR TO SHIPPING SAMPLES, YOU MUST CONTACT THE URCC RESEARCH BASE TO MAKEARRANGEMENTS TO RECEIVE YOUR SAMPLES.

Call:
Libby Nagalski
585-275-1364

Ship Samples To:
ATTN: Libby Nagalski
University of Rochester Medical Center
Wilmot Cancer Institute, PEAK Laboratory (B-5035)
601 Elmwood Avenue, Box 704
Rochester, NY 14642

Samples are to be stored in URCC-supplied freezer boxes as outlined in the Blood Procedures Manual found on the URCC Research Base website. Samples must be stored at a minimum of -20C, but preferably at -80C. Samples cannot be stored at -20C for longer than 3 months.

The NCORPs are responsible for shipping all samples to the Research Base within 3 months of sample collection. All samples must be shipped priority overnight and frozen on dry ice. Each NCORP is responsible for adhering to Federal Guidelines for shipping biosafety level II biohazards as well as URCC NCORP Research Base biosafety level II guidelines (outlined in the blood procedures manual provided), their NCORP institutional biosafety level II guidelines and the shipping company guidelines when packing and shipping the frozen blood samples to the Research Base.

9.0 Design Consideration

9.1 **Decision to conduct a trial comparing YOCAS©® to a gold standard insomnia treatment for the general population:** We considered proposing a dismantling trial to determine which component of YOCAS©® is the most active. However, after much deliberation with colleagues, we believe the study comparing YOCAS©® to CBT-I has significantly greater potential to impact standard of care for insomnia among cancer survivors and, potentially, other populations.

9.2 **Changes From Our Prior Yoga RCT:** In this study, we extend our previous findings by comparing YOCAS©® to CBT-I (a gold-standard treatment for insomnia in the general population) and a health education intervention controlling for time and attention. We also blind study participants to control for demand characteristics and bias. We provide participants with "Yoga Kits," including mat, strap, Subject DVD, and manual to facilitate home practice during the intervention period and sustained practice during the following 6 months and assess the durability of intervention benefits at 3 and 6 months following completion of the interventions. We add assessments of cardiopulmonary function, muscular function and inflammation to test the direct effects of yoga on these outcomes and their mediational effects on insomnia through YOCAS©®.

9.3 **Length of Intervention—Why 4 and 8 Weeks:** We used a 4-week intervention period for YOCAS©®in our first study for two main reasons: 1) 4 weeks was the minimum length, in the published literature, shown to be efficacious for improving sleep problems, and 2) for practical purposes, we felt this length was reasonable for implementation in community settings via private oncology practices and would have good adherence. We have chosen to retain the 4-week period for YOCAS©® as it was previously shown to be effective and to compare it to CBT-I delivered over the gold-standard 8-week period. We are aware that new versions of brief and electronic CBT-I are currently being evaluated for efficacy among survivors, but we feel it is important to use the form of CBT-I shown to be effective among groups of cancer survivors in published literature.

9.4 **Length of Follow-Up—Why 3 and 6 Months:** We chose 3- and 6-month follow-up assessments because they will provide good information on the short and longer-term benefits of the yoga intervention, and, while clearly reflective of long-term influence, a 12-month follow-up is not practical within the time period of this R01-funded project.

9.5 **Decision to Conduct a Multicenter Study:** It is not possible to recruit the necessary 720 cancer survivors at a single location within the 5-year time period of an R01. We have considerable experience successfully conducting large, multicenter phase III RCTs through the Research Base with our NCORP affiliates—accrual of the required 720 participants in this environment is possible, and our previous studies demonstrate that it is highly probable they will be successfully accrued within the timeframe of this R01-funded project.

10.0 Data Handling and Statistical Considerations

10.1 **Sample Size and Statistical Power:** Allowing for 30% of participants who may not provide complete data (as in our prior study), we will need to enroll a total of 720 participants to have 504 fully evaluable participants (168 evaluable in each of the three study arms). Fully evaluable participants is defined as having completed the On Study/ Participant Interview and the Clinical Record Information (baseline), the ISI, PSQI, Daily Diaries, and actigraphy (baseline and post-intervention assessments) for primary and secondary endpoints. With 504 fully evaluable participants, will have 80% power at a 0.025 significance level to test our hypotheses. We will use a significance level of 0.025 to control for type I error because two hypotheses (i.e., 1 inferiority [yoga vs. CBT-I] and 1 superiority [yoga vs. health education]) will be tested in our primary aim. *[Note: We will reimburse survivors for participating in this study in an effort to decrease attrition and data loss.]*

10.2 **Power for Primary Aim 1:** The two primary hypotheses to be tested in our primary aim include: (1) YOCAS©® will be as effective as CBT-I, and (2) YOCAS©® will be more effective than the health education control.

10.2.1 ***Power for Hypothesis 1:*** Based on baseline data from our previous phase III RCT examining the effects of yoga on insomnia and data from Savard[58] and Morin,[116] we assume an ISI standard deviation of 4.6. Since half a standard deviation is commonly accepted as appropriate for estimating a clinically important change, we regard a difference of 2.3 (half a standard deviation) between YOCAS©® and CBT-I as nontrivial. Following the same methods as Garland and colleagues,[117] we set the non-inferiority margin to 1.15 (half of the 2.3 difference). We will test the **null** hypothesis that the difference in mean change on the ISI between YOCAS©® and CBT-I is greater than 1.15; that is, YOCAS©® is *inferior* to CBT-I.[118,119] Rejection of the null hypothesis means that YOCAS©® is as effective (*non-inferior)* as CBT-I. Using ANCOVA to estimate differences in mean change between YOCAS©® and CBT-I, a correlation of 0.576 (from our prior study), and a sample of 168 subjects per group, we will have sufficient (80%) power to detect non-inferiority using a margin of 1.15 at $p = 0.025$.

