Official Study Title: eHealth Insomnia Intervention for Adult Survivors of Childhood Cancer

CTG Number: NCT04317742

Document Date: 05/04/2021

St. Jude
SLEEPWELL - NCT04317742
Initial version, dated: 04-17-19, (IRB Approved: 07-30-19) Activation Date:
Resubmitted, dated 09-13-19 (IRB Approved: 10-24-19) Activation Date: 12-17-19
Amendment 1.0, dated 12-12-19 (IRB Approved: 01-22-2020) Activation Date:
Amendment 2.0, dated 09-02-20 (IRB Approved: 10-23-2020) Activation Date: 10-27-20
Amendment 3.0, dated 10-28-20 (IRB Approved: 11-20-2020) Activation Date: 12-10-2020
Amendment 4.0, dated 01-14-2021 (IRB Approved: 02-10-2021) Activation Date: 02-19-2021
Revision 4.1, dated 03-02-2021 (IRB Approved: 03-04-2021) Activation Date: 03-16-2021
Amendment 5.0, dated 04-09-2021 (IRB Approved:) Activation Date:

eHEALTH INSOMNIA INTERVENTION FOR ADULT SURVIVORS OF CHILDHOOD CANCER: A RANDOMIZED CLINICAL TRIAL

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Protocol MNEMONIC and Title: SLEEPWELL: eHEALTH INSOMNIA INTERVENTION FOR ADULT SURVIVORS OF CHILDHOOD CANCER: A RANDOMIZEDCLINICAL TRIAL

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IND Holder: Not Applicable

Brief Overview: There is evidence that survivors of childhood cancer have a high prevalence of poor sleep, including symptoms of insomnia. Insomnia is highly comorbid and has been associated with impaired cognitive performance, a range of psychiatric disorders, cardiovascular disease, and reduced quality of life. However, we still lack knowledge about the direct impact of available internet-based insomnia treatment programs for survivors of childhood cancer experiencing insomnia, in addition to how improving insomnia symptoms impacts neurocognitive function and late health morbidities in this population. Therefore, in this study, we will utilize the resources available in the Childhood Cancer Survivor Study (CCSS) to use an accepted, established, efficacious internet-delivered CBTi insomnia treatment program and evaluate the efficacy of this program in adult survivors of childhood cancer. We are leveraging two electronic health platforms to treat insomnia and facilitate data collection. Positive results from this study and our use of an internet-based intervention are likely generalizable and be scalable to the large and geographically diverse population of childhood cancer survivors with chronic health conditions. The CCSS provides a unique opportunity for cost-effective evaluation of the efficacy of remote treatment of insomnia in such a large sample of childhood cancer survivors.

Protocol MNEMONIC and Title: SLEEPWELL: eHEALTH INSOMNIA INTERVENTION FOR ADULT SURVIVORS OF CHILDHOOD CANCER: A RANDOMIZEDCLINICAL TRIAL
Evaluation: Eligible participants will complete a 9-week internet-based insomnia treatment program or receive sleep education, depending on group assignment. CCSS participants who have been previously identified as having neurocognitive impairment will be approached for recruitment. An approach packet consisting of an introduction letter, a single page study brochure, and informed consent documents will be mailed to potentially eligible participants. Interested participants will be able to return the consent via mail using a pre-paid envelope. Alternatively, the packet will include instructions for visiting the study webpage, where participants can sign-up and provide informed consent on-line. Those who have not responded after two weeks will receive an email alerting them to the study and providing a link to the study webpage. Starting three weeks after the initial mailing, a trained study interviewer housed within the CCSS Call Center will begin calling non-responders to provide information, answer questions, and encourage participation. Participants will have the opportunity to consent to the study verbally while speaking with the CCSS Call Center. Alternatively, survivors who wish to participate will enroll online via DatStat Connect (the current online data collection tool for the CCSS). Prospective participants will complete an online consent form. After consenting, they will complete a series of short online questionnaires to determine study eligibility. We anticipate needing to recruit 352 participants to reach the targeted enrollment of 320 at 9 weeks and 280 at 6 months. Upon enrollment, participants will be asked to complete all the study activities completely remotely. For the baseline remote evaluation, participants will complete a computerized remote cognitive assessment and will provide a blood sample using the Dried Blood Spot (DBS) method. Participants will be asked to complete online questionnaires and sleep diaries. Participants will be mailed a WHOOP wrist monitor to wear for 7 to 11 consecutive days. Two more identical remote evaluations will occur, one immediately after the intervention is completed and one 6 months after completion of the intervention.
Study Design: Randomized Controlled Trial
Sample Size: Approximately 352 research participants
Data Management: Collection of eHealth Data Using the RICE Platform: Interaction with participants and collection of data will be accomplished using the Research Infrastructure Containing E-interventions (RICE) Platform developed at the Center for Behavioral Health and Technology at the University of Virginia by Dr. Ritterband (Co-Investigator). Through a subcontract with Dr. Ritterband and the University of Virginia, a study-specific module within the RICE Platform will be used for post-enrollment study activities. The platform will be used to: (1) provide access to instructional and demonstration videos; (2) collect data, including questionnaires; (3) implement the SHUTi program (intervention group) and educational program (control group); and (4) secure transmission of data to the study team. The platform allows for input constraints in the tools as well as real-time validation of data formats and ranges, providing real-time feedback to the user if "out-of-range" values are recorded. Participants will need to be able to access the internet on a device of their choosing. We anticipate enrollment of 352 participants within a 4-year period.
Human Subjects: The risk of harm anticipated in the proposed research is not greater than that encountered during daily activities or during the performance of routine physical

examinations. Monitoring will be performed by the PI, co-investigators, and the IRB through annual continuing reviews. All study activities will be done completely remotely, and the main requirement is to have internet access, access to a computer or laptop, and access to a smart phone or tablet. During the intervention, participants will be instructed on how to minimize the risk associated with sleep restriction and to contact study staff if they have any significant concerns. As needed, study staff will instruct participants to contact their primary care provider. Participants will not be required to complete any of the assessments they wish to omit, nor will they be required to answer any questionnaire items they do not wish to answer.

TABLE OF CONTENTS

1.0 OBJECTIVES

1.1. Primary Objective

To examine the efficacy of an eHealth intervention for improving symptoms of insomnia among adult survivors of childhood cancer.

