The following protocol information is provided solely to describe how the authors conducted the research underlying the published report associated with the following article:

A Multi-Center Randomized Controlled Trial of Yoga for Sleep Quality Among Cancer Survivors

Mustian, et al

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UNIVERSITY OF ROCHESTER
CANCER CENTER CCOP RESEARCH BASE

Yoga for Persistent Sleep Disturbance in Cancer Survivors
NCI Protocol URCC 04-01
URCC U3905

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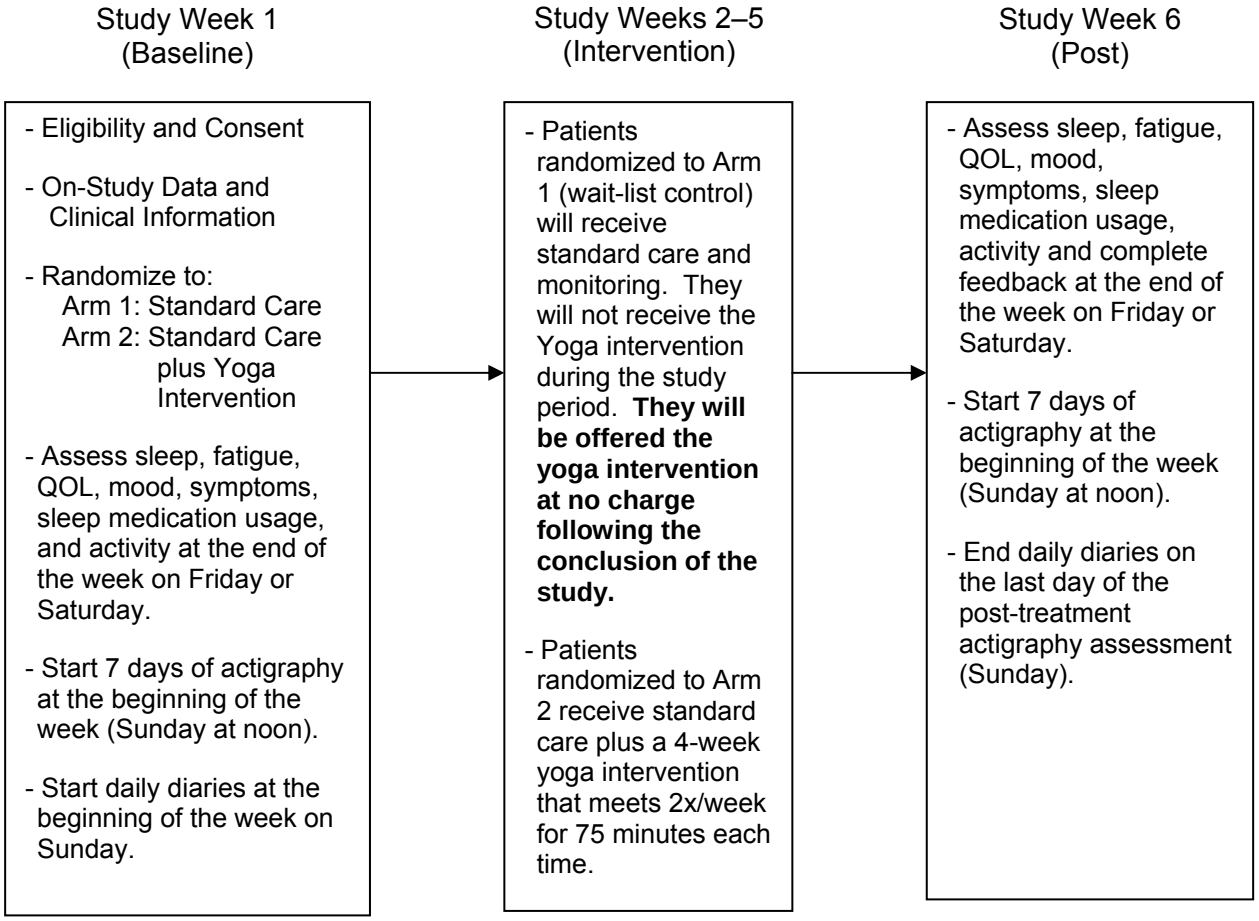
Study Schema



Notes:

- A Study Week is defined as one calendar week beginning on Sunday at 12:00 noon and ending the following Sunday at 11:59 am.
- QOL = quality of life.

1.0 Introduction

Why Cancer-Related Sleep Disturbance (CRSD) is a Concern. Cancer-related sleep disturbance (CRSD) is reported by 31% to 54% of cancer patients and is one of the most frequently experienced side effects resulting from cancer diagnosis and treatment.[1-3] Additionally, persistent sleep disruptions have been documented in 23% to 44% of cancer survivors for years after diagnosis and treatment.[4,5] Moreover, results from a prospective "Patient Needs Assessment Survey" conducted by our group through the University of Rochester Cancer Center Community Clinical Oncology Program Research Base (URCC CCOP) suggest that 79% of cancer patients report CRSD during chemotherapy or radiation therapy and 65% of cancer survivors (N = 652) continue to report CRSD 6 months after the completion of treatments. When assessed by the 11-point URCC Symptom Inventory (0 = symptom not present to 10 = as bad as you can imagine), the mean level of CRSD reported by patients was 5.36 (SE = 0.11) during treatment and remained high at 4.23 (SE = 0.13) 6 months after the completion of treatment.

2.0 Background

Despite the high frequency of CRSD reported by patients, this area has received very little attention from clinicians and researchers, resulting in a paucity of large randomized controlled trial data to guide standard clinical practice.[1,6,7] Several reasons are posited for this lack of attention to CRSD among patients and survivors, such as 1) sleep disruptions are often viewed as a normal and only temporary reaction to cancer diagnosis and treatment, 2) sleep disturbances are viewed as secondary symptoms concomitant with depression or anxiety and are expected to resolve naturally with adequate treatment of these other symptoms, 3) patients and clinicians may fail to adequately communicate regarding the extent of sleep disruptions, and 4) oncology professionals may not possess adequate knowledge of diagnostic and treatment options regarding sleep difficulties.[1]

Indeed, evidence suggests that CRSD is a common problem for cancer patients and survivors and that this problem presents more frequently in cancer patients and survivors than in the general population.[8,9] Importantly, sleep disruptions portend a less than optimal recovery, which may prevent the resumption of a cancer survivor's normal daily activities and impair quality of life (QOL). In addition, CRSD may lead to other debilitating problems, such as fatigue, mood disturbance, muscle weakness and cognitive impairment, and the inability to pursue occupational and social activities.[1,10-15]

Current Methods for Managing CRSD

The established pharmacological approaches to managing sleep disturbance or insomnia include the use of benzodiazepines (e.g., temazepam), benzodiazepine-receptor agonists (e.g., zolpidem) and sedating antidepressants (e.g., trazodone). Acutely, benzodiazepines and benzodiazepine-receptor agonists produce a 30–50% reduction in illness severity, and these effects are maintainable for periods of up to 6 months. It is unclear from current data whether long-term maintenance therapy is possible with standard hypnotic regimens or whether these

approaches can yield long-term gains in the absence of continued therapy. Regarding sedating antidepressants, there are few data regarding their acute effects, their comparability to standard therapeutics, and their durability over time. Nonetheless, the use of sedating antidepressants is preferred by many for essentially two reasons, which are independent of efficacy and effectiveness concerns: 1) clear evidence of safety with long-term use combined with low abuse potential and 2) the common perception that insomnia is a sub-clinical symptom of depression and is thus appropriately treated with antidepressants. Behavioral therapy, generally involving sleep restriction, cognitive therapy, and attention to good sleep hygiene, although costly and time consuming, is also used either independently or in conjunction with pharmacological aids to treat sleep problems.

Given the persistent and pervasive nature of sleep disturbances among cancer survivors despite currently available pharmacological and behavioral treatment options, additional effective interventions are needed. Thus, phase II and phase III randomized controlled trials to ascertain the efficacy and eventually the effectiveness of behavioral interventions that show promise in alleviating CRSD problems are warranted to provide additional care options.

Yoga Therapies

Patients distressed about treatment side effects, such as CRSD, are increasingly turning to complementary and alternative medicine (CAM) for non-pharmacological solutions.[16-18] In fact, data from the previously mentioned URCC CCOP survey indicate that 91% of patients (N=750) utilized CAM during treatment and 94% (N=651) used CAM during the 6-month period after the completion of standard treatments (e.g., surgery, chemotherapy, radiation therapy, biological response modification therapy).[19] The most common forms of CAM used by patients who completed the survey include prayer, relaxation and exercise. Other CAM interventions utilize mindfulness practices (e.g., meditation, visualization and breathing) integrated with movement (e.g., hand gestures and postures) to promote a state of well-being and health.