10.2.2 ***Power for Hypothesis 2:*** Using ANCOVA to estimate differences in mean change between YOCAS©® and health education, a correlation of 0.576 (from our prior study), and a sample size of 168 evaluable subjects per group, we will have sufficient power to detect differences on the ISI of at least 1.3, 1.5 and 1.6 (all larger than our 1.15 non-inferiority margin) at 80%, 90%, and 95% power, respectively.[118,119] (Note: It is already well-established that CBT-I is superior to general health education and equal time and attention, as such an overall test of group differences is not necessary or sufficient—the differences in question are specifically between yoga and CBT-I and yoga and health education and require two separate hypotheses be tested.)

10.3 **Study Timeline:** Based on our prior experience conducting studies in the URCC Research Base, we anticipate that study start-up activities (e.g., obtaining NCI and IRB approvals, presenting the protocol and training NCORP site staff, setting up databases, registration and randomization, ordering supplies and making kits and manuals, sending kits and other study supplies to NCORPs) will take approximately 6 months. Screening and accruals will

begin during the 7th month and continue through month 54. The final 6 months will be used to retrieve any remaining data, supplies and equipment from NCORPs, to conduct final audits of the data, to conduct analyses, to write abstracts and papers, and to present findings at meetings. We expect it will take between 24 and 47 months to accrue the 720 participants needed for this study.

10.4 **Representation of Women and Minorities:** None of the eligibility criteria for the study involve gender or ethnicity. Past enrollment in our NCORP studies has closely paralleled the gender and ethnic composition of the available population. See section 12.0 on Gender and Minorities.

10.5 The same **protocols and procedures for data quality and control** that we have used for our previous URCC Research Base protocols will be used for this study. Data will be entered on scannable forms (Teleform) and electronically sent to a Microsoft Access database. After scanning, data are audited visually for errors, and then the entire database is re-audited. MPLus, R and SAS statistical packages will be used for the analyses.

10.6 Unless otherwise stated, all statistical tests will be performed at the two-tailed 5% level of significance. Likewise, 95% confidence intervals will be constructed for estimation of effects (e.g., difference in mean CRF, aerobic capacity, strength and QOL between the active treatment group and the control group). Data will be analyzed on an "intent-to-treat" basis; participant data will be included in the treatment group to which the participant was randomized, regardless of any subsequent changes to the treatment (treatment in this study is considered the study intervention, i.e., exercise intervention, CBT-I, or Health education standard care).

10.6.1 ***Assumptions.*** The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[109,110] For the ANCOVA analyses, the assumptions are bivariate normality of the Pre- and Post-treatment responses with common covariance matrices, after correction for the model fixed effects. Bivariate normality will be assessed with Roysten's procedure, and equality of the covariance matrices will be assessed with the Box M test. The ISI data from our previous trial did not show violations of these assumptions. If distributions are markedly skewed, we will apply transformations as appropriate. The biomarker data will likely require a logarithmic transformation, as is common practice. If heteroscedistic variance is found in the residuals for any of the models, a Box-Cox transformation will be applied to the data. As a last resort, appropriate nonparametric methods will be attempted, e.g. Wilcoxon rank sum test on change scores.[111,112] If outliers or influential data are detected, the accuracy of the data will be investigated. If no errors are found, analyses may be repeated after removing these cases to evaluate their impact on the results. However, the final analyses will include these data points.

10.6.2 ***Missing Values.*** Every effort will be made to facilitate participants' completion of questionnaires and provision of actigraphy and physical function data, and blood.[120] In the event of missing data, the reasons for missing data will be recorded and tabulated according to treatment group. Some missing data are inevitable. Under the missing at random (MAR) assumption, we will use multiple imputation to obtain unbiased estimates of key parameters. If data are suspected to be missing not at random (MNAR), a sensitivity analysis using the methods of Liublinska and Rubin (2014)[121] will be run to determine the impact on results. [112] If the estimates are similar to the ones obtained from the simpler analysis of only complete cases, we will report the complete-case analysis results. [112]

10.7 **Statistical Analyses**:

10.7.1 **Primary Aim 1 Analyses:** To determine if YOCAS©® is as effective as CBT-I and more effective than health education for improving **insomnia (ISI total)**, two separate analyses will be performed, each aimed at estimating the difference between arms in mean change from baseline with associated confidence intervals. The comparison of YOCAS©® to CBT-I is a non-inferiority hypothesis with a one-sided alpha, and the comparison of YOCAS©® to the health education control is a traditional null hypothesis of no difference with a two-sided alpha.[118,119] See the Statistical Power section for more details. A linear mixed effects ANCOVA will be used to assess the statistical significance of the differences in mean changes from baseline for the two groups (Hypothesis 1 = YOCAS©® vs. CBT-I;

Hypothesis 2 = YOCAS©® vs. health education). ***The response will be post-treatment ISI total score.*** The model fixed effects will be Group and Baseline ISI. NCORP Site will be included as a random effect. The REML method will be used to estimate the random effect variance components. If the NCORP Site variance component is significant, the fixed effects will be tested using F tests with the Kenward-Roger degrees of freedom adjustment.[122] If the NCORP Site variance component is not statistically significant, we will use ordinary least-squares estimation and F-Tests for testing the fixed effects. The mean difference between groups with associated 95% confidence intervals will be estimated using the appropriate contrasts. An alpha level of 0.025 will be used to adjust for multiple comparisons. Additional follow-up analyses will include NCORP site and cohort as covariates and examine possible interactions.