Hypothesis 1.1.a.: Survivors randomized to an eHealth CBTi intervention will report significantly fewer symptoms of insomnia post-intervention compared to survivors randomized to online patient education only.

1.2. Secondary Objectives

1.2.1. To examine the impact of an eHealth intervention for insomnia on the clinical severity of insomnia symptoms in adult survivors of childhood cancer.

Hypothesis 1.2.1.: A larger proportion of survivors randomized to the CBTi intervention will no longer meet clinical criteria for insomnia post-intervention compared to survivors randomized to online patient education.

1.2.2. To determine whether treatment of insomnia symptoms will improve neurocognitive function in adult survivors of childhood cancer with both insomnia and neurocognitive impairment.

Hypothesis 1.2.2.a: Survivors randomized to an eHealth CBTi intervention will report significantly fewer symptoms of neurocognitive impairment post-intervention compared to survivors randomized to online patient education only.

Hypothesis 1.2.2.b.: Improvement in insomnia symptoms will mediate the association between intervention status (CBTi vs. online patient education) and improved neurocognitive function post-intervention.

Hypothesis 1.2.2.c.: Symptoms of emotional distress and cardiac health will be associated with improved insomnia symptoms and neurocognitive function.

1.2.3. To explore the mediating effects of improved neurocognitive function, emotional distress, and cardiovascular health on the association between insomnia symptoms and quality of life.

Hypothesis 1.2.3.a.: Survivors with improved insomnia symptoms following completion of an eHealth CBTi intervention will report better health-related quality of life compared to survivors without improved insomnia symptoms.

Hypothesis 1.2.3.b.: Neurocognitive function, symptoms of emotional distress, and biomarkers of cardiovascular health following completion of the eHealth CBTi intervention will mediate the association between improved insomnia symptoms and quality of life 6-months post-intervention.

2.0 BACKGROUND AND RATIONALE

2.1. Background

Childhood Cancer Survivors Are a Growing Population with a High Burden of Morbidity - More than 80% of children diagnosed with a new cancer now survive five years, with most becoming long-term survivors.[1] This has resulted in a growing population of childhood cancer survivors, estimated to approach half a million by 2020.[2] Unfortunately, curative treatments also result in toxicities that leave many survivors with substantial burden of adverse physical and mental health outcomes.[3] Morbidities commonly observed after cancer treatment include fatigue and sleep disturbance, neurocognitive impairment, emotional distress, cardiovascular disease, and diminished quality of life (QoL).

Defined as difficulty initiating or maintaining sleep, or nonrestorative sleep resulting in decreased daytime function[4], insomnia is the most commonly reported sleep disturbance among adults. In the general population, rates of insomnia range from 10 to 15%, with higher prevalence observed among women than men.[5] Insomnia also impacts a substantial proportion of childhood cancer survivors. A recent report indicated that 28% of adult survivors of childhood cancer (excluding CNS tumor survivors) experience symptoms severe enough to warrant active treatment for insomnia.[6] Compared to siblings, adult survivors of childhood cancer are significantly more likely to report poor sleep efficiency (PR=1.3; 95% CI, 1.-1.5), with one-third reporting delayed onset and less than 7 hours of sleep per night. Notably, sleep disturbances following treatment for childhood cancer are often present in adolescence and likely persist for decades into adult survivorship. It has been recently reported that approximately two-thirds of adolescent survivors of acute lymphoblastic leukemia (ALL) experience delayed sleep onset and 30-40% had frequent nighttime and premature awakenings.[7] Insomnia has been associated with many of the late health complications observed in survivors of childhood cancer, including neurocognitive impairment, emotional distress, and cardiovascular disease. Because adult survivors of childhood cancer have been exposed to neurotoxic and cardiotoxic chemotherapies and radiation, their compromised cardiovascular and neurologic systems may be more sensitive to the effects of insomnia on neurocognitive and cardiac functions. Thus, there is not only a need

for a widely available therapy to treat insomnia, but there is also a need to understand how improved insomnia symptoms impact neurocognitive function and late health morbidities in childhood cancer survivors.

2.2. Rationale

Insomnia and Neurocognitive Morbidity

In non-cancer populations, insomnia has been associated with impaired cognitive performance, particularly in the domains of attention, memory, and executive function.[8] A recent meta-analysis revealed moderate effects sizes for the impact of insomnia on episodic memory (ES = -0.51), problem solving (-0.42), and working memory (ES = -0.42).[9] Working memory impairment has been observed on direct performance-based measures as well as through assessment of neural function via integrity of the hippocampus in adults with insomnia.[10-11] Insomnia also has been associated with dementia in the general population[12-14] and emerging evidence suggests that adult survivors of childhood cancer may experience accelerated cognitive aging. Using data from the Childhood Cancer Survivor Study (CCSS), we demonstrated that among adult survivors (n=1,426), after adjustment for neurotoxic therapies [e.g., cranial radiation], poor sleep quality is associated with impaired task efficiency (RR=1.23, 1.01-1.49) and memory (RR=1.45, 1.19-1.76); daytime sleepiness is associated with emotional regulation problems (RR=1.38, 1.14-1.67), diminished organization (RR=1.80, 1.31-2.48), and impaired memory (RR=2.05, 1.63-2.58).[15] There are no data to suggest that neurocognitive deficits precede the onset of insomnia symptoms; however, sleep distribution has been shown to exacerbate neurocognitive deficits.