One particular type of CAM intervention, collectively known as yogas, is based on Eastern traditions from India (e.g., Classical, Advaita Vedanta, Tantra), Tibet (e.g., Tibetan), and China (e.g., Chi Kung, Tai Chi).[7,20] 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. The earliest forms of yoga were firmly rooted in introspective and meditative practices based on Vedic, Upanishad and Sutra texts. These early forms ultimately led to what is known today as classical yoga. The philosophical purpose of classical yoga is to connect the body and mind in order to separate one’s true self from the body and mind or, in other words, to get into the body so that one can transcend it. The system of classical yoga based largely on the yoga Sutras is the most common style of yoga taught today in the West. [7,20,21 20]

Yoga has established programs of training, specialized training centers, and a national governing body, called the Yoga Alliance, to regulate the discipline of yoga instruction. In order to be considered a Registered Yoga Teacher by the Yoga Alliance, practitioners must have 200 hours of training to receive their initial certification and over 500 hours of training to be designated an advanced yoga practitioner. Practitioners must also complete training in the specific areas of yoga techniques (e.g., asanas, meditation, pranayama), pedagogical methods, anatomy and physiology, philosophy and ethics, as well as complete supervised practicums. Conversations with local Yoga Alliance certified instructors revealed that a traditional holistic yoga session typically lasts 75-90 minutes and utilizes meditation (dhyana), gazes (drishtis), breathing (pranayama), hand gestures (mudras) and yoga postures (asanas) to encourage the individual (e.g., cancer patient/survivor) to become aware of various sensations, attune to the

self, and adopt a daily regimen of yoga practice that will ultimately lead to feelings of relaxation, symptom relief, personal empowerment and health. These classes are commonly taught in monthly sessions (approximately 4 weeks) during which participants are able to attend 1–3 classes a week; however, there is variation from one yoga studio to another and from community to community.

Preliminary Studies

Results from five previous studies provide the primary support for the current proposal. These studies have shown that participation in stress reduction programs consisting of traditional holistic yoga and mindfulness-based exercises result in statistically significant improvements in CRSD, QOL, stress, and tolerance of cancer treatment, as well as reductions in sleep medication usage. Furthermore, these studies indicate that clinicians and patients are very receptive to stress reduction programs, including yoga and mindfulness practices, as a treatment modality in traditional cancer centers, and that it is feasible to recruit patients and conduct these types of interventions in a wide variety of communities.

Joseph and colleagues[22] conducted an early study comparing yoga, support therapy and meditation interventions among 125 cancer patients undergoing radiation therapy. The 8-week yoga intervention consisted of simple yoga relaxation exercises two times a week for 90 minutes, and included yoga postures, breathing and visualization. Participants in the yoga arm of this study reported improvements in sleep, QOL, treatment tolerance, mood, appetite and bowel function. However, this study has several limitations. The researchers did not utilize psychometrically sound self-report or objective measures to assess sleep. Furthermore, there was no control group that did not receive a behavioral intervention for comparison, making it impossible to discern if yoga had an actual positive influence on sleep or if the natural course of sleep simply would have improved without intervention. Despite these limitations, this study suggests that cancer patients derive sleep benefits from participation in yoga.

Speca and collegues[23] also conducted a preliminary study, with 109 early or late stage cancer patients, comparing the efficacy of a 7-week mindfulness-based stress reduction (MBSR) program that included yoga, group support, meditation and imagery sessions to a wait-list control group. The yoga portion of the intervention included gentle Hatha yoga stretches and poses, breathing and meditation exercises performed once a week as part of the 90-minute class for 7 weeks. Cancer patients in the MBSR program reported significant improvements in mood and stress compared with the wait-list control patients. This study also has limitations, including 1) the patient sample was a convenience sample (any patient with a diagnosis of cancer could enroll), 2) the yoga was offered as part of a larger MBSR program, 3) no comparisons were made with a control group, and 4) changes in sleep were not reported. Although these limitations cannot be ignored, the results of this study support the positive benefits of yoga for cancer survivors.

Additionally, Carlson and colleagues[24,25] conducted a quasi-experimental pilot study examining the efficacy of an 8-week MBSR program for improving QOL, mood, stress, immune function and hypothalamus–pituitary–adrenal (HPA) axis function among 59 breast and prostate cancer patients. The program was modeled after the Massachusetts Medical Center program headed by Kabat-Zinn[26] and included one 90-minute session a week for 8 weeks along with a 3-hour silent retreat between weeks 6 and 7. The curriculum consisted of the following three major components: 1) experiential practice of gentle Hatha yoga (including yoga stretches and poses, and breathing and meditation exercises) performed once a week during the 90-minute sessions and at home; 2) educational materials related to mindfulness, relaxation, meditation and yoga;

and 3) group processing and discussion. Cancer patients completing the study reported significant improvements in sleep and QOL, as well as shifts in immune and HPA axes functioning that are consistent with more normal profiles. Limitations of this study include the following: 1) although the study involved well-defined eligibility criteria, patients were not randomized to the intervention; 2) the yoga was part of a larger MBSR program; 3) there was no control group for comparison; and 4) changes were not assessed using psychometrically sound self-report and/or objective measures specifically focused on sleep. In spite of these limitations, preliminary evidence from this study indicates that participation in yoga provides positive benefits in sleep for cancer survivors.

Shapiro and colleagues[27] also recently conducted a preliminary study comparing the efficacy of an MBSR program and a "free choice" condition for improving sleep among 63 women who were previously diagnosed with breast cancer, were currently disease free, and were within 2 years post-treatment. This MBSR intervention was also modeled after the Massachusetts Medical Center program headed by Kabat-Zinn[26] and included one 120-minute session a week along with a 6-hour silent retreat over the course of 6 weeks. The intervention consisted of 1) gentle Hatha yoga stretches and poses, and breathing and meditation exercises, and 2) additional mind-body exercises with emphasis on meditation and attentional focus. Cancer patients completing the study reported improvements in sleep, with those women in the MBSR program who reported a higher level of practice demonstrating significantly improved sleep quality. The limitations of this study are 1) there was no control group that did not receive a behavioral intervention for comparison, 2) in the "free choice" condition it is not clear whether patients may have chosen to participate in yoga on their own, 3) the yoga was offered as part of a larger program, and 4) there was no objective measure of sleep. However, as previously noted, these results are consistent with those summarized from other studies and provide preliminary evidence regarding the positive influence of yoga on sleep in cancer survivors.

More recently, Cohen and colleagues[7] conducted a pilot study comparing the effectiveness of a Tibetan yoga stress reduction program to a wait-list control for improving sleep, fatigue and psychological adjustment among 39 lymphoma patients who were actively receiving treatment or within 12 months post-treatment. The Tibetan yoga intervention consisted of one yoga session a week for 7-weeks, with foci on yoga postures, visualization, breathing, and mindfulness. Importantly, this is the first and only study examining a form of yoga other than gentle Hatha yoga. Personal communications with the yoga instructor (Alejandro Chaoul-Reich) for this study revealed two important considerations: 1) gentle Hatha yoga provides some of the fundamental basis for Tibetan yoga and 2) certified Tibetan yoga instructors are exceptionally rare in the United States (approximately 6 nationwide). Despite the subtle differences in the yoga intervention, cancer patients and survivors in the yoga arm reported significantly less sleep disturbance, better sleep quality, shorter sleep latency, longer sleep duration, and less use of sleep medications compared with patients in the wait-list control. Although this study employed a yoga intervention exclusively, not as part of a larger program, the data are limited because the sample was small and a very specific form of yoga, Tibetan yoga, which is not readily available in most communities in the United States, was used. However, this form of yoga, as noted, does incorporate aspects of gentle Hatha/restorative yoga. Again, the results of this study provide preliminary support for the efficacy of yoga in improving sleep quality among cancer survivors.

Most recently, Rosenbaum and colleagues[28] published a program evaluation report of the Stanford Cancer Supportive Care Program (SCSCP) at the Center for Integrative Medicine at Stanford Hospital and Clinics, a multifaceted program that is free to cancer patients and their families and provides programming in eight domains (physical well-being, knowledge, coping,

support, good medical care, life goals, financial stability and spirituality/religion). One particular component of the physical well-being program domain involved offering gentle restorative yoga classes twice a week for patients that included stretching, poses, breathing and the use of props when necessary. Although this program report is not a clinical report on a randomized controlled trial using psychometrically validated subjective and/or objective measures of sleep, the results do suggest that yoga was the most popular class attended by a large number of the cancer patients participating in the SCSCP and, interestingly, the convenience sample of patients participating in yoga reported improvements in sleep, energy, stress, well-being and pain.