10.7.2 **Secondary Aim 2 Analyses:** To examine if YOCAS©® is effective for improving **objective symptoms of insomnia** (sleep latency, sleep efficiency, wake after sleep onset, sleep duration, and daytime napping via actigraphy) and **global sleep quality impairment** (PSQI total) compared to CBT-I and a health education control, we will use the same methods as for Primary Aim 1 with no multiple comparison adjustments.[123]

10.7.3 **Secondary Aim 3 Analyses:** To examine if YOCAS©® and CBT-I are effective for **maintaining improvements in insomnia at 3 and 6 months post-intervention** compared to a health education control, we will perform a longitudinal analysis[124] using the ISI total score at all five time points as the response. The fixed effects will be Time, Group (all three in this analysis), and Time by Group interaction. Within-subject random effects will initially be modeled assuming an unstructured covariance matrix, but will be simplified after inspection of the estimated covariance structure (e.g., compound symmetry). If NCORP Site variance in the primary analysis is statistically significant at the 0.05 level, it will be included as an additional random effect, independent of the within-subject random effects. REML estimation will be used. Fixed effects will be tested using F tests with the Kenward-Roger degrees of freedom adjustment.[122] The impact of group on the time trajectory of insomnia will be tested via the Time*Group interaction. Least-squares means for each Time and Group combination will be plotted to visualize and understand the time trajectories of insomnia. Differences in time trajectories between the three groups will be tested with no adjustments for multiple comparisons.[123]

10.7.4 **Exploratory Mechanistic Aim 4 Analyses:** To explore whether YOCAS©® is effective for improving **circadian activity rhythms (24 and 12 hour amplitudes and acrophases via actigraphy), physical function (i.e., cardiopulmonary [6-min. walk] and muscular function [dynamometry]), and inflammation (IL-6, IL-8, IL-10, IL-1β, IFN-γ, & TNFR1 via standardized ELISAs and multiplexes)** compared to CBT-I and a health education control, we will use the same analytical methods as for Primary Aim 1 to assess changes in the estimated parameters of the two-oscillator (12 and 24 hours) cosinor model[97] and the Hill function model.[125] These parameters include **Mesor (M), Amplitude (A1) and Acrophase (Phi1) for the 24-hour oscillator and Amplitude (A2) and Acrophase (Phi2) for the 12-hour oscillator**. Estimates will be from the log-transformed activity counts using nonlinear regression. Degree of rhythmicity will be assessed with the Fisher-transformed model multiple correlation. We will also fit single-oscillator models (24-hour Mesor, Amplitude, and Acrophase) for comparison with other published studies.[20,24] The time participants woke up in the morning and fell asleep in the evening will be extracted from weekly diaries. We will apply the same methods as for physical function and inflammation outcomes; inflammatory biomarkers will be log-transformed as needed.

10.7.5 **Exploratory Mechanistic Aim 5 Analyses:** To explore **whether changes in physical function, circadian rhythm and inflammation mediate the effect of YOCAS©® on insomnia**, we will use separate mediation analyses performed on pre-post ISI change scores (CS) and the above outcomes as potential mediators. Path analysis will be used, where the intervention affects CS, the intervention affects the mediator, and the mediator, in turn, affects the CS. We will also use structural equation modeling. Mediation will be assessed via indirect effect estimation using bootstrap-based 95% confidence intervals.[126,127] Latent variables will be introduced into the model for multiple measures of a common entity (e.g., cytokines for inflammation). If multiple measures are weakly correlated, we will split them

into separate measurement terms (e.g., pro- and anti-inflammatory cytokines). MPlus software will be used, with full-information maximum likelihood (FIML) estimation. Under MAR, this provides less biased estimates due to missing data.

10.7.6 **Additional Analyses:** The following analyses will be interpreted cautiously for hypothesis generation. We will use the same analytical methods described for Aims 2, 3, 4 and 5 to explore the interrelationships between insomnia, SQI, sleep chronotype, CRF, depression, anxiety, mood, hormone therapy, pain, cognitive problems, symptoms, exercise, cardiopulmonary function, strength, inflammation, stimulant and sleep medication use.

10.7.7 **Interim Analyses:** No interim analyses of efficacy data from the trial are planned.

11.0 Records To Be Kept

Measure	Screening	Baseline	Mid-Point Intervention	Post-Intervention	3 Month Follow-Up	6 Month Follow-Up
Eligibility and Consent		✓				
DSM-V	✓					
Insomnia Severity Index Screening	✓					
On-Study Data/Participant Interview		✓				
Clinical Record Information		✓				
Cancer Treatment Notes		✓				
Sleep Medication and CAM Use		✓	✓	✓	✓	✓
Stimulant Medication and CAM Use		✓	✓	✓	✓	✓
Insomnia Severity Index (ISI)		✓	✓	✓	✓	✓
Sleep Quality (PSQI)		✓	✓	✓	✓	✓
Sleep Chronotype (MEQ-SA)		✓	✓	✓	✓	✓
Actigraphy		✓	✓	✓	✓	✓
6-Minute Walk Test		✓	✓	✓	✓	✓
Handgrip Dynamometer Test		✓	✓	✓	✓	✓
Fasting Blood Draw (Blood Requisition Form)		✓	✓	✓	✓	✓
Symptom Inventory (SI)		✓	✓	✓	✓	✓
Fatigue Interference (BFI)		✓	✓	✓	✓	✓
Cancer-Related Fatigue (FACIT-F)		✓	✓	✓	✓	✓
Cancer-Related Fatigue (MFSI)		✓	✓	✓	✓	✓
Depression Symptoms (CES-D)		✓	✓	✓	✓	✓
Anxiety (STAI)		✓	✓	✓	✓	✓
Mood (POMS)		✓	✓	✓	✓	✓
Cognitive Problems (FACIT-COG)		✓	✓	✓	✓	✓
Quality of Life (FACIT)		✓	✓	✓	✓	✓
Pain (BPI)		✓	✓	✓	✓	✓
Pain (VAS)		✓	✓	✓	✓	✓
Leisure Time Physical Activity (GODIN)		✓	✓	✓	✓	✓
Daily Diary		✓	✓	✓	✓	✓
Feedback Questionnaire						✓
Qualitative Exit Interview						✓

Call Log		✓✓[1]	✓	✓	✓	✓
Attendance Log				✓		

[1]A second phone call is made at the end of baseline.