Insomnia and Psychiatric Morbidity

Insomnia is highly comorbid with a range of psychiatric disorders. Comorbidity estimates range between 30% and 50% with depression and anxiety being among the most highly comorbid conditions.[16-18] Though temporal relations are difficult to confirm, insomnia has repeatedly been shown to be a clinical predictor of subsequent depression.[19] Recent path analyses suggest that sleep problems cause significantly more dysphoria than dysphoria causes sleep problems.[20] Among survivors enrolled in the CCSS, we have shown that survivors with elevated depressive symptoms are four times more likely to report disrupted sleep, including symptoms of insomnia (OR, 4.4; 95% CI, 3.1 to 6.3).[21]

Insomnia and Cardiovascular Morbidity and Mortality

In the general population, insomnia is associated with cardiovascular disease, including risk of myocardial infarction, coronary heart disease, and stroke as well as increased risk of cardiopulmonary mortality.[22, 23] Furthermore, chronic insomnia has been shown to be an independent risk factor for new onset hypertension, even when controlling for other risk factors including smoking, alcohol consumption, depression, race, diabetes, and obesity.[24] Elevated resting heart rate, lower heart rate variability,[25] and poorer cardiorespiratory fitness[26] have been observed among adults with insomnia. Insomnia also has been associated with dyslipidemia and hypercholesterolemia.[27] In a recent meta-

analysis, sleep disturbance was significantly associated with increased inflammation (i.e. levels of C-reactive protein [CRP] and interleukin-6 [IL-6]).[28] Among survivors of ALL we have demonstrated associations between symptoms of insomnia and worse neurocognitive function as well as higher levels of IL-6, IL-1β, and high sensitivity CRP and worse performance on measures of executive function and processing speed.[7] These data suggest a link between sleep, systemic inflammation, and neurocognitive function in survivors. Moreover, in survivors of childhood cancer, systemic inflammation has been implicated as promoting development of cardiovascular disease.[29, 30] Because symptoms of insomnia are often present many years before the onset of cardiac disease in survivors of childhood cancer, we hypothesize that these symptoms temporally precede cardiovascular morbidity observed in adult survivors.

Treatment of Insomnia

Given the significant mental and physical health burden of insomnia, effective treatment is critical. Cognitive behavioral therapy for insomnia (CBTi) has become the benchmark for treatment and incorporates three key strategies for improving sleep: sleep restriction, stimulus control, and cognitive restructuring. A recent meta-analysis of CBTi in adults with insomnia found it produced moderate to large effect sizes in improved sleep, improvements which lasted up to 18 months.[31] An additional study in cancer survivors found CBTi performed better than a pharmacologic intervention in treating insomnia and improving fatigue.[32]

Although studies are limited, there is emerging evidence that treatment of insomnia with CBTi can lead to improved emotional distress and physical health outcomes in non-cancer samples with chronic health care needs.[33-36] In addition, successful treatment of insomnia has been shown to reduce biomarkers of inflammation associated with cardiovascular risk.[37, 38] However, no study has examined the impact of a CBTi intervention on insomnia symptoms in long-term adult survivors of childhood cancer, nor has any study examined the impact of improved insomnia symptoms on neurocognitive function or late health morbidities in childhood cancer survivors. Despite established efficacy, traditionally delivered CBT (i.e. face-to-face psychotherapy) is often underutilized due to limited access to trained professionals, cost, stigma associated with mental health treatment, and time constraints. These barriers are even more pronounced in cancer survivors who report limited health care access and utilization due to lack of insurance and poor physical health.[39] In fact, mental health care services are significantly underutilized by survivors of adolescent and adult onset cancers.[40-43] To reduce access barriers and promote participation in CBTi (i.e., treatment uptake), alternative delivery models have been developed. One such approach is electronic health delivery or internet-based CBTi. A recent systematic review and meta-analysis of 15 internet-based CBTi studies reported improvements in sleep efficiency and total sleep time as well as reductions in insomnia severity and depressive symptoms. Moreover, no differences were observed between internet-delivered versus in-person therapy with a trained therapist.[44] The internet-delivered insomnia intervention for the proposed study, Sleep Healthy Using the Internet (SHUTi), was chiefly studied

in a randomized controlled trial including 44 adults with primary insomnia who were randomly assigned to either the internet intervention or wait-list control group. Sleep diary data showed significant improvements for SHUTi users in sleep efficiency (SE), nighttime awakenings (number and time spent awake), and total sleep time; whereas the control group showed no significant changes. SHUTi participants also showed clinical improvement in insomnia severity, where 73% of SHUTi users fell in the "no insomnia" category after treatment; no control participants met this criterion. In addition, although SHUTi was not specifically designed to target comorbid symptoms, significant improvements were found in mood (e.g., depressive and anxious affect), physical symptoms

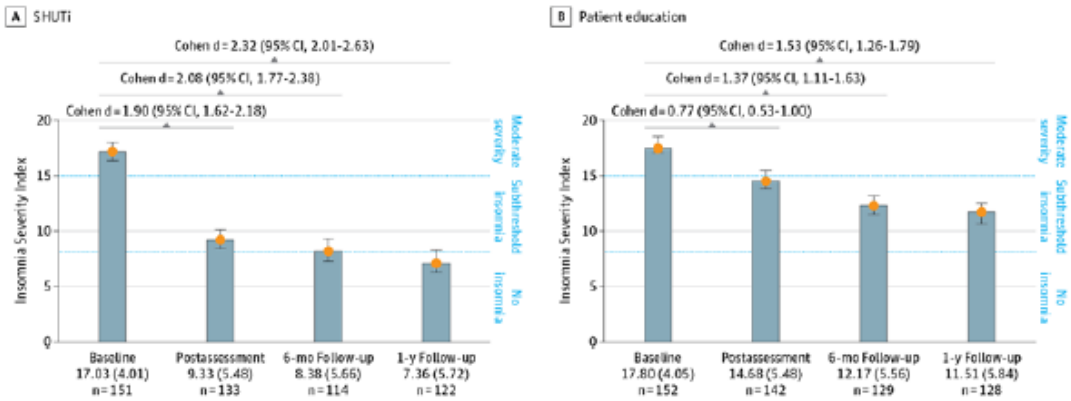


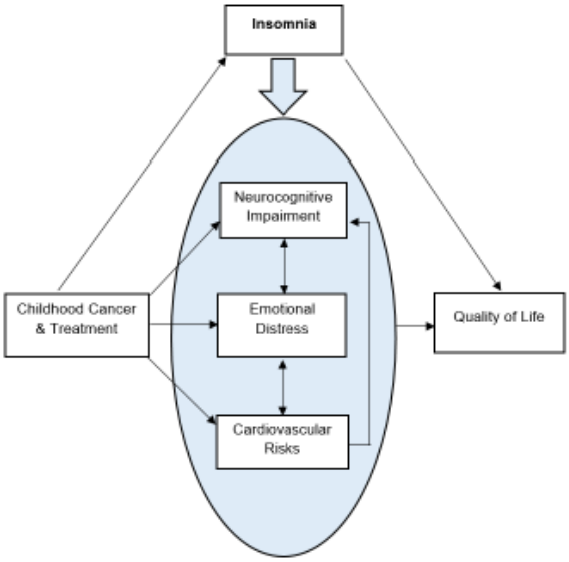
Figure 1. Improvement in insomnia symptoms following SHUTi intervention

(e.g., fatigue), and QoL.[45] More recently, a national trial of SHUTi with 303 adults with chronic insomnia, including those with psychological comorbidities provided further evidence that SHUTi users exhibit greater improvements in insomnia severity, sleep onset latency (SOL), and wake after sleep onset (WASO) than users of a Patient Education website (Figure 1).[46] In sum, internet-delivered CBTi has been accepted as an established, efficacious treatment for insomnia in adults. However, because sleep disturbances in adult survivors of childhood cancer may have persisted for many years, if not decades, we aim to evaluate the efficacy of an eHealth CBTi program to improve insomnia in this population.