Rationale for Choosing Gentle Hatha Yoga as the Intervention for the Proposed Study

Just as there are many different paths a person can take and ultimately end up at the same final destination, there are multiple paths of yoga, even within classical yoga, all of which seek to meet the spiritual, cultural, transcendent and healthful needs of an individual. One such path, Hatha yoga, is a particular form of yoga that is traditionally characterized by a holistic sequence of meditative, breathing and physical alignment exercises all of which are designed to promote health and well-being.[20] Moreover, Hatha yoga is often taught as a fundamental basis for other types of yoga.[20,29] Currently, Hatha yoga is the most popular form of yoga in the West[7,20,21] and likely the most widely used and accepted form of yoga for therapy in traditional Western medicine.

Hatha yoga, which includes the traditional holistic breathing and meditative components, has an emerging body of research in clinical settings that is suggestive of significant positive contributions to a patient's well-being.[21,30-32] For example, this type of yoga has been found to improve arthritis,[7,33] asthma,[7,33,34] lipid profiles,[35] hypertension,[36] epileptic seizures,[37] and musculoskeletal disease. Furthermore, preliminary research has demonstrated the ability of yoga to improve sleep,[7,20,22,24,25,27] QOL, stress, appetite, mood, bowel habits, immune function, HPA axis function, and treatment tolerance [22-24,38] among cancer patients.

Rev 11/06 Thorough training and credentialing of yoga instructors for the current study will be ensured by the requirement of being (or eligible to be) a Registered Yoga Teacher by the Yoga Alliance and receiving approval to teach the yoga sessions from the study PI, Dr. Mustian, and/or the study yoga consultant. The designation of gentle Hatha yoga, with its traditional components of movement, breath and awareness, as the form of restorative yoga to be taught will help ensure a higher degree of consistency across the intervention. Moreover, the popularity and accessibility of gentle Hatha yoga in the West will provide for easier logistics regarding CCOP affiliate participation across the United States and ultimately patient accrual. Lastly, given that the majority of the extant research supporting the healthful benefits of yoga have utilized gentle Hatha yoga,[21,30-32] this form of yoga may ultimately be met with greater acceptance by mainstream physicians, who may be more likely to refer patients to seek out yoga if it is found to be effective for improving CRSD.

The intervention we will use was designed by our study yoga consultant, Ms. Marget Braun, a certified yoga teacher and cancer survivor with experience teaching cancer survivors. Dr. Mustian also consulted with Dr. Kabat-Zinn and several certified yoga instructors, including the Tibetan yoga instructor for the Cohen et al.[7] study. The program is based on the holistic yoga interventions in the previously summarized studies and is a gentle Hatha yoga sequence that includes the traditional components of movement, breathing and mindfulness to induce release and relaxation, reduce mental activity, and provide a physiologic basis for deep relaxation and transition to sleep. This intervention provides the experience of mind–body connection through

the use of postures and awareness of breath and sensation, all components that were used in the interventions in the previously described yoga studies. One modification that will make the intervention slightly different from previous studies is its length. Interventions in these earlier studies typically involved between six and 16 sessions spread over six to eight weeks. Our gentle Hatha yoga intervention will consist of two 75-minute sessions a week and last for four weeks, resulting in a total of eight sessions. The decision to provide a 4-week yoga intervention in the current study was based primarily on the consideration that it would be important to see a sleep benefit within four weeks, given other possibly available interventions that may provide a sleep benefit within a short period of time (e.g., pharmaceuticals, exercise). An additional benefit of the shorter 4-week time frame is its ease of implementation in a community setting. (Note: At the 2004 and 2005 Annual URCC CCOP Research Base meetings of the CCOP PIs, the PIs indicated accessibility to yoga instructors in their communities and a high degree of feasibility and support for the type and length of intervention proposed.) Lastly, we have designed the study with a standard care/monitoring wait-list control group to increase accrual and retention, where the standard care control group will receive the 4-week yoga intervention free of charge upon completion of the study with no formal study assessments. We consider this time period to be an appropriate length that is not too long or short to request that the control group wait to receive the yoga intervention.

Summary and Hypotheses

Despite the very high prevalence of CRSD, with its concomitant negative effect on numerous aspects of daily living, no effective, successful and generally accepted interventions for CRSD have been developed. Pharmacological interventions do not provide efficacious treatments all of the time; most often are only prescribed for very short periods of time and provide limited acute relief of CRSD if any relief at all. However, the CAM practice of gentle Hatha yoga, which emphasizes the mind and body connection through movement, breathing and awareness, may prove to be a gentle modality for alleviating CRSD and the associated symptoms of cancer-related fatigue (CRF) and diminished QOL. Our own data as well as that of other researchers make it clear that cancer survivors are very amenable to CAM and frequently use CAM therapies to alleviate side effects resulting from treatment.

The preliminary body of literature on the effectiveness of yoga in alleviating CRSD, although very suggestive, does not meet the criterion of being persuasive as it does not meet several of the CONSORT guidelines outlined by the Journal of the American Medical Association[39] and the Lancet,[40] or the Oxford Center for Evidence-Based Medicine guidelines [www.cebm.net/levels_of_evidence, 04.25.05] for a strong evidence base on which to inform standard clinical practice. For example, there is a lack of “no intervention” control groups for comparison purposes, the sample sizes are small, there is a lack of psychometrically sound subjective/objective measures to assess sleep, there is a lack of blinding/masking when appropriate, and there is a lack of reporting of adverse events.

Given the limitations of the current literature and the design of the proposed yoga intervention, we feel that it is scientifically prudent to conduct a phase II trial to compare the proposed 4-week yoga intervention to a “standard care/monitoring” (no yoga intervention) control group to determine the efficacy of the proposed yoga intervention on CRSD. Evidence from this initial phase II randomized controlled trial will provide preliminary information regarding the ability of the proposed “dose” (e.g., type, intensity, frequency, duration) of yoga to influence CRSD. In turn, these data will provide the necessary information to develop hypotheses and appropriately design a future phase III randomized controlled trial. This sequence of studies will conform to the recommendations in the CONSORT guidelines for high quality randomized controlled trials.

The knowledge gained will, eventually, lead to a solid basis on which to inform the development of future evidence-based standards of care. In order to facilitate this objective, we will use a "standard care/monitoring" (no yoga intervention) control group for comparison and we will offer the 4-week intervention to the patients randomized to the control group, gratis, upon completion of the study employing a wait-list control format. No study assessments will be made on the control group when they receive the yoga sessions after completing the study as this would create increased study complexity, time and cost, which is not feasible as part of this investigation.

We are also aware that it may ultimately be desirable to discern what particular aspect of a behavioral intervention, such as yoga (e.g., attention, movement, breathing, meditation), is the salient component so the intervention can be tailored to provide the most economical treatment for patients in terms of actual cost and time. However, we believe it is first important and necessary, as recommended in the CONSORT guidelines, to determine if the intervention as a whole is efficacious for improving the outcome of interest (e.g., quality of sleep). Therefore, at this time, we primarily seek to establish that our proposed yoga intervention in its will influence CRSD and we will not examine the beneficial effects of each individual component of the traditional holistic Hatha yoga intervention (e.g., attention, movement, breathing, meditation) on sleep disturbance, but will investigate the influence of the proposed yoga intervention in its traditional and common holistic form.

Despite the reporting and design limitations of the previously summarized studies, they do provide strong preliminary evidence that gentle yoga interventions are well-accepted by cancer patients and are associated with significant improvements in a variety of cancer-related side effects, including CRSD, with the most consistent aspects of yoga employed in each of the previously mentioned studies including gentle Hatha/restorative yoga exercises. Given the positive preliminary results as well as the noted limitations, further research is warranted to provide a solid evidence base on which to inform standard clinical practice. The NCI CCOP mechanism provides an excellent forum for conducting this research on a large nationwide scale in a timely, cost-effective manner among patients in community settings.

Hypothesis: Yoga will be efficacious in relieving cancer-related sleep disturbances that persist following standard treatments for cancer.

Therefore, we propose to conduct a timely phase II randomized, controlled trial employing psychometrically sound self-report and objective measures to provide preliminary information regarding the efficacy of gentle Hatha yoga for improving persistent CRSD among cancer survivors following completion of their treatment.

3.0 Objectives

Specific Aims

3.1 Primary Aim

To examine the efficacy of yoga for improving sleep quality in cancer survivors experiencing persistent sleep disturbance.

3.2 Secondary Aims

3.2.1 To examine the efficacy of yoga for improving fatigue and QOL in cancer survivors.

3.2.2 To determine if the positive effects of yoga on sleep are related to concurrent changes in fatigue and QOL.

4.0 Participant Eligibility

4.1 Study participants must:

Rev 3/07 4.1.1 Have a confirmed diagnosis of any type of cancer.; participant can have more than one primary, but cannot have metastatic cancer.