11.1 All written materials will be kept confidential, locked in the file room at the Research Base that is accessible only by Research Base personnel, and identified by study ID numbers. Electronic databases are password-protected with limited access.

11.2 Any treatment notes related to the study participant's cancer treatment should be submitted with the baseline assessment.

11.3 The Case Summary should accompany ALL data submissions. Completed forms must be electronically submitted through the URCC Box upload system within 30 days of assessment time point

11.4 All electronic data collected, i.e., actigraphy files and video recordings must be stored on a HIPAA compliant, regularly backed up network storage or computer immediately after collection until notified by URCC to destroy it.

12.0 Gender and Ethnic/Racial Minorities

12.1 **Minority Groups or Subgroups:** This clinical trial is open to both women and men who are survivors of cancer.

An estimate of minority participation from our URCC Research Base accruals between 3/1/2011 and 2/29/2012 for three large phase III clinical trials in our target population of cancer survivors indicates minority participation will be approximately 13%. Our research group found 142 of the 1078 (13.17%) patients accrued to these clinical trials categorized themselves as being from an ethnic or racial minority. One of these studies was Dr. Mustian's recently completed phase III clinical trial testing the effects of an exercise intervention on cancer-related fatigue.

Dr. Mustian has recently had success increasing minority accruals on her local single-site studies in Rochester, NY by implementing strategies suggested by the Recruitment and Retention Core of the URMC CTSI.

Male cancer patients have been underrepresented in yoga trials for cancer patients. In a systematic review and meta-analysis conducted in 2012, Buffart et al. found 13 published trials of yoga for cancer patients.[118] Twelve of these trials focused specifically on breast cancer; 11 recruited only female patients, and one reported that 5% of their sample was male. The thirteenth trial was a small (N=38) pilot trial focused on lymphomas; 39% of this sample was male.[53] In an analysis of population-based data, similarly, only 3.5% of men in the United States reported practicing yoga, compared to 10% of women.[119]

To ensure sufficient representation of male cancer patients in the current trial, the following steps will be taken. Research coordinators at the NCORP sites will be instructed to screen specifically for and oversample male cancer patients in their recruitment efforts, to account for the potential reticence of men to engage in a group-based yoga intervention. Where possible, coordinators conducting recruitment will be gender matched to the patients they are recruiting (i.e., male coordinators recruiting male patients, female coordinators recruiting female patients). Recruitment and study materials, including study manuals include both male and female models.

For this study, our goal is to increase minority recruitment to18% (a 5% increase). We will work closely with our minority-based NCORPs to ensure they have the resources and help they need to open this study and to effectively recruit participants and conduct the study. We will also work closely with our non-minority-based NCORPs to support increased minority accruals at all of our affiliated NCORPs. We will provide each NCORP with culturally

sensitive recruitment materials. Lastly, our IRB and all of our NCORP IRBs mandate that all study materials and measures meet federal guidelines and can be easily understood by individuals without a high school degree.

In addition, we will meet quarterly with Research Base staff and annually with all NCORPs; at face-to-face meetings and on audits where we will discuss minority recruitment levels and make adjustments in our recruitment strategies as needed in an earnest effort to increase minority recruitment for this trial.

Projected participation is shown below.

Racial Categories	Not Hispanic or Latino: Female	Not Hispanic or Latino: Male	Hispanic or Latino: Female	Hispanic or Latino: Male	Total
American Indian/Alaska Native	11	2	0	0	13
Asian	18	11	0	0	29
Native Hawaiian or Other Pacific Islander	8	7	0	0	15
Black or African American	43	22	5	1	71
White	483	80	17	5	585
More Than One Race	5	1	1	0	7
Total	568	123	23	6	720

13.0 References

1. Ancoli-Israel S. Recognition and treatment of sleep disturbances in cancer. *J Clin Oncol.* Dec 10 2009;27(35):5864-5866.

2. Savard J, Ivers H, Villa J, Caplette-Gingras A, Morin CM. Natural course of insomnia comorbid with cancer: an 18-month longitudinal study. *J Clin Oncol.* Sep 10 2011;29(26):3580-3586.

3. Palesh OG, Roscoe JA, Mustian KM, et al. Prevalence, demographics, and psychological associations of sleep disruption in patients with cancer: University of Rochester Cancer Center-Community Clinical Oncology Program. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jan 10 2010;28(2):292-298.

4. Berger AM, Farr LA, Kuhn BR, Fischer P, Agrawal S. Values of sleep/wake, activity/rest, circadian rhythms, and fatigue prior to adjuvant breast cancer chemotherapy. *Journal of pain and symptom management.* Apr 2007;33(4):398-409.

5. Ancoli-Israel S, Liu L, Marler MR, et al. Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Mar 2006;14(3):201-209.

6. Savard J, Simard S, Blanchet J, Ivers H, Morin CM. Prevalence, clinical characteristics, and risk factors for insomnia in the context of breast cancer. *Sleep.* Aug 01 2001;24(5):583-590.

7. Schultz PN, Klein MJ, Beck ML, Stava C, Sellin RV. Breast cancer: relationship between menopausal symptoms, physiologic health effects of cancer treatment and physical constraints on quality of life in long-term survivors. *J Clin Nurs.* Feb 2005;14(2):204-211.

8. Berger AM, Grem JL, Visovsky C, Marunda HA, Yurkovich JM. Fatigue and other variables during adjuvant chemotherapy for colon and rectal cancer. *Oncol Nurs Forum.* Nov 1 2010;37(6):E359-369.

9. Savard J, Morin CM. Insomnia in the context of cancer: a review of a neglected problem. *J Clin Oncol.* Feb 1 2001;19(3):895-908.

10. Pinto AC, de Azambuja E. Improving quality of life after breast cancer: dealing with symptoms. *Maturitas.* Dec 2011;70(4):343-348.