Theoretical Model

It has been established that childhood cancer and its treatment may result in symptoms of insomnia, neurocognitive impairment, emotional distress, and cardiovascular risks (Figure 2), and that these factors contribute to survivor QoL. We propose that insomnia may have an overarching impact on neurocognition, emotional distress, and cardiovascular health, consistent with observations from the general population, but that this impact may be particularly salient in survivors with compromised neurologic and cardiovascular systems related to prior cancer therapy. Using this model, we propose that insomnia may serve to exacerbate or maintain neurocognitive impairment, emotional distress, and cardiovascular risks in long-term survivors of childhood cancer, and that improved insomnia may serve to improve these late effects, ultimately improving survivor QoL. We recognize the potential for bidirectional influences among variables; however, based on past literature and the temporal developmental of late effects in childhood cancer survivors we propose to test our a priori hypothesized theoretical model.

Figure 2. Theoretical model



Barriers to Progress

Three major factors have limited progress in identifying efficacious interventions for neurocognitive impairment in adult survivors of childhood cancer: (1) limited large cohorts of adult survivors of childhood cancer; (2) hurdles associated with commonly considered interventions; and (3) lack of consideration of comorbid health conditions. Limited research has focused on developing interventions for improving late effects in cancer survivors. There are few childhood cancer centers that follow survivors into their adult years and even fewer have the infrastructure to support large intervention trials. The Childhood Cancer Survivor Study (CCSS) provides a unique opportunity for such interventions, as it consists of >24,000 five-year survivors of childhood cancer who were diagnosed between 1970-1999 at one of 31 participating centers in the U.S. and Canada. Availability of treatment options for a geographically diverse cohort (i.e. survivors relocate with age) have also been a barrier. Cancer survivors may be less likely to engage in face-to-face CBTi for several reasons including poor physical health, lack of health insurance, stigma, and restricted access to the physical environment secondary to chronic disease. Internet delivery of CBTi will eliminate many of the physical and emotional barriers associated with mental health treatment for survivors. Specifically, survivors will be able to independently complete CBTi at home thereby facilitating access to and uptake of treatment for insomnia. Finally, prior research examining late-effects has focused on the direct impact from cancer and cancer therapies. For

survivors, these treatment-related risk factors are no longer modifiable. As such, interventions have included direct attempts at improving neurocognitive function through cognitive stimulation, or adaptive approaches that teach survivors to compensate for their deficits. Cognitive training is intended to strengthen neural networks through repeated co-activation, with the goal of improving efficiency;[47] however, our pilot data suggest limited efficacy in isolation. Most cognitive interventions are limited by problems of feasibility (i.e. high dropout rates, limited disseminability) and resource requirements (i.e. time intensive, on-site supervision). Similarly, interventions for depression, anxiety, and cardiovascular health have focused on treating specific symptoms (e.g. antidepressants for depression, stimulants for fatigue, antihypertensive medication for high blood pressure), without consideration of possible comorbid conditions that may exacerbate or serve to maintain symptoms. Moreover, these pharmacologic approaches place survivors at-risk for adverse drug side effects as well as potential drug-drug interactions. This study will address each of these barriers by focusing on a large nationally representative cohort of adult survivors of childhood cancer, providing an accessible intervention, and considering a behaviorally modifiable health condition (insomnia).

3.0 RESEARCH PARTICIPANT ELIGIBILITY CRITERIA AND STUDY ENROLLMENT

According to institutional and NIH policy, the study will accession research participants regardless of gender and ethnic background. Institutional experience confirms broad representation in this regard.

3.1. Inclusion Criteria

3.1.1. Enrollment in CCSS

3.1.2. Between the ages of 18 and 65 years old

3.1.3. Meeting at least one of the following three insomnia criteria:

3.1.3.1 Clinically significant insomnia (i.e. score ≥8 on the Insomnia Severity Index)
3.1.3.2 Delayed sleep onset latency (SOL) (i.e. cannot get to sleep within 30 minutes, three or more times a week)
3.1.3.3 Excessive wake after sleep onset (WASO) (i.e. nighttime awakenings lasting a total of at least 30 minutes, three or more times per week)

3.1.4. Neurocognitive impairment (i.e. score ≥84th %ile of sibling normative data in at least one domain on the CCSS-NCQ)

3.1.5. Regular access to the internet (at least 2-3 days per week)

3.1.6. Access to a desktop computer or a laptop

3.1.7. Access to a smart phone (android or iPhone), tablet or iPad with Bluetooth Low Energy BLE 4.2 or higher.

3.1.8. Ability to read and speak English

3.2. Exclusion Criteria

3.2.1. History of a brain tumor

3.2.2. An irregular schedule that would prevent adoption of intervention strategies (i.e. work schedule resulting in usual bedtime earlier than 8 PM or later than 2 AM or arising time earlier than 4 AM or later than 10 AM)