4.1.2 Have undergone some type or combination of standard treatment (surgery, chemotherapy, radiation therapy) for cancer.

Rev 3/07 4.1.3 Have completed all forms of standard treatment (surgery, chemotherapy, radiation therapy) for cancer between 2 and 24 months prior to enrollment in the study. Participants can be taking hormones (such as Tamoxifen) or monoclonal antibodies (such as Herceptin).

4.1.4 Have persistent sleep disturbance, as indicated by a response of 3 or greater when asked to rate their sleep on an 11-point scale anchored by “0” = no sleep disturbance and “10” = worst possible sleep disturbance.

4.1.5 Be able to read English (because the assessment materials are in printed format).

4.1.6 Be 21 years of age or older.

4.1.7 Give written informed consent.

4.2 Study participants must not:

Rev. 11/06 4.2.1 Participants cannot have regularly (one or more days a week) participated in yoga classes or maintained a regular personal practice of yoga in any form within the 3 months prior to enrolling in the study. Participants cannot be planning to start yoga on their own during the time they are enrolled in the study.

4.2.2 Have a confirmed diagnosis of sleep apnea.

4.2.3 Be receiving any form of treatment for cancer, with the exception of hormonal therapy.

Rev 3/07 4.2.4 Have metastatic cancer.

5.0 Registration and Randomization

5.1 Prior to entering participants on this protocol, the following must be on file at the URCC CCOP Research Base:

- Documentation of Internal Review Board (IRB) approval in the form of an HHS Form 310 or CTSU approval form or signed letter from IRB

- A copy of the institution's IRB-approved informed consent document with written justification for any substantive modifications made to the informed consent document concerning information on risks or alternative procedures. These documents are submitted to:

  Ms. Jacque Lindke
  James P. Wilmot Cancer Center
  URCC CCOP Research Base
  601 Elmwood Av, Box 704
  Rochester, NY 14642

5.2 To enroll a participant who meets the eligibility criteria and who has signed the informed consent document, either:

- log on to the URCC CCOP Research Base website at http://extranet.urmc.rochester.edu/ccop/, enter your CCOP's username and password and enter the information outlined in section 5.3 below, or

- call the University of Rochester Cancer Center at (585) 275-6303 between 8.30 AM and 4.30 PM on weekdays to verbally give the URCC registrar the information in section 5.3.

5.3 The following information will be requested:

5.3.1 CCOP site

5.3.2 Most recent IRB approval date

5.3.3 Name and telephone number of person registering study participant

5.3.4 Eligibility verification, including numerical level of sleep disturbance. (participants must meet all eligibility requirements listed in Section 4.0)

5.3.5 Verification that consent form has been signed

5.3.6 Facility (coincides with IRB approval)

5.3.7 Participant's identification
- 5.3.7.1 First and last names or initials
- 5.3.7.2 Birth date (MM/DD/YYYY)
- 5.3.7.3 Gender
- 5.3.7.4 Race

5.3.7.5 Nine-digit zip code
5.3.7.6 Payment code

5.4 An e-mail confirmation of registration will be forwarded by the URCC and, if requested, a faxed confirmation will be sent to the CCOP's coordinating center.

5.5 Randomization of participants will occur when an entire cohort has been registered. A cohort consists of a treatment group and a control group at a single CCOP location. The minimum number of participants to comprise a cohort is 20, the maximum is 30. The CCOP must notify the URCC CCOP Research Base when the final participant of the cohort is being registered. The Research Base requires a 24-hour turn around time to randomize a cohort of participants. The CCOP will be informed of the randomization arm for each participant within 24 hours after notifying the URCC to randomize the cohort. The participants randomized to the yoga condition will all participate in the yoga session together and the class will contain only study participants. ((Note: the URCC CCOP has had success using this method of randomization in our past studies, U2991 and U9994, where cohorts of participants were randomized to receive either support group therapy or a control condition.) Participants will be randomized in cohorts by CCOP location to allow for analyses by site.

5.6 Randomization will be stratified by two factors: gender (male or female) and degree of sleep disturbance reported on the eligibility assessment questionnaire (two levels: ≤5 or >5), with a block size of 2.

5.7 The two study arms are as follows:

Arm 1 = standard care/monitoring (wait list control group will participate in the yoga sessions immediately following the 6-week study period)
Arm 2 = standard care plus a 4-week gentle Hatha yoga intervention

Rev. 10/08 5.8 The randomization will assign participants to the two arms in the ratio 1:1 and will be administered at the URCC using software provided by the project biostatistician. A total enrollment of 400 participants is planned, with 200 participants in each study arm.

6.0 Treatment Protocol, Study Outline

Rev 11/06 6.1 *Yoga Intervention*: The yoga intervention will be provided by Registered Yoga Teachers who have been credentialed or are eligible to be credentialed by the Yoga Alliance upon completion of 200 hours in yoga instruction-related coursework and training. Study participants will not be charged for the yoga sessions. The gentle Hatha yoga intervention will consist of two 75-minute sessions a week and last for 4 weeks. The participants randomized to the yoga condition will all participate in the yoga session together and the class will contain only study participants. The sessions will be comprised of the usual components of a yoga intervention, including mindfulness, breathing and visualization exercises, as well as gentle hand, seated, and standing yoga postures all derived from the holistic gentle Hatha yoga form. Each instructor will be provided with a sequence list and DVD of mindfulness, breathing and visualization exercises, as well as the specific postures to be taught. However, in keeping with the

traditional system of gentle Hatha yoga, instructors will be permitted to modify these mind–body exercises and postures to meet the specific needs of participants and participants will be allowed to use yoga props as needed. (See Appendix B for a detailed description of the yoga intervention.)

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6.1.1 Each participating CCOP will be responsible for finding a suitable yoga instructor. The study PI, Dr. Karen Mustian, and the yoga consultant for this study will be available to work with CCOPs to assist them in selecting an appropriate yoga instructor. Each yoga instructor will be required to provide the following:

- copy of his/her resume or vitae
- documentation of his/her yoga instructor training and certification status
- 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 Supplier Questionnaire and Size Certification Form
    - a University of Rochester Acceptance form to follow the terms and conditions of working with the University

. Additionally, the instructor will sign a statement promising to follow the yoga intervention exactly as outlined in the training DVD.
The CCOP site will submit these materials to the URCC Research Base for review by Dr. Mustian and the research base yoga consultant to approve the yoga instructor for consultation and teaching the yoga intervention. A decision regarding approval of the yoga instructor will be made within two weeks.

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6.1.2 Details on where the yoga sessions will be conducted, obtaining props and specifics regarding participant transportation will be individualized by each CCOP site.

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6.1.3 The CCOP coordinator will review the instructional DVD and written manual for the yoga intervention prior to the start of the first session. The coordinator will attend the first yoga session and at least one additional, randomly selected session. (Yoga instructor should not be notified in advance of this visit.) Coordinators can attend all eight intervention sessions, however, they cannot participate in them. Coordinators must observe the entire session and give verbal feedback to the yoga instructor regarding the quality and fidelity of the yoga intervention being delivered. If the yoga protocol is not being followed properly, coordinators must notify the study PI immediately.

6.1.4 Potential risks from taking part in the Hatha yoga intervention are minimal and may include possible orthopedic injuries (e.g., muscle strains, joint sprains).

6.1.5 Yoga instructors will complete an Attendance Log and Comment Sheet for each session.

6.2 *Participant Accrual:* The study will be available to affiliates of the URCC CCOP Research Base. Three hundred participants with persistent CRSD who have completed treatments for cancer within the last 2–24 months will be accrued. As this is a phase II clinical trial each CCOP affiliate will initially be able to enroll one cohort.

Rev 3/07 6.3 *Informed Consent Process:* Participants will be consented within 2-24 months of completing standard treatment for cancer. During the informed consent process, it will be explained to the participant that the study lasts for approximately six weeks and will involve completing some questionnaires and wearing a wristwatch-like actigraph for seven days to assess sleep both prior to and following the 4-week intervention. Reminder phone calls will be made by study personnel prior to each assessment (baseline and post-intervention) to assist the participant in remembering to complete the study forms. One phone call will also be made by study personnel during each of Study Weeks 3 and 4 to check in with participants and remind them to attend the yoga sessions and to complete and mail in their first two weeks of the daily, sleep and hot flash diaries. (Permission will be obtained to leave messages on a participant's answering machine before any messages are left.) Self-addressed stamped envelopes will be provided to each participant so they can return the completed questionnaires and diaries after each assessment or the questionnaires and diaries can be collected in person by a clinical research coordinator. As part of the informed consent process, participants will be asked if they agree to be contacted for participation in future research studies for which they may be eligible. Participants may accept or decline this option. If they agree, the necessary information (e.g., name, maiden name, contact information, and name and contact of an individual who will most likely know how to get in touch with them in the event they move) in order to contact participants to let them know about future follow up studies will be kept on site in their local CCOP affiliate research file. Importantly, participants in both study arms will receive equal attention (e.g., phone calls, meetings) from study coordinators, with the only difference being that participants in the yoga arm will also receive the yoga intervention.