11. Partinen M HC. *Epidemiology of sleep disorders.* Philadelphia: Elsevier; 2005.

12. Mormont MC, Levi F. Circadian-system alterations during cancer processes: a review. *International journal of cancer. Journal international du cancer.* Jan 17 1997;70(2):241-247.

13. Mormont MC, Waterhouse J. Contribution of the rest-activity circadian rhythm to quality of life in cancer patients. *Chronobiology international.* Jan 2002;19(1):313-323.

14. Mustian KM, Janelsins M, Sprod L, et al. YOCAS©® Yoga Significantly Improves Circadian Rhythm, Anxiety, Mood and Sleep: A Randomized, Controlled Clinical Trial Among 410 Cancer Survivors. *Supportive Care in Cancer.* 2011;19(2):317-318.

15. Eismann EA, Lush E, Sephton SE. Circadian effects in cancer-relevant psychoneuroendocrine and immune pathways. *Psychoneuroendocrinology.* Aug 2010;35(7):963-976.

16. Sephton S, Spiegel D. Circadian disruption in cancer: a neuroendocrine-immune pathway from stress to disease? *Brain Behav Immun.* Oct 2003;17(5):321-328.

17. Ford DE, Kamerow DB. Epidemiologic study of sleep disturbances and psychiatric disorders. An opportunity for prevention? *Jama.* Sep 15 1989;262(11):1479-1484.

18. Vgontzas AN, Bixler EO, Lin HM, et al. Chronic insomnia is associated with nyctohemeral activation of the hypothalamic-pituitary-adrenal axis: clinical implications. *J Clin Endocrinol Metab.* Aug 2001;86(8):3787-3794.

19. Nader N, Chrousos GP, Kino T. Interactions of the circadian CLOCK system and the HPA axis. *Trends Endocrinol Metab.* May 2010;21(5):277-286.

20. Berger AM, Wielgus K, Hertzog M, Fischer P, Farr L. Patterns of circadian activity rhythms and their relationships with fatigue and anxiety/depression in women treated with breast cancer adjuvant chemotherapy. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Apr 19 2009.

21. Berger AM, Hertzog M, Geary CR, Fischer P, Farr L. Circadian rhythms, symptoms, physical functioning, and body mass index in breast cancer survivors. *Journal of cancer survivorship : research and practice.* Apr 7 2012.

22. Fernandes R, Stone P, al. e. Comparison between fatigue, sleep disturbance, and circadian rhythm in cancer inpatients and healthy volunteers: evaluation of diagnostic criteria for cancer-related fatigue. *Journal of Pain & Symptom Management.* 2006;32(3):245-254.

23. Fiorentino L, Rissling M, Liu L, Ancoli-Israel S. The Symptom Cluster of Sleep, Fatigue and Depressive Symptoms in Breast Cancer Patients: Severity of the Problem and Treatment Options. *Drug discovery today. Disease models.* Winter 2011;8(4):167-173.

24. Berger AM, Farr L. The influence of daytime inactivity and nighttime restlessness on cancer-related fatigue. *Oncology Nursing Forum.* 1999;26(10):1663-1671.

25. Ryan JL, Carroll JK, Ryan EP, Mustian KM, Fiscella K, Morrow GR. Mechanisms of cancer-related fatigue. *The Oncologist.* 2007;12(1):22-34.

26. Bower JE, Bower JE. Cancer-related fatigue: links with inflammation in cancer patients and survivors. [Review] [52 refs]. *Brain, Behavior, & Immunity.* 2007;21(7):863-871.

27. Bower JE, Ganz PA, Aziz N, Fahey JL. Fatigue and proinflammatory cytokine activity in breast cancer survivors. *Psychosomatic Medicine.* 2002;64(4):604-611.

28. Bower JE, Ganz PA, Aziz N, Fahey JL, Cole SW. T-cell homeostasis in breast cancer survivors with persistent fatigue. *Journal of the National Cancer Institute.* 2003;95(15):1165-1168.

29. Bower JE, Ganz PA, Aziz N, et al. Inflammatory responses to psychological stress in fatigued breast cancer survivors: relationship to glucocorticoids. *Brain, Behavior, & Immunity.* 2007;21(3):251-258.

30. Bower JE, Ganz PA, Dickerson SS, Petersen L, Aziz N, Fahey JL. Diurnal cortisol rhythm and fatigue in breast cancer survivors. *Psychoneuroendocrinology.* 2005;30:92-100.

31. Ardies CM. Exercise, cachexia, and cancer therapy: A molecular rationale. *Nutrition & Cancer.* 2002;42(2):143-157.

32. Cleeland CS, Bennett GJ, Dantzer R, et al. Are the symptoms of cancer and cancer treatment due to a shared biologic mechanism? A cytokine-immunologic model of cancer symptoms. *Cancer.* 2003;97(11):2919-2925.

33. Wood LJ, Nail LM, Gilster A, et al. Cancer chemotherapy-related symptoms: evidence to suggest a role for proinflammatory cytokines. [Review] [96 refs]. *Oncology Nursing Forum.* 2006;33(3):535-542.

34. Bluthe RM, Michaud B, Poli V, Dantzer R. Role of IL-6 in cytokine-induced sickness behavior: a study with IL-6 deficient mice. *Physiology & Behavior.* 2000;70(3-4):367-373.

35. Sprod LK, Palesh OG, Janelsins MC, et al. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. *Community Oncology.* Oct 2010;7(10):463-471.

36. Sprod LK, Janelsins MC, Palesh OG, et al. Health-related quality of life and biomarkers in breast cancer survivors participating in tai chi chuan. *Journal of cancer survivorship : research and practice.* Jun 2012;6(2):146-154.

37. Sprod LK, Palesh OG, Janelsins MC, et al. Exercise, sleep quality, and mediators of sleep in breast and prostate cancer patients receiving radiation therapy. *Community oncology.* Oct 2010;7(10):463-471.