3.2.3. Currently pregnant or breast feeding

3.2.4. Behavioral treatment for insomnia in the past 12 months

3.2.5. Diagnosis of a schizophrenia or psychotic disorder

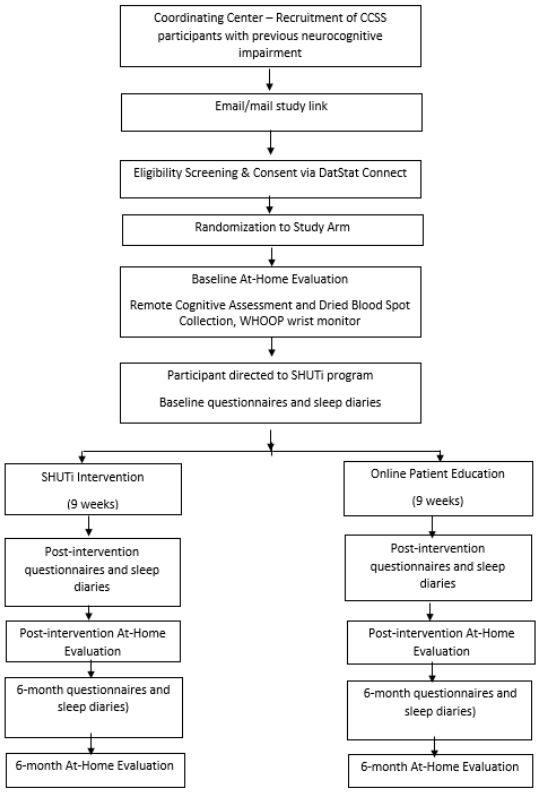
3.2.6. Alcohol or drug abuse in past year

3.2.6.1. Per exclusion criteria 3.2.6., The Alcohol Use Disorders Identification Test (AUDIT) will be used to screen for individuals who have active alcohol use disorders and the Drug Abuse Screen Test (DAST-10) will be used to screen for individuals with drug abuse. Both questionnaires include 10 items and are well-validated.

3.2.7. Other concurrent sleep disorders, including narcolepsy, obstructive/central sleep apnea, or restless leg syndrome

3.2.8. Current treatment or intervention for cognitive impairment (i.e. stimulant medication, transcranial direct current stimulation)

3.3. Research Participant Recruitment and Screening



Recruitment will be conducted by the CCSS Coordinating Center at St. Jude. As illustrated in Figure 3 to the right, survivors participating in CCSS who have been previously identified as having neurocognitive impairment in at least one of three domains in the NCQ[48] will be approached for recruitment. An approach packet consisting of an introduction letter, a single page study brochure, and informed consent documents will be mailed to these potentially eligible participants. Interested participants will be instructed to visit the study webpage, where participants can sign-up and provide informed consent on-line. Those who have not responded after two weeks will receive an email alerting them to the study and providing a link to the study webpage. Starting three weeks after the initial mailing, a trained study interviewer housed within the CCSS Call Center will begin calling non-responders to provide information, answer questions, and encourage participation. Eligible participants will have the opportunity to consent to the study verbally while speaking with a trained study interviewer from the CCSS Call Center. Alternatively, survivors who wish to participate will complete an online consent form and then a series of short questionnaires to determine study eligibility. This data collection will take place in DatStat Connect, which is the online consenting and data collection tool utilized for the CCSS. To date, there are 11,579 non-CNS tumor survivors who were previously administered the CCSS-NCQ. Based on those surveys, 4,465 were impaired and, conservatively we estimate that 30% of these will have comorbid symptoms of insomnia (n=1,339). We anticipate enrolling 52 participants in year 1 and 100 participants per year in years 2-4, each year divided equally by sex.

3.4. Enrollment on Study at St. Jude

A member of the CCSS study team will create an initial list of potentially eligible participants and will send letters/emails containing the information for the study website through which consent will be obtained followed by additional eligibility questions that cannot be obtained prior to consent by the study team.

This will confirm participant eligibility as defined in Section 3.1-3.2 (similar to eligibility criteria being confirmed after consent on traditional St. Jude studies). Once eligibility is confirmed, the post eligibility questionnaires and assessments will be administered and scheduled. The website will provide safeguards to ensure that additional assessments and questionnaires cannot be obtained until eligibility is confirmed. CCSS team members will monitor this process

3.5. Procedures for Identifying and Randomizing Research Participants

Prior to initiating the study, team members will be trained on the protocol and study procedures. The background to the study, study procedures, consent processes for the online or the verbal consent, data transfer, and plans to monitor intervention integrity and data quality will be part of the training.

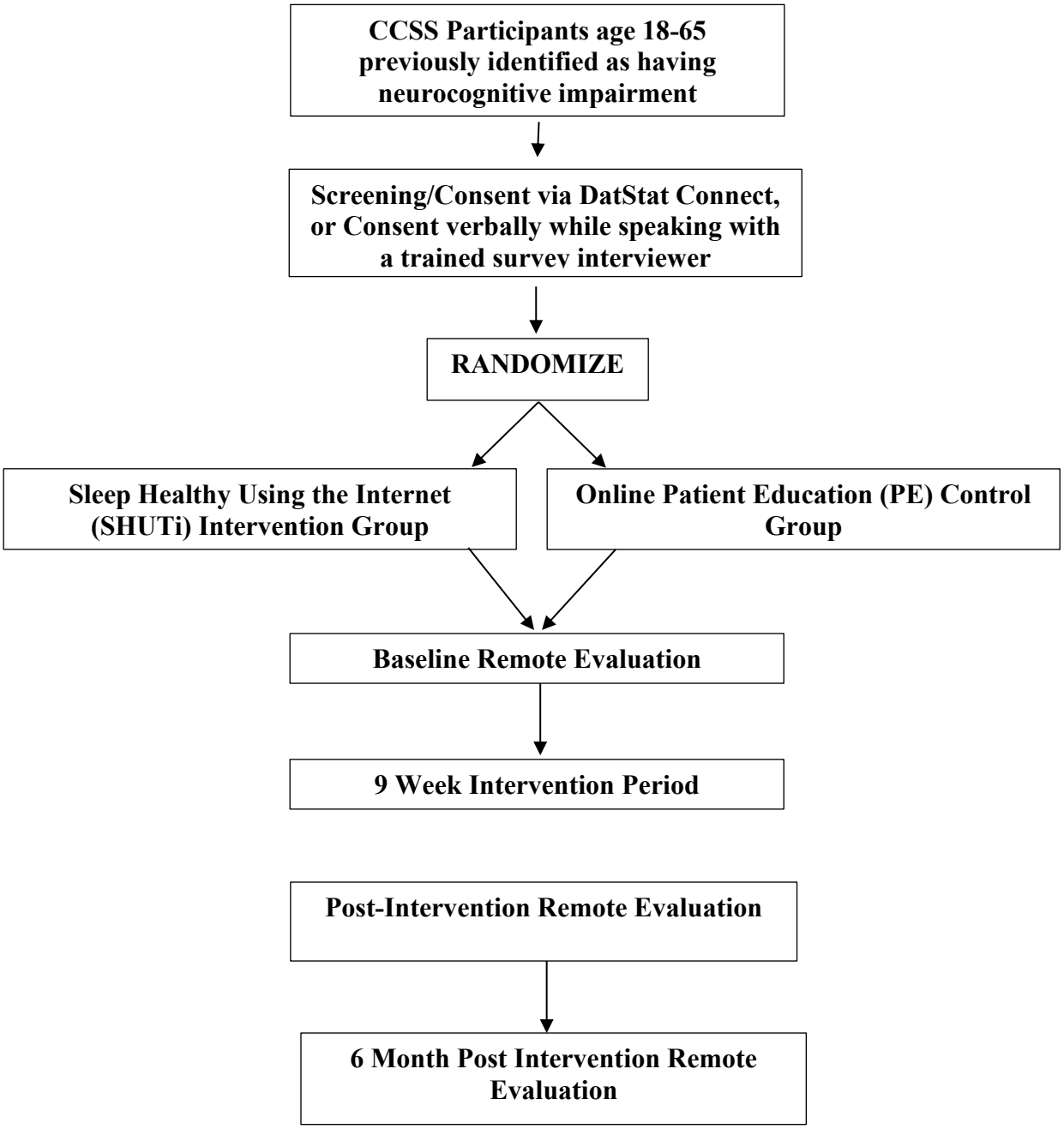
Following the study preparation, initial screening for eligibility, consent and additional eligibility verification for the research participants will begin. Once consented and eligibility is confirmed, participants will be randomized using a permuted-block method with random block sizes, stratified on sex, age (<40 vs. ≥ 40), and cranial radiation therapy (Y/N). Following randomization, participants will complete the remote cognitive assessment, will provide a blood sample using the Dried Blood Spot (DBS) method and wear a WHOOP wrist monitor for 7 to 11consecutive days. Following the remote evaluation, they will receive a direct link to access the SHUTi program or online patient education (per randomization).