Rev 3/07 6.4 *Questionnaires: Participants will complete baseline assessments within 2-24 months of completing standard treatment for cancer.* After providing written informed consent, demographic data will be obtained via the completion of the "On-Study" form and clinical data will be extracted from the participants' medical records, along with copies of chemotherapy flow sheets, treatment summaries and lab tests (only if within the last three months). Participants will be given their first packet of questionnaires [i.e., Pittsburgh Sleep Quality Inventory, Insomnia Severity Index, Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Sleep Medication and CAM Usage, Symptom Inventory, Multidimensional Fatigue Symptom Inventory, Profile of Mood States and Aerobic Center Longitudinal Study Physical Activity Questionnaire] to complete within the 3 days prior to the first calendar week of the intervention (yoga or standard care). We have used these questionnaires extensively in previous local and URCC CCOP studies and found that packets including 8 questionnaires take on average about 30 minutes for participants to complete. Participants will also be given the diaries (sleep, daily, and hot flash) to complete on a daily basis during the entire six week study period. We have used this daily diary format in our local studies and participants report that it takes on average 2 minutes each day to complete all of the diary information. [Note. There is reasonable evidence to suggest that hot flashes may be associated with sleep disruption.[41-43] Therefore, we have included an assessment of hot flashes to examine their potential as a confounding influence on the observed relationships between the proposed yoga intervention and CRSD. Participants not experiencing hot flashes will not be required to complete this portion of the diary and will simply check a box indicating that they are not experiencing any hot flashes.]

6.5 *Actigraphs:* An actigraph will be provided to participants prior to the beginning of the study. They will be asked to put it on and wear it for seven consecutive days immediately prior to the first calendar week of the intervention (yoga or standard care) and they will be instructed not to remove it during these seven days, except when swimming (Note: actigraphs are shower safe and can be worn continuously other than when swimming. See Appendix A for actigraph instructions).

6.5.1 The URCC must receive notification that a study cohort is going to begin at least three full calendar weeks prior to the expected start date for baseline assessments so that the appropriate number of actigraphs may be assembled, inventoried, initialized and mailed to the CCOP affiliate.

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6.5.2 Each CCOP site will be responsible for designating a clinical research coordinator to be in charge of receiving the actigraphs for each cohort of participants enrolled at the CCOP site. Using the Actigraph Inventory Form, the coordinator will confirm that the shipment contains the correct number of actigraphs, verify the identification numbers for each unit and make sure that the actigraphs are in good condition. Each coordinator will distribute the actigraphs to study participants and explain the procedures for wearing the actigraph (e.g., wear it on their non-dominant wrist and do not take it off except when going swimming; see Actigraph Instructions in Appendix A). Participants will also get written instructions. As the actigraph portion of the study begins at 12:00 noon Sunday at the beginning of the first full calendar week of baseline assessments, the actigraph must be delivered to participants prior to that time. Participants should be instructed to put the actigraph on when they get out of bed on Sunday morning so they do not inadvertently miss the 12:00 noon start time. Participants will remove the actigraph the evening of the following Sunday, after wearing it for 7 days.

The coordinator at each CCOP site will also be responsible for collecting the actigraphs from each of the participants enrolled, inventorying them, and shipping them to URCC within the first three days of Study Week 2 (immediately after the completion of the baseline assessments). The data from the actigraphs will be downloaded by URCC staff, the batteries will be exchanged, and the actigraphs will be shipped back to the CCOP site for post-intervention assessments.

6.6 *Post-Intervention Assessments (Study Week 6):*

6.6.1 All participants will be given a second packet of questionnaires identical to the baseline measures (i.e., Pittsburgh Sleep Quality Inventory, Insomnia Severity Index, FACIT-F, Sleep Medication and CAM Usage, Symptom Inventory, Multidimensional Fatigue Symptom Inventory, Profile of Mood States, Aerobic Center Longitudinal Study Physical Activity Questionnaire and Feedback Questionnaire) to complete within the sixth week of the study period.

6.6.2 The seven-day actigraphy assessment will be repeated using the exact same procedures for handling, distributing, wearing, retrieving and returning the actigraphs as for the baseline assessment.

6.6.3 The responsible study coordinator at each CCOP site will make arrangements for the device to be returned by the participant and for sending all actigraphs to the URCC Research Base within one week of the conclusion of the study.

6.6.4 All participants, regardless of study arm, will complete all study measures.

6.7 *Study Retention*: In order to improve study retention in the standard care arm, participants will be offered the 4-week yoga intervention, gratis, after the final assessments (end of Study Week 6). No data will be collected during this time period.

6.8 *Adverse Event Reporting Requirements:*

6.8.1 Adverse events will be reported using URCC Adverse Event form and the following guidelines:

WHAT TO REPORT: Any *unexpected* (not listed in section 6.1.3 of the protocol), serious (grade 4 or 5), life-threatening or fatal adverse event with an attribution of possible, probable, or definite.

WHEN TO REPORT: Unexpected, fatal or life threatening events should be reported by phone or email within 24 hours. Other serious (grade 4 or 5, or grade 3 with hospitalization), unexpected events should be reported within ten (10) working days of learning of the event.

WHERE TO REPORT: Adverse events must be reported to URCC using the URCC Adverse Event form. (A copy can be obtained from the URCC CCOP Research Base web site.)

HOW TO REPORT:

(1) By mail:

Jacque Lindke
James P. Wilmot Cancer Center
URCC CCOP Research Base
601 Elmwood Avenue, Box 704
Rochester, NY 14642

(2) By phone:

585-275-5514

(3) By fax:

585-461-5601

6.8.2 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 experience when, based on 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.

6.8.3 Adverse events should be reported to the local Internal Review Board (IRB) as per their requirements.

6.9 *Data Safety and Monitoring:*

6.9.1 All adverse events requiring expedited reporting will be reported to the Safety Monitor, Ms. Jacque Lindke, as described in section 6.8. Adverse events are tracked using an Access database. Each time an event is received, it is reviewed by the Safety Monitor and entered into the database. The Safety Monitor continually reviews the database as each event is entered. If the same event is being reported frequently, the study chair and/or research base principal investigator is notified, and he/she reviews the reports in detail immediately.

6.9.2 The URCC Data Safety Monitoring Committee (DSMC) will review study progress and cumulative reports of adverse events at semi-annual meetings. An overall assessment of accrual, toxicities and responses will enable the committee members to assess whether significant benefits or risks are occurring that would warrant study closure. The study chair will be notified in writing of the outcome of this review, including any concerns or recommendations. Serious safety concerns will be discussed with the study chair, head of the URCC Protocol Review Committee and University IRB immediately. The DSMC Committee Chair will determine if further action is required.

6.9.3 The URCC will notify the CCOPs immediately of any serious safety concerns identified by the DSMC.

7.0 Measures

7.1 The **On-Study Data/Participant Record** questionnaire is used to record demographic and clinical information. Diagnostic, treatment and other clinical information will be abstracted from the participant's chart and recorded on the **Clinical Record Information** form. These data will be used for descriptive purposes, to aid in participant monitoring, for moderator analyses, additional exploratory analyses, and to aid in the refinement of the yoga intervention and study assessments in a future phase III trial.

7.2 Sleep assessments

7.2.1 The **Sleep Medication and CAM Usage** form will track the participant's use of prescription and non-prescription sleep medication, as well as any other sleep aids used during the baseline and post-intervention assessments conducted during Study Weeks 1 and 6. Importantly, this form will also specifically ask participants to report the use of any other CAM modalities for any reason.

7.2.2 Quality of sleep will be assessed subjectively using the ***Pittsburgh Sleep Quality Inventory (PSQI)***, the ***Insomnia Severity Index (ISI)***, and a ***Sleep Diary***, as well as objectively using ***actigraphy***.