38. Janelsins MC, Davis PG, Wideman L, et al. Effects of Tai Chi Chuan on insulin and cytokine levels in a randomized controlled pilot study on breast cancer survivors. *Clinical breast cancer.* Jun 2011;11(3):161-170.

39. Mustian KM, Sprod LK, Palesh OG, et al. Exercise for the management of side effects and quality of life among cancer survivors. *Curr Sports Med Rep.* Nov-Dec 2009;8(6):325-330.

40. Mustian KM, Hofman M, Morrow GR, et al. Cancer-Related Fatigue and Shortness of Breath Among Cancer Survivors: A Prospective URCC CCOP Study. *NCI Cancer Survivorship Conference.* 2006.

41. Mustian KM, Katula J, Williams J, Moynihan JA, Morrow GR. Tai Chi Chuan, Immune Function, and Cardiorespiratory Fitness Among Breast Cancer Survivors. *Annals of Behavioral Medicine.* 2007;33:95.

42. Mustian KM, Katula JA, Gill DL, Roscoe JA, Lang D, Murphy K. Tai Chi Chuan, health-related quality of life and self-esteem: A randomized trial with breast cancer survivors. *Supportive Care in Cancer.* 2004;12(12):871-876.

43. Mustian KM, Katula JA, Zhao H. A pilot study to assess the influence of tai chi chuan on functional capacity among breast cancer survivors. *The Journal of Supportive Oncology.* 2006;4(3):139-145.

44. Mustian KM, Palesh O, Heckler CE, et al. Cancer-Related fatigue interferes with activities of daily living among 753 patients receiving chemotherapy: A URCC CCOP study. *J Clin Oncol.* 2008;26:(May 20 suppl; abstr 9500).

45. Mustian KM, Palesh OG, Flecksteiner SA. Tai Chi Chuan for breast cancer survivors. *Med Sport Sci.* 2008;52:209-217.

46. Quillin JM, Tracy K, Ancker JS, et al. Health care system approaches for cancer patient communication. *Journal of health communication.* 2009;14 Suppl 1:85-94.

47. Peppone LJ, Mustian KM, Janelsins MC, et al. Effects of a Structured Weight-Bearing Exercise Program on Bone Metabolism Among Breast Cancer Survivors: A Feasibility Trial. *Clin Breast Cancer.* 2010;10:224-229.

48. Palesh O, Peppone L, Innominato P, et al. Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. *Nature and Science of Sleep.* 2012;4:151-162.

49. Chen ML, Yu CT, Yang CH. Sleep disturbances and quality of life in lung cancer patients undergoing chemotherapy. *Lung cancer.* Dec 2008;62(3):391-400.

50. Savard J, Ivers H, Savard MH, Morin CM. Cancer treatments and their side effects are associated with aggravation of insomnia: Results of a longitudinal study. *Cancer.* May 15 2015;121(10):1703-1711.

51. Roscoe JA, Garland SN, Heckler CE, et al. Randomized placebo-controlled trial of cognitive behavioral therapy and armodafinil for insomnia after cancer treatment. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology.* Jan 10 2015;33(2):165-171.

52. Heckler CE, Garland SN, Peoples AR, et al. Cognitive behavioral therapy for insomnia, but not armodafinil, improves fatigue in cancer survivors with insomnia: a randomized placebo-controlled trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* May 2016;24(5):2059-2066.

53. Kamen C, Garland SN, Heckler CE, et al. Social Support, Insomnia, and Adherence to Cognitive Behavioral Therapy for Insomnia After Cancer Treatment. *Behavioral sleep medicine.* Jan 27 2017:1-13.

54. Savard J, Ivers H. The evolution of fear of cancer recurrence during the cancer care trajectory and its relationship with cancer characteristics. *Journal of psychosomatic research.* Apr 2013;74(4):354-360.

55. Savard J, Ivers H, Savard MH, Morin CM. Long-Term Effects of Two Formats of Cognitive Behavioral Therapy for Insomnia Comorbid with Breast Cancer. *Sleep.* Apr 01 2016;39(4):813-823.

56. NCCN. NCCN Clinical Practice Guidelines in Oncology Survivorship. 2016; https://www.nccn.org/professionals/physician_gls/pdf/survivorship.pdf. Accessed 3-7-2017, 2017.

57. Espie CA, Fleming L, Cassidy J, et al. Randomized controlled clinical effectiveness trial of cognitive behavior therapy compared with treatment as usual for persistent insomnia in patients with cancer. *J Clin Oncol.* Oct 1 2008;26(28):4651-4658.

58. Savard J, Simard S, Ivers H, Morin CM. Randomized study on the efficacy of cognitive-behavioral therapy for insomnia secondary to breast cancer, part II: Immunologic effects. *J Clin Oncol.* Sep 1 2005;23(25):6097-6106.

59. Carson JW, Carson KM, Porter LS, Keefe FJ, Seewaldt VL. Yoga of Awareness program for menopausal symptoms in breast cancer survivors: results from a randomized trial. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* Oct 2009;17(10):1301-1309.