4.0 DESIGN AND METHODS

4.1. Design and Study Overview

This is a randomized controlled trial looking to evaluate the efficacy of an internet-based cognitive behavioral therapy intervention (SHUTi) on insomnia and other highly prevalent late effects of childhood cancer: neurocognitive impairment, emotional distress, cardiovascular risk factors, and quality of life (compared to an online patient education control group). Once consented, participants will be asked to complete the baseline remote evaluation portion of the study. Participants will complete a remote cognitive assessment (CNS Vital Signs) wear a WHOOP wrist monitor and will provide a blood sample using Dried Blood Spot (DBS) method. Questionnaires and the SHUTi program will be completed via the RICE platform hosted by the University of Virginia. The post-intervention remote evaluation will occur approximately 10 weeks after baseline. The final remote evaluation will occur approximately 6 months post intervention. The study schema is illustrated in Figure 4.

Figure 4. Study Schema



4.2. Study Procedures / Intervention:

4.2.1. The eHealth Data Using the RICE Platform:

Participants will complete the post enrollment questionnaires and the assigned intervention arm (SHUTi or patient education) using the RICE (Research Infrastructure Containing E-interventions) framework developed by the University of Virginia (Dr. Lee Ritterband, Co-Investigator).

RICE includes two core elements: Electronic Study Manager (ESM) and Content Management System (CMS), which plays a central role in intervention development. The first core element, the ESM, provides a range of research study management tools. ESM controls the delivery, access and timing of the study data capture for all research participants, including interested and consenting candidates as well as experimental, control, and wait-list participants. Typically, the research study includes an interest website (providing information about the study), online interest and consent forms (to be completed online by those interested in being considered for participation), online study assessment forms, and dynamically generated email notifications and reminders. It contains a field-tested toolset that includes integrated components used to define and manage the unique study workflow, online interest and consent forms, assessment criteria for purposes of eligibility, and participant progress.

The optional second core element, the CMS, uses the ESM toolset and the optional Module Builder to deliver a web-based intervention program. Intervention content may include text, images, video files, audio files, quizzes and custom responses, interactive elements, tailored feedback, and other custom programming. CMS is fully integrated with ESM, providing the System Administrator with the flexibility to also control the presentation, delivery, access, and timing of the intervention content.

The RICE framework contains five primary core components: (1) Flow Builder: Used to define the unique combination of procedural and temporal logic that determines the paths by which the assessment and online intervention content are presented to the user; (2) Questionnaire Builder: Web-based tool for creating questionnaires composed of data capture fields, including integers, text, checkbox, dropdown, images, or electronic signatures, as part of the participant's online experience. Questionnaires may be used during the assessment process, online interest capture, diary collection, and intervention follow-ups; (3) Automated E-mailer: Sends out e-mails based on study flow logic, with a web-based authoring system for creating the e-mail prompts that are sent given developed triggers in the intervention; (4) Module Builder (Optional): Authoring tool that brings together the text, images, animations, video, audio, and interactive elements that compose an intervention. Modules each contain presentation layouts, decoupling the task of content presentation from the task of entering and updating study content, resulting in the rapid

prototyping of modules; and (5) Administrative System: Centralized tool that allows study administrators, regardless of location, to track study progress, manage subject accounts and view complete communications audit trail. More specifically, this administrative and semi-automated system allows us to track participants, including storing all contact information, interview data, participant's current position in the study and intervention, a calendar of events that are automatically established for each subject once recruited, tracking of all contacts with participants, a robust reporting system providing details about which participants need to be contacted for what, on-the-fly reporting of critical study parameters (number of recruited subjects, number of participants in each condition, completers, drop-outs, etc.), payments, and notes.

The only patient specific information that will be entered in the RICE platform includes participant email addresses (necessary for communication and delivery of the intervention) and time zones (necessary for data collection purposes).