7.2.3 The ***Pittsburgh Sleep Quality Inventory (PSQI)*** is a commonly used, 25-item psychometrically sound measure scored for both global severity and subscale scores that assess sleep initiation and maintenance problems and possible etiologic factors (e.g., pain, nightmares, hot flashes).[44]

7.2.4 The ***Insomnia Severity Index (ISI)*** is a commonly used, 5-item psychometrically validated measure used to rate insomnia as not clinically significant, sub-threshold insomnia, clinical insomnia (moderate) and clinical insomnia (severe).[45,46]

7.2.5 Self-report of sleep will also be assessed with a ***Sleep Diary*** completed prior to going to bed and immediately upon awakening. It takes 2–3 minutes to report the following: time to bed, time out of bed, number of times got out of bed during the night, time awake during the night because of hot flashes, time awake during the night because of other reasons, total sleep time and a measure of perceived sleep quality. Questions are also asked concerning medications, alcohol consumption, naps during the day, and levels of sleepiness, tension and fatigue upon going to bed.

7.3 ***Ambulatory monitoring of participant activity*** will be done using actigraphy at baseline (Study Week 1) for seven consecutive days immediately prior to beginning the intervention (yoga or standard care) and again post-intervention (Study Week 6) for seven consecutive days immediately after completing the intervention. The actigraph used for the study will be the Octagonal Motionlogger® SleepWatch manufactured by Ambulatory Monitoring, Inc., 731 Saw Mill River Road, Ardsley, New York 10502. This waterproof device (shower safe), approximately the size of a watch, is worn on the wrist and contains an accelerometer to measure motion. Features of the actigraph include the following: 1) an event marker; 2) visual feedback; 3) LCD with time-of-day display; 4) 2 MB memory; 5) 2-3 Hz filter; 6) sensitivity .01G at mid band; 7) Zero Crossing (ZC), Time-Above-Threshold (TAT), ZC/TAT Dual, Proportional Integrated Measure (PIM) and Tri-Mode (ZC, TAT, and PIM simultaneously) modes of operation; and 8) a 60-day battery life. A 60-second epoch length, the standard employed for sleep scoring, will be used. Use of this device is prompted not only by the face validity of the activity assessment derived from it (participants with disrupted sleep and fatigue universally show markedly abnormal activity patterns), but also the fact that the original clinical diagnosis of Cancer Fatigue Syndrome contained a definition based on reductions in patient activity.[47] Using actigraphy, negative relationships between sleep continuity and self-reported fatigue[48] and between fatigue and activity levels during the day have been found in cancer patients.[49-51]

The company's companion analysis program, Action-W, which separates each day into an "up" or out-of-bed portion of the day and a "down" or in-bed portion, will be used to determine mean activity levels during the two portions of the day. The motion data will also be analyzed using the Cole/Kripke sleep scoring algorithm to provide an estimate of the proportion of time asleep during the "up" and "down" periods. Thus, two measures that objectively assess components of sleep and fatigue (e.g., the average activity level and proportion of time resting or sleeping in the "down" and "up" portions of the day) can be abstracted from the raw motion data. These data, in turn, can be averaged separately to create variables that objectively assess components of sleep (e.g., **"mean activity during the night"** and **"percent sleep during the night"**) for each of the 1-week assessment periods. Two other variables that can be created to objectively

assess fatigue for each of the 1-week assessment periods examined in our analyses are **"mean activity during the day"** and **"percent sleep during the day."** A fifth variable that is labeled **"circadian rhythm"** will also be calculated for each of these 1-week assessment periods. The latter is a measure of similarity or dissimilarity of rest and activity patterns across the seven measurement days. Circadian rhythm will be calculated using the autocorrelation feature of the Action-3 analysis program (Ambulatory Monitoring, Inc., Ardsley, New York). The autocorrelation coefficient can, in theory, range between -1 and 1 (see Mormont [52] for a description of how autocorrelation is calculated).

7.4 In addition to actigraphy, fatigue will be assessed subjectively via the **Multidimensional Fatigue Symptom Inventory (MFSI)**. The MFSI is a 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.[53-55]

7.5 Quality of life (QOL) will be assessed subjectively via the ***Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F).*** The FACIT is a 28-item QOL scale developed specifically for use in cancer clinical trials, and the FACIT-F includes 13 additional questions directly related to the impact of fatigue on daily activities.[56] 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.[57,58] Along with a total score representing QOL, there are psychometrically validated subscales of physical, functional, social and cognitive-emotional status. The FACIT-F has become one of the most commonly used measures in oncology, and we have used this scale in our previous studies.

7.6 Activity will be assessed subjectively using the ***Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS),*** and a ***Daily Diary***, as well as objectively using **actigraphy (see section 7.3 on actigraphy).**

7.6.1 The ***Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)***,[59] is an assessment of lifestyle physical activity. Participants report their engagement in 14 different physical activities (frequency, intensity and duration) over the last month. Estimates of energy expenditure are calculated using the following equation: (sessions/week) · (min/session) · (hour/min) · MET for each activity and then summed to provide total MET hours of energy expenditure for a week (Note: MET = metabolic energy expenditure rate). The index of walking, jogging and running predicted a treadmill performance time (r = .31), and there is a moderate relationship between energy expenditure estimates and treadmill performance (r = .41). Additionally, this instrument has been effectively used to predict the relative risk of prostate cancer based on cardiorespiratory fitness.[60]

7.6.2 The ***Daily Diary*** is designed to track attendance and participation in the yoga intervention, additional daily activity and use of sleep medications and aids. The participant will be asked to take 1–2 minutes and complete the journal each night immediately prior to sleeping and record participation in yoga, other daily activity, a rating of perceived exertion, and use of sleep medication and sleep aids.

7.6.3 The yoga instructors will maintain formal ***Attendance Records*** to provide information on participant adherence and compliance to the intervention.

7.7 Potential depressive affect and general mood will be assessed through the short form of **Profile of Mood States (POMS)**. 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 [61,62].

7.8 General symptomatology will be measured with a ***Symptom Inventory,*** a list of 13 symptoms modified from measures created at the M.D. Anderson Cancer Center. This measure is a series of uniscales in which 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." Medical oncologists at URCC use this measure in clinical care. It will serve as a concurrent self-report measure of symptoms that will be used in exploratory analyses.

7.9 Hot flashes will be evaluated by a self-report **Hot Flash Diary** originally developed by the North Central Cancer Treatment Group (NCCTG) and used by the URCC CCOP Research Base in previous protocols. [Note. Participants not experiencing hot flashes will not be required to complete this form; they will simply check a box at the top of the page indicating they are experiencing no hot flashes.]

7.10 **The *Feedback Questionnaire,*** concerning participants' views on the study treatment, will be completed at the conclusion of the sixth week on study. This questionnaire will provide information, for use in future studies, to alter aspects of the interventions with which participants were displeased and to find out participants' reactions to the intervention.

The schedule for data collection is shown in the table in section 10.1. All measures are included in Appendix A.

8.0 Design Considerations

8.1 Actigraphy is included in the protocol because this objective measure of participants' sleep and activity levels is unlikely to be affected by experimenter bias.

8.2 The design we have chosen allows each subject to act as his/her own control. By having each person complete baseline data before the intervention is given, we can compare pre- and post-levels of CRSD in each participant individually. This will also allow us to use baseline CRSD as a covariate in statistical analyses, which strengthens the design of the study.

8.3 The decision to provide a 4-week yoga intervention that meets twice a week for 75 minutes in the current study was based on 1) the consistently reported aspects of the studies providing the preliminary data of this trial, 2) the typical course structure of Hatha

yoga offered in community settings, 3) support from the CCOP PIs nationwide regarding their ability to offer an intervention of this nature and 4) consideration that it would be important to see a sleep benefit within four weeks given other possibly available interventions that may provide a sleep benefit within a short period of time (e.g., pharmaceuticals, exercise).

8.4 Although we are aware that it is ultimately desirable to discern the effectiveness of the proposed yoga intervention and, ultimately, what particular aspect of a behavioral intervention, such as yoga (e.g., attention, movement, breathing, meditation), is the salient component as a means to tailor the intervention and provide the most economical, in terms of both actual cost and time, treatment for participants, we believe it is first important and necessary to determine if the intervention as a whole is efficacious for improving the outcome of interest (e.g., quality of sleep). Therefore, we have chosen a standard care/monitoring waitlist control comparison group in order to provide preliminary data concerning the magnitude and variance of the proposed yoga intervention on CRSD. Secondly, we plan to use the data collected in this phase II clinical trial to design an appropriate follow-up phase III study comparing our yoga intervention to different types of interventions to discern the effectiveness of the yoga intervention In order to facilitate accrual of a "standard care/monitoring" (no-intervention) control group for comparison, we will be offering the 4-week intervention to the participants randomized to the control group gratis upon completion of the study.

9.0 Data Handling and Statistical Considerations

9.1 The same protocols and procedures for data quality and control that we have used for our previous 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 is audited visually for errors. SPSS and SAS statistical packages will be used for the analyses.

9.2 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 CRSD and fatigue severity between the active treatment group and the control group). Data will be analyzed on an "intent-to-treat" basis; that is, participant data will be included in the study arm to which the participant was randomized, regardless of compliance to that arm (yoga vs. standard care).