60. Chandwani KD, Thornton B, Perkins GH, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. *Journal of the Society for Integrative Oncology.* Spring 2010;8(2):43-55.
61. Cohen L, Warneke C, Fouladi RT, Rodriguez MA, Chaoul-Reich A. Psychological adjustment and sleep quality in a randomized trial of the effects of a Tibetan yoga intervention in patients with lymphoma. *Cancer.* May 15 2004;100(10):2253-2260.
62. Duncan MD, Leis A, Taylor-Brown JW. Impact and outcomes of an Iyengar yoga program in a cancer centre. *Curr Oncol.* Aug 2008;15 Suppl 2:s109 es172-108.
63. Joseph CD. Psychological supportive therapy for cancer patients. *Indian J Cancer.* Nov-Dec 1983;20(5):268-270.
64. Mustian KM, Palesh OG, Sprod LK, et al. YOCAS©® Yoga Significantly Improves Sleep, Fatigue and Quality of Life: A URCC CCOP Randomized, Controlled Clinical Trial Among 410 Cancer Survivors. *Journal of Clinical Oncology.* 2010;28(15):639.
65. Mustian KM, Palesh OG, Sprod LK, et al. YOCAS©® Yoga Improves Insomnia Among 410 Cancer Survivors. *International Journal of Behavioral Medicine.* 2010;17(1):209.
66. Rao A, Nagendra HR, Raghuram N, et al. Influence of yoga on postoperative outcomes and wound healing in early operable breast cancer patients undergoing surgery. *International journal of yoga.* 2008;1(1):33-41.
67. Rao RM, Nagendra HR, Raguhuram N, et al. Influence of yoga on mood states, distress, quality of life, and immune outcomes in early stage breast cancer patients undergoing surgery. *International journal of yoga.* 2008;1(1):11-19.
68. Raub JA. Psychophysiologic effects of Hatha Yoga on musculoskeletal and cardiopulmonary function: a literature review. *J Altern Complement Med.* Dec 2002;8(6):797-812.
69. Rosenbaum E, Gautier H, Fobair P, et al. Cancer supportive care, improving the quality of life for cancer patients. A program evaluation report. *Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer.* May 2004;12(5):293-301.
70. Speed-Andrews AE, Stevinson, C., Belanger, L.J., Mirus, J.J., Courneya, K.S. Pilot evaluation of Iyengar yoga program for breast cancer survivors. *Cancer Nursing.* 2010;33(5):369-381.
71. Ulger O, Yagl, N.V. Effects of yoga on the quality of life in cancer patients. *Complement Ther Clin Pract.* 2010;16:60-63.
72. Vadiraja HS, Raghavendra RM, Nagarathna R, et al. Effects of a yoga program on cortisol rhythm and mood states in early breast cancer patients undergoing adjuvant radiotherapy: a randomized controlled trial. *Integrative cancer therapies.* Mar 2009;8(1):37-46.
73. Vadiraja SH, Rao MR, Nagendra RH, et al. Effects of yoga on symptom management in breast cancer patients: A randomized controlled trial. *International journal of yoga.* Jul 2009;2(2):73-79.
74. Kirk M, Boon B. *Hatha Yoga for greater strength, flexibility, and focus.* Champaign, IL: Human Kinetics; 2003.
75. Bower JE, Woolery A, Sternlieb B, Garet D. Yoga for Cancer Patients and Survivors. *Cancer Control.* 2005;12(3):165-171.
76. Bower JE, Garet D, Sternlieb B, et al. Yoga for persistent fatigue in breast cancer survivors: A randomized controlled trial. *Cancer.* Dec 16 2011.
77. Ross A, Thomas S. The health benefits of yoga and exercise: a review of comparison studies. *J Altern Complement Med.* Jan 2010;16(1):3-12.
78. Drake CL, Roehrs T, Roth T. Insomnia causes, consequences, and therapeutics: an overview. *Depress Anxiety.* 2003;18(4):163-176.
79. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nature reviews. Genetics.* Oct 2008;9(10):764-775.
80. Ko CH, Takahashi JS. Molecular components of the mammalian circadian clock. *Human molecular genetics.* Oct 15 2006;15 Spec No 2:R271-277.
81. Kalsbeek Aea. SCN Outputs and the hypothalamic balance of life. *J Biol Rhythms.* 2006;21:458-469.
82. Petersen AM, Pedersen BK, Petersen AMW. The role of IL-6 in mediating the anti-inflammatory effects of exercise. [Review] [65 refs]. *Journal of Physiology & Pharmacology.* 2006;57 Suppl 10:43-51.
83. Kirshbaum MN. A review of the benefits of whole body exercise during and after treatment for breast cancer. *J Clin Nurs.* Jan 2007;16(1):104-121.
84. McArdle W, Katch F, Katch V. *Exercise Physiology: Energy, Nutrition, and Human Performance.* Philadelphia, PA: Lippincott, Williams and Wilkins; 2007.