4.3. Study Procedures:

Assessment of Sleep

1) Insomnia Severity Index (ISI) is a 7-item, Likert scale, self-report questionnaire assessing perception of sleep and consequences of insomnia. The ISI has had extensive validity and reliability testing, including for electronic delivery and for use in evaluating treatment response. Cronbach α for internal consistency is 0.90, convergent validity with measures of fatigue, quality of life, anxiety and depression have been reported.[50, 51] The scores range from 0 (no insomnia) to 28 (severe insomnia); scores < 7 are considered "no clinically significant insomnia". The ISI will be administered at baseline, post-intervention, and 6-month follow-up.

2) Sleep Diary will be an online diary and will be included in the SHUTi program (including the patient education arm). Each diary entry contains 10 standard sleep questions including bedtime, sleep onset latency, number of awakenings, total length of awakenings, wake time, arising time, daytime naps, rating of soundness of previous night's sleep, rating of refreshed feeling upon morning awakening and inquiry about sleep aids (over the counter medication/alcohol). In addition to the 10 pre-assessment entries required before the intervention begins, participants are encouraged to complete the diary daily, but entries that are up to 3 days old will be accepted. Sleep diary data will generate data on sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency (SE) and number of awakenings. Data from the sleep diaries will be correlated with actigraphy data.

3) Actigraphy will be collected to measure sleep-patterns of each participant. A WHOOP wrist monitor to be worn over 7 to 11 consecutive days at three specified intervals [baseline, post-intervention, 6 months]. Actigraphy provides objective assessment of wrist movement that infers wakefulness and sleep.

Functionally, the WHOOP devices provide sleep-pattern measures including: SOL, WASO, SE, and total sleep time (TST). Movement triggering the device is relatively high during wakefulness and decreases to near-zero values during sleep. Analysis of actigraphic records reveals sleep-wake patterns that correlate closely with patterns obtained via polysomnographic recordings and behavioral observations.[52-59] Furthermore, actigraphy is a reliable method for assessing sleep-wake patterns and monitoring of treatment response among insomnia patients.[59,60] Actigraphy is able to sensitively capture change in sleep-wake patterns before and after behavioral or medical interventions, and actigraphic data from either wrist is highly similar. The mailing of the WHOOP wrist monitors will be coordinated by study personnel at St. Jude in collaboration with the CCSS coordinating center. Participants will receive a WHOOP wrist monitor along with a pre-paid return package. A WHOOP wrist monitor will be mailed at baseline and maintained by the participant until the 6-month follow-up. Participants will download the WHOOP app to their device (smart phone or tablet/iPad with BLE 4.2 or higher) so they can remotely upload their data to a secure cloud-based platform hosted by WHOOP and securely accessible by the study team at St. Jude.

4) Questionnaires to measure fatigue and daytime sleepiness will be completed via the RICE Platform at baseline, post-intervention, and 6-month follow-up. These questionnaires will assess the functional symptoms of insomnia using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) and Epworth Sleepiness Scale (ESS).

Neurocognitive Functioning

1) The Childhood Cancer Neurocognitive Questionnaire (CCSS-NCQ)[61] is a 32 item self-report questionnaire evaluating 4 domains (8 questions per domain) of neurocognitive function: (1) memory; (2) task efficiency; (3) organization; (4) emotional regulation. The CCSSNCQ was developed specifically to address neurocognitive concerns of adult survivors of childhood cancer. It has been administered to over 12,000 non-brain tumor survivors within the CCSS cohort,[48] and age- and sex-adjusted normative data are available from over 3,000 siblings of childhood cancer survivors. Extensive psychometric analysis of the CCSS-NCQ has been conducted, with the most recent involving Item Response Theory analysis and validation with traditional neuropsychological testing.[62] The CCSS-NCQ will be used to screen participants for eligibility. For this study we will not utilize organization as an outcome because in our previous studies this domain has been shown to be less sensitive in detecting neurocognitive impairment. This questionnaire will be completed at baseline, post-intervention, and 6-month follow-up via the RICE Platform.

2) We will obtain a direct measure of cognitive function among participants using a remotely administered assessment (CNS Vital Signs). This remote assessment is completed using a desktop computer or laptop, and is self-administered. This assessment presents minimal risk to participants and enables them to complete the evaluation from their home. The CNS Vital Signs

instrument provides written instructions to the participant before beginning of each test. The tests evaluate cognition through evaluation of memory, attention, non-verbal reasoning, processing speed and reaction time The cognitive assessment will include the following tests: Verbal Memory (VBM), Visual Memory (VIM), Finger Tapping (FT), Symbol Digital Coding (SDC), Stroop Test (ST), Shifting Attention (SAT) Continuous Performance (CPT). The total administration time is approximately 25-30 minutes.

Emotional Distress

Symptoms of emotional distress will be assessed using the Patient Health Questionnaire – 9 (PHQ-9) for depression and the Generalized Anxiety Disorder – 7 (GAD-7). The PHQ-9 is designed for the screening and monitoring of depressive symptoms as well as for the presence and duration of suicide ideation. The PHQ-9 provides cut-off scores for mild, moderate, moderately severe, and severe depression. PHQ-9 scores >10 have sensitivity of 88% and specificity of 88% for major depression. The GAD-7 is designed for the screening and monitoring of anxiety symptoms. Cut-off scores are provided for mild, moderate, and severe anxiety. Using the threshold score of 10, the GAD-7 has a sensitivity of 89% and a specificity of 82% for generalized anxiety disorder. These questionnaires have undergone reliability and validity testing across individuals with range of health conditions and demographic characteristics. The PHQ-9 and GAD-7 will be administered at baseline, post-intervention, and 6-month follow-up via the RICE Platform.

Cardiovascular Health Indices

1) Using the Dried Blood Spot (DBS) method, blood will be collected to measure:

a. **serum biomarkers of inflammation**: interleukin [IL] IL 6, high sensitivity C reactive protein [hsCRP]
b. **oxidative stress:** myeloperoxidase
c. **lipid profile:** triglycerides, total Cholesterol, HDL Cholesterol

We will mail the participants a Dried Blood Spot (DBS) Kit, including written directions and a link to a video that explains the procedure in detail [https://bcove.video/2LIxHIr]. Participants will collect about six drops of blood by pricking their finger. The 6 blood drops usually required to fill a specimen card are equal to a total blood volume of about ¼ teaspoon and the collection of a dried blood spot sample usually takes about 10 minutes. The samples will be shipped to St. Jude Children's Hospital, where they will be stored until the end of the study. At the end of the study, the Dried Blood Spot (DBS) cards will be shipped to the University of Washington for analysis. All samples will be assayed in duplicate and the average of the two measures will be used for data analyses. All samples from individual participants will be run on the same assay plate to reduce intra-assay variation. Serum biomarkers will be measured at baseline, post-intervention, and 6-month follow-up.