9.2.1 *Assumptions*: The assumptions underlying all statistical analyses will be thoroughly checked using appropriate graphical and numerical methods.[63,64] In the case of violations of the assumptions, appropriate nonparametric methods will be attempted.[65,66] 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.

9.2.2 *Missing Values*: Every effort will be made to encourage and facilitate participants' completion of questionnaires. In the event of missing data, the

reasons for missing data will be recorded, and tabulated according to treatment groups.

9.3 Statistical Analyses

9.3.1 The primary outcome measure for this study is the change score of CRSD from baseline to the end of Week 6, as assessed by the PSQI total score.

9.3.2 To assess the **Primary Aim (**i.e., to examine the efficacy of the yoga intervention for improving CRSD, as assessed by the PSQI total score) an ANCOVA analysis will be performed to compare mean change scores in CRSD (e.g., CRSD at Week 6 minus CRSD at baseline) between the two treatment groups while adjusting for baseline CRSD values.

9.3.3 *Secondary Aims*: The secondary outcome measures for this study are CRF and QOL at the end of Week 6, as assessed by the MSFI and FACIT-F total scores, respectively. To assess the **Secondary Aims (**i.e., to examine the efficacy of the yoga intervention in improving CRF and QOL, as assessed by the MFSI and FACIT-F, respectively), ANCOVA analysis will be performed to compare mean change scores in CRF and QOL (i.e., CRF/QOL at Week 6 minus CRF/QOL at baseline) between the two treatment groups while adjusting for baseline values.

9.3.4 Potential moderators and/or mediators of the intervention will be investigated through a series of hierarchical regression and correlational analyses. A moderator variable precedes and is not correlated with treatment. It affects the strength and direction of the relationship between treatment and clinical outcome, providing information about *when* and *for whom* a treatment will be effective. A mediator, by contrast, occurs during and is correlated with treatment, and accounts for the relationship between the treatment and clinical outcome, defining *how* or *why* a treatment works and possible causal mechanisms.[67,68] Establishing moderators and mediators of treatment outcomes is essential to understanding treatment mechanisms and is of considerable benefit in guiding clinical practice, as well as in the design of future studies.[67] We will follow procedures set forth by Baron and Kenny[68] and Kraemer[67] for these analyses.

9.3.4.1 Potential clinically meaningful **moderators** of the efficacy of the intervention for improving CRSD during the sixth week of the study, as assessed by the PSQI and that meet the assumption of precedence (i.e., moderators must precede the intervention),[67] that we will examine include age, gender, baseline CRSD, baseline CRF, baseline QOL, baseline depression, baseline anxiety and hot flashes. CRSD will be assessed using the baseline PSQI total score, CRF using the baseline MSFI total score, QOL using the baseline FACIT-F total score, depression and anxiety using the POMS subscales and hot flashes using the score derived from the baseline week of the Hot Flash Diary. Statistically speaking, a moderator of a treatment intervention must meet the following two criteria: 1) it must be **uncorrelated** with treatment condition, and 2) the interaction of the treatment condition(s) and the putative moderator must be a statistically and/or clinically significant predictor of treatment outcome.

To determine whether or not the first criterion is satisfied, bivariate analyses (Spearman's rho) and/or Chi-square analyses, as appropriate, will be used to examine whether the variables are correlated ($p \leq .05$) with treatment condition. Only those variables established as uncorrelated with either of these treatment vectors will be further analyzed for moderator status.[67] (Note: Because this is a randomized trial, treatment condition would not be expected to correlate with any of these variables.) Any of these variables that are found to correlate with treatment outcome will be used as additional covariates in the analyses testing both the Primary and Secondary Aims described earlier, instead of being examined as potential moderators of treatment outcome.

To determine whether or not the second criterion (i.e., there being a significant interaction between the putative moderator and treatment condition on the treatment outcome) is satisfied, the above-mentioned variables that are uncorrelated with treatment condition will be further examined through hierarchical regression analyses. As in the analysis for the Primary Aim, described earlier, the dependent variable in each of these regression equations will be CRSD, as assessed by the PSQI, at the end of the fifth week on study. CRSD severity at baseline will be controlled by entering it at the first step in each equation. A coded variable for treatment condition will be entered at the second step. The putative moderator will be entered at the third step and the interaction terms (created by multiplying the putative moderator score by the coded treatment variable at the second step) will be entered at the fourth and final step. The examined variable, whether or not it has a significant main effect, will be considered a moderator only if one or both of the interaction terms are a statistically and/or clinically significant predictor of treatment outcome.[67]

9.3.4.2 The potential **mediators** of yoga in reducing CRSD during the sixth week on study (as assessed by the PSQI) that we will examine include changes in CRF, QOL, depression, anxiety and hot flashes from baseline to the sixth week on study. These potential mediators meet the assumption of precedence (i.e., mediators do not precede the intervention).[67] CRF and QOL for these analyses will be assessed using the total score from the MFSI and FACIT-F, respectively. Depression and anxiety will be assessed using the subscales from the POMS, and hot flashes using the score derived from the Hot Flash Diary. Sleep quality will be assessed with the PSQI, mean activity during the night will be measured with the actigraph, and percent sleep during the night and quality of sleep (QOS) will be assessed by the sleep log (averaged across the same 1-week assessment periods used for the actigraphy assessments). Changes in potential mediators will be determined by calculating simple change scores (i.e., subtracting the score of the variable when measured after the intervention during the sixth on-study week from the corresponding score measured at baseline during the first on-study week). A mediator of a treatment intervention must meet the following two criteria: 1) it must be **correlated** with treatment condition and 2) the putative mediator and/or the interaction of the treatment condition(s) and the putative

mediator must be a statistically and/or clinically significant predictor of treatment outcome.

To determine whether or not the first criterion is satisfied, bivariate analyses (Spearman's rho) will be used to examine whether the above variables are correlated ($p \leq .05$) with treatment condition. Only those variables established as correlated with treatment condition will be further analyzed for mediator status.[67]

To determine whether or not the second criterion (i.e., there being a significant main effect and/or interaction between the putative mediator and treatment condition on treatment outcome) is satisfied, the above-mentioned variables that are correlated with treatment condition will be further examined through hierarchical regression analyses. These regression analyses will be identical in construct to those described in the second bullet under moderators (directly above), although the interpretation of findings will be slightly different. The examined variable will be considered a treatment mediator if it is a statistically and/or clinically significant predictor of treatment outcome or if one or both of the interaction terms are a statistically and/or clinically significant predictor of treatment outcome.[67]

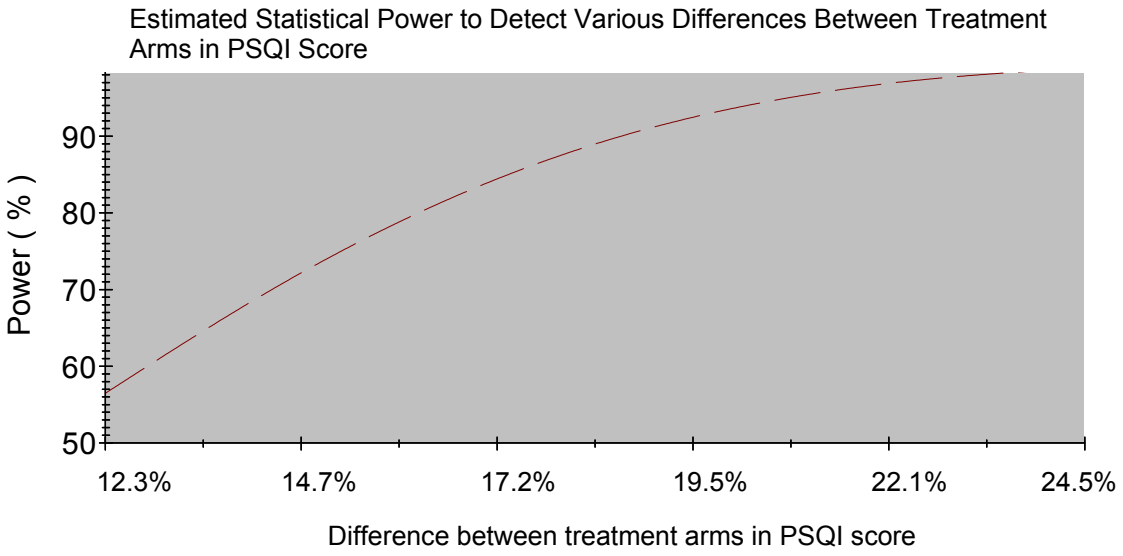
9.3.4.3 These analyses of potential moderators and mediators of the efficacy of the intervention in reducing CRF are numerous. At present, findings from these analyses would not be considered anything other than information to be used in the design of further randomized controlled investigations.