85. Kubitz KA, Landers DM, Petruzzello SJ, Han M. The effects of acute and chronic exercise on sleep. A meta-analytic review. *Sports medicine.* Apr 1996;21(4):277-291.
86. Sherrill DL, Kotchou K, Quan SF. Association of physical activity and human sleep disorders. *Archives of internal medicine.* Sep 28 1998;158(17):1894-1898.
87. Youngstedt SD. Effects of exercise on sleep. *Clinics in sports medicine.* Apr 2005;24(2):355-365, xi.
88. Driver HS, Taylor SR. Exercise and sleep. *Sleep medicine reviews.* Aug 2000;4(4):387-402.
89. Field T. Yoga clinical research review. *Complementary therapies in clinical practice.* Feb 2011;17(1):1-8.
90. Lipton L. Using Yoga to Treat Disease: An Evidence-Based Review. *Journal of the American Academy of Physician Assistants.* 2008;21(2):94-41.
91. Innes KE, Bourguignon C, Taylor AG. Risk indices associated with the insulin resistance syndrome, cardiovascular disease, and possible protection with yoga: a systematic review. *The Journal of the American Board of Family Practice / American Board of Family Practice.* Nov-Dec 2005;18(6):491-519.
92. Jayasinghe SR. Yoga in Cardiac Health. *European Journal of Cardiovascular Prevention and Rehabilitation.* 2004;11:369-375.
93. Mustian KM, Sprod L, Janelsins M, et al. A Multicenter Randomized Controlled Trial of Yoga for Sleep Quality Among Cancer Surivors. *Journal of Clinical Oncology.* 2013;In Press.
94. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Research.* 1989;28(2):193-213.
95. Savard MH, Savard J, Simard S, Ivers H. Empirical validation of the Insomnia Severity Index in cancer patients. *Psycho-oncology.* Jun 2005;14(6):429-441.
96. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep medicine.* Jul 2001;2(4):297-307.
97. Teicher MH, Barber NI. COSIFIT: an interactive program for simultaneous multioscillator cosinor analysis of time-series data. *Computers and biomedical research, an international journal.* Jun 1990;23(3):283-295.
98. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med.* Jul 2001;2(4):297-307.
99. Yang M, Morin CM, Schafer K, Wallenstein G. Defining the minimally important difference for Insomnia Severity Index. APSS (Associated Professional Sleep Societies); 2008; Baltimore, MD.
100. Morin CM. *Insomnia: Psychological assessment and management.* New York, NY: Guilford Press; 1993.
101. Beck SL, Schwartz AL, Towsley G, Dudley W, Barsevick A. Psychometric evaluation of the Pittsburgh Sleep Quality Index in cancer patients. *J Pain Symptom Manage.* Feb 2004;27(2):140-148.
102. Buysse DJ, Reynolds CF, 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res.* May 1989;28(2):193-213.
103. Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. *International journal of chronobiology.* 1976;4(2):97-110.
104. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. *Cancer.* Oct 1 2000;89(7):1634-1646.
105. Hann DM, Denniston MM, Baker F. Measurement of fatigue in cancer patients: further validation of the Fatigue Symptom Inventory. *Qual Life Res.* 2000;9(7):847-854.
106. Mendoza TR, Wang XS, Cleeland CS, et al. The rapid assessment of fatigue severity in cancer patients: Use of the Brief Fatigue Inventory. *Cancer.* 1999;85(5):1186-1196.
107. Stein KD, Jacobsen PB, Blanchard CM, Thors C. Further validation of the multidimensional fatigue symptom inventory-short form. *J Pain Symptom Manage.* Jan 2004;27(1):14-23.
108. Lai JS, Butt Z, Wagner L, et al. Evaluating the dimensionality of perceived cognitive function. *J Pain Symptom Manage.* Jun 2009;37(6):982-995.
109. Cleeland CS, Ryan KM. Pain assessment: global use of the Brief Pain Inventory. *Ann Acad Med Singapore.* Mar 1994;23(2):129-138.
110. Godin G, Shephard RJ. A simple method to assess exercise behavior in the community. *Canadian journal of applied sport sciences. Journal canadien des sciences appliquees au sport.* Sep 1985;10(3):141-146.
111. Jacobs D, Ainsworth B, Hartman T, Leon A. A simultaneous evaluation of 10 commonly used physical activity questionnaires. *Medicine and Science in Sport and Exercise.* 1993;25 81-91.
112. Courneya KS, Friedenreich CM. Relationship between exercise pattern across the cancer experience and current quality of life in colorectal cancer survivors. *Journal of Alternative & Complementary Medicine.* Fall 1997;3(3):215-226.

113. Courneya KS, Friedenreich CM. Relationship between exercise during treatment and current quality of life among survivors of breast cancer. *Journal of Psychosocial Oncology.* 1997;15:35-57.
114. Courneya KS, Friedenreich CM. Physical exercise and quality of life following cancer diagnosis: a literature review. *Annals of Behavioral Medicine.* Spring 1999;21(2):171-179.
115. Courneya KS, Keats MR, Turner AR. Physical exercise and quality of life in cancer patients following high dose chemotherapy and autologous bone marrow transplantation. *Psycho-Oncology.* 2000;9(2):127-136.
116. Morin CM, Vallieres A, Guay B, et al. Cognitive behavioral therapy, singly and combined with medication, for persistent insomnia: a randomized controlled trial. *JAMA : the journal of the American Medical Association.* May 20 2009;301(19):2005-2015.
117. Garland SN, Carlson LE, Antle MC, Samuels C, Campbell T. I-CAN SLEEP: rationale and design of a non-inferiority RCT of Mindfulness-based Stress Reduction and Cognitive Behavioral Therapy for the treatment of Insomnia in CANcer survivors. *Contemporary clinical trials.* Sep 2011;32(5):747-754.
118. Borm GF, Fransen J, Lemmens WA. A simple sample size formula for analysis of covariance in randomized clinical trials. *Journal of clinical epidemiology.* Dec 2007;60(12):1234-1238.
119. Julious SA. *Sample sizes for clinical trials.* Boca Raton: CRC Press/Taylor & Francis; 2010.
120. Wisniewski SR, Leon AC, Otto MW, Trivedi MH. Prevention of missing data in clinical research studies. *Biological psychiatry.* Jun 1 2006;59(11):997-1000.
121. Liublinska V, Rubin DB. Sensitivity analysis for a partially missing binary outcome in a two-arm randomized clinical trial. *Stat Med.* Oct 30 2014;33(24):4170-4185.
122. Kenward MG, Roger JH. Small sample inference for fixed effects from restricted maximum likelihood. *Biometrics.* 1997;53(3):983-997.
123. Dmitrienko A, Tamhane AC, Bretz F. *Multiple testing problems in pharmaceutical statistics.* Boca Raton, FL: Chapman & Hall/CRC; 2010.
124. Diggle PJ, Heagerty P, Liang KY, Zeger. *Analysis of Longitudinal Data* Oxford, UK: Oxford University Press; 2002.
125. Marler MR, Gehrman P, Martin JL, Ancoli-Israel S. The sigmoidally transformed cosine curve: a mathematical model for circadian rhythms with symmetric non-sinusoidal shapes. *Statistics in medicine.* Nov 30 2006;25(22):3893-3904.
126. MacKinnon D. *Introduction to Statistical Mediation Analysis.* New York: Lawrence Erlbaum Associates; 2008.
127. Hays A. Beyond Baron and Kenny: Statistical Mediation Analysis in the New Millennium. *Communication Monographs.* 2009;76(4):408-420.