9.3.5 *Additional Exploratory Analyses*: The data analytic techniques described above for analysis of the Primary Aim and the first of the Secondary Aims will be used to determine if there are any observed positive benefits of the intervention on medication and sleep aid use, as assessed by the medication form; activity, as assessed by the ACLS and the actigraph measures of mean activity during the day, percent sleep during the day, mean activity during the night and percent sleep during the night; and sleep medication usage. In addition, the effect of the intervention on QOS and level of tension, as assessed by the sleep log and averaged across the same 7-day assessment periods used for the actigraphy assessments, will be examined. The effect of the intervention on insomnia as assessed by the ISI will also be examined. Because of the large number of additional exploratory analyses that will be conducted, positive findings, if any, will be interpreted cautiously.

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

Rev. 10/08 9.4 **Sample Size**: 400 participants will be enrolled in total. Allowing for 20% of participants who may not provide complete data, we expect to have 160 evaluable participants for each of the two treatment arms. This sample size generally provides the ability to detect a 15%–20% improvement in symptoms in our treatment group compared to our control group with an 80%–95% power. The 15%–20% improvement in symptoms is generally considered the minimum amount for determining clinical significance of a symptom control intervention.

The primary aim in this study is to evaluate whether the intervention is effective for improving CRSD as assessed with the PSQI during the participants' sixth on-study week. The primary analysis is a comparison of the total PSQI scores for the two treatment groups. Although there is no adequately-sized study of which we are aware that provides an estimate of PSQI scores in patients with post-treatment sleep disturbance, one recent study[69] does provide an estimate of scores during treatment. In a sample of 214 cancer patients, the mean score on the PSQI was 8.15, with a standard deviation of 4.7. Based on this preliminary data, if we make the conservative assumption that the pre-post treatment observations have a correlation coefficient of 0.5, then given an N of 120 participants per group, we will have 80% power to detect a mean difference of 1.7 in PSQI change scores between study arms. The following graph indicates estimates of power with varying degrees of mean difference on the PSQI change scores between study arms.



Rev. 10/08 9.5 Study Timeline: Enrollment of the 400 participants is expected to take 24 to 36 months.

9.6 Representation of Women and Minorities: None of the eligibility criteria for the study involve gender or ethnicity. Past enrollment in our CCOP studies has closely paralleled the gender and ethnic composition of the available population.

10.0 Records To Be Kept

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10.1 Schedule of data collection

FORM	On Study (At time of consent)	Baseline Assessment (During Week 1)	End of Study Assessment (During Week 6)
URCC Clinical Trial Patient Registration Form, Eligibility Checklist, Consent Form	✓[3]		
Participant Contact Form for Future Research	✓		
On-Study Data/Participant Form (Demographic, sleep history, etc)	✓		
Clinical Record Information (Clinical data)	✓		
Chemotherapy Flow Sheet and/or RT Treatment Summary (copy from chart)	✓		
Lab Tests (if within last 3 months) (copy from chart)	✓		
Sleep Medication and CAM Usage (SMU)		✓[3]	✓[3]
Pittsburgh Sleep Quality Inventory (PSQI)		✓[3]	✓[3]
Insomnia Severity Index (ISI)		✓[3]	✓[3]
Multidimensional Fatigue Symptom Inventory (MFSI)		✓[3]	✓[3]
Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F)		✓[3]	✓[3]
Profile of Mood States (POMS)		✓[3]	✓[3]
Aerobic Center Longitudinal Study Physical Activity Questionnaire (ACLS)		✓[3]	✓[3]
Symptom Inventory		✓[3]	✓[3]
Diaries: Sleep, Daily & Hot Flash		✓[1,3]	✓[1,3]
Actigraphy		✓[2]	✓[2]
Feedback Questionnaire			✓[3]
Participant Contact Sheets (4)			✓
Yoga Session Attendance Log			✓
Yoga Instructor Comment Sheet			✓
Actigraph Inventory Form			✓

[1]Begin on the same day that actigraphy commences during baseline and continue for the entire study period ending on the last day of actigraphy at the end of the entire study period

[2]Assessed for 7 consecutive days during Study Week 1, which is immediately prior to the beginning of the study intervention (yoga or standard care) and again for 7 consecutive days immediately post-intervention during Study Week 6.

[3]Completed by participants; all other study forms are completed by study personnel.

10.2 All written materials will be kept confidential, locked in the private offices of the Research Base and identified by ID numbers. All electronic information will be kept confidential with password-protected, limited access.

10.3 The Case Summary should accompany ALL data submissions. All completed forms must be submitted within 30 days of the randomization and should be sent to:

Shonda Ranson
URCC CCOP Research Base
601 Elmwood Avenue, Box 704
Rochester, NY 14642

11.0 Participant Consent and Peer Judgment

11.1 All investigational, FDA, NCI, state, federal and institutional regulations concerning informed consent and peer judgment will be fulfilled.

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Appendix A: Protocol Forms

1. URCC Clinical Trial Patient Registration Form
2. Eligibility Checklist
3. On-Study Data/Participant Form
4. Clinical Record Information
5. Participant Contact Form for Future Research
6. Pittsburgh Sleep Quality Inventory
7. Insomnia Severity Index
8. Multidimensional Fatigue Symptom Inventory
9. Functional Assessment of Chronic Illness Therapy-Fatigue
10. Profile of Mood States
11. Aerobic Center Longitudinal Study Physical Activity Questionnaire
12. Symptom Inventory
13. Diaries: Daily, Sleep, Hot Flash (+rating scales)
14. Sleep Medication and CAM Usage
15. Feedback Questionnaire
16. URCC Clinical Trial Patient Registration Form
17. Participant Contact Sheets (4)
18. Yoga Session Attendance Log
19. Actigraphy Inventory Sheet
20. Actigraphy Instructions
21. Yoga Instructor Comment Sheet
22. Case Summary Form

Appendix B: Description of Gentle Hatha Yoga Intervention

Rev 11/06 *As noted in the protocol, all yoga instructors working with the URCC CCOP affiliates will receive a detailed instructional DVD that explains and demonstrates each individual component of the yoga sequence, the appropriate modifications, and use of props.*

The program is a gentle Hatha yoga sequence to induce release and relaxation, reduce mental activity and provide a physiologic basis for deep relaxation and transition to sleep. It provides the experience of mind–body connection through awareness of breath and sensation.

Hatha yoga includes the three components of movement, breath and awareness. The movement component includes asana (postures). In this program asana includes seated, standing, transitional and supine poses, with an emphasis on restorative poses utilizing supports. All asanas will be given with modifications to address multi-levels of experience. The breath component includes pranayama (breathing exercises) to regulate breathing. The awareness component consists of mindfulness meditation instruction, visualization and affirmation. Mindfulness is incorporated throughout the program as the practice of paying attention with non-judgmental observation, to the present experience, for the purpose of attending to both external and internal impressions.

The program consists of two sessions, 75 minutes each, weekly for 4 weeks. A 4-week period increases the likelihood of compliance and completion, while providing for consistency in the yoga practice to maximize observation of potential effects.

Sequence

Seated
Ynana mudra (mindfulness sitting meditation)
Parvatasana. (seated mountain pose).
Lateral extension with breath
Bharadvajasana (seated twist)
Janu Sirasana (head-to-knee pose)
Modification: Adhomukha Paschimottanasana (supported forward bend from chair)
Spinal waves
Balasana (extended child pose)

Standing
Adhomukha Svanasana (downward dog)
Uttanasana (standing forward extension)
Prasaritta Padotanasana (forward stretch extended legs)
Balasana (lateral arm child pose)
Balasana (child pose with shoulder extension transition to supported backbend)

Transition
Supine curl to floor
Savasana (lateral extension with open jaw)
Jathara Parivartanasana (supine twist bi-laterally)
Suptapadangusthasana (supine leg stretch)
Sethubandhasana (supine pelvic lift)

Restorative
Supta Baddhakonasana (supported back bolster, belt, legs cobbler, blankets)
Adhomukha Virasana (supported child pose with twist)
Setubandha Sarvangasana (supported legs and back to shoulder blades, legs belted)
Viloma II (regulated exhalation)
Viparita Karani (legs up wall, pelvis on bolster)
Savasana (corpse pose)

Mudra
Ynana (Seal of Wisdom; link index finger and thumb together)

Pranayama
Equalize breath with pause post-exhalation.
Hmm breath
Viloma II

Mindfulness Meditation
Body scan and sensation.
Internal viewing
Nostril breathing, gravity tailbone, tactile cues

Visualization
Mind turn inward to heart
Dive beneath surface
Lying into back body

Affirmation
My senses turn inward and I relax into peace