2) Resting Heart Rate (RHR) and Heart Rate Variability (HRV) will be measured by having participants wear the WHOOP wrist monitor. We will use a time domain measure of heart rate variability (HRV), a non-invasive, albeit indirect way to investigate autonomic nervous system function. It is attractive in this large cohort study, with participants distributed around North America, because today's sensor technology allows remote collection of data in participants usual environments while doing their usual activities. We will use the WHOOP® strap wearable biosensor to obtain standard deviation of NN (normal to normal RR) intervals (SDNN) measured over a 24-hour period and recorded in milliseconds (ms). SDNN captures total HRV; low values over a 24-hour period indicate lack of circadian rhythm. We selected this measure as our primary outcome because of its documented associations with morbidity and mortality in several large studies. Data from the Framingham Heart Study (N=2501) indicate that a one standard deviation decrement in the SDNN (log transformed), captured remotely over 2 hours, is associated with a nearly 50% increased risk (HR 1.47, 95% CI 1.16-1.86) of new onset cardiac conditions, even after accounting for other known risk factors for autonomic dysfunction. In addition, among persons with congestive heart failure (UK-heart, N=433), in adjusted models, a 41.2ms decrement in SDNN, measured over 24-hours, was associated with a 1.62 (95% CI 1.16-2.44) increased risk for all-cause mortality, and the strongest predictor of death related to progressive heart failure.[63] The WHOOP device includes a photoplethysmography-based heart rate/heart rate variability sensor, an accelerometer, and sensors to detect ambient temperature and galvanic skin response. For this study participants with 24-hour SDNN <50ms will be classified with unhealthy HRV, those with values 50-100ms with compromised HRV, and those with values >100ms with normal HRV. The participants will wear the WHOOP wrist monitor for a period of 7 to 11 consecutive days at three specified intervals [baseline, post-intervention, 6 months]. The mailing of WHOOP wrist monitors will be coordinated by study personnel at St. Jude in collaboration with the CCSS coordinating center. Participants will receive a WHOOP wrist monitor along with a pre-paid return package. The WHOOP wrist monitor will be mailed to the participant at baseline and maintained by the participant for the duration of the study. Heart rate data will be uploaded by participants using their smart phone or tablet to a secure cloud-based platform hosted by WHOOP and securely accessible by the study team at St. Jude

3) Physical Activity will be measured by having participants wear the WHOOP wrist monitor This device includes atri-axial accelerometer that detects wrist movement, which is used to collect objective information on intensity and duration of common locomotion activities such as walking and jogging. Physical activity of each participant will be measured with the WHOOP wrist monitor, which will be worn by the participant for 7 to 11 consecutive days at three specified intervals [baseline, post-intervention, 6 months] corresponding to the same period when sleep patterns are measured.

Quality of Life

Health-related quality of life (HRQoL) will be assessed at baseline, post-intervention, and 6-month follow-up. HRQoL will be measured with the PROMIS Global Health questionnaire. This is a widely used 10-item generic health profile that provides physical and mental health summary scores.[64] The Global Health measure will be completed via the RICE Platform.

Exploratory Outcomes

In addition to quality of life we will evaluate, in an exploratory manner, the impact of improved insomnia symptoms on work and social adjustment 6-months post intervention. The work productivity and activity impairment questionnaire (WPAI)[65, 66] is a 6-item measure that assesses work-related impairment reflected by amount of absenteeism, presenteeism, and daily activity measures. This measure has good discriminatory and construct validity, as well as the ability to detect significant changes in symptoms. The work and social adjustment scale (WSAS)[67] measures social and work-related impairment resulting from mental health problems. The internal consistency is high, with Cronbach's α ranging from .70 to .94 and test-retest reliability is also good (r=0.73). The WPAI and WSAS will be completed by participants via the RICE Platform.

4.4. Intervention

Participants will receive a direct link to access the SHUTi program or online patient education (per randomization) from the study team. This will include login and password information. Through the RICE platform, St. Jude study staff will track and monitor participants who are randomized to SHUTi or patient online education.

SHUTi

SHUTi is a fully automated, interactive and tailored web-based program that incorporates the primary tenets of face-to-face CBT-I, including sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relapse prevention. Intervention content is presented in six "Cores," metered out over time. Each Core
was developed to parallel traditional weekly sessions conducted when delivering CBT-I in a face-to-face format, following a similar general structure: 1) examination of Core objectives, 2) review and feedback on homework and sleep diary data from the previous week, 3) teaching of new intervention material, 4) summary of the main points of the Core, and 5) assignment of homework. The participant will have nine weeks to complete the six cores and at week 10 will be asked to complete post-intervention questionnaires/sleep diaries as well as to complete the post intervention remote evaluation. Data will be available on total number of participant logins, sleep diaries completed, and core modules completed. All participants will be able to access human support through UVA for technical difficulties with SHUTi. Intervention content is enhanced through

a variety of interactive features, including personalized goal-setting, graphical feedback based on reported symptoms, animations and illustrations to enrich comprehension, quizzes to test and enhance user knowledge, vignettes to promote identification with material, and video-based expert explanations. Weekly automated emails are also sent to increase engagement and encourage program adherence. However, no human support will be provided to increase treatment adherence. Removing human support from provision of care can vastly increase the ability to widely disseminate treatment, however, it may be associated with reduced adherence. Despite this, a recent study of SHUTi with breast cancer survivors indicated that intervention group participants completed 4.1 (SD = 2.5) cores, with 82.1%, 75.1%, 67.2%, 64.2%, 62.7%, and 59.7% completing cores 1, 2, 3, 4, 5, and 6, respectively. The number of cores completed was associated with improvements in insomnia symptoms. Therefore, we will complete a sensitivity analysis to examine the impact of treatment adherence on insomnia symptoms.

Online Patient Education (PE) Control Group
The online PE program provides static information about: insomnia symptoms; the impact, prevalence, and causes of insomnia; when to see a doctor; and basic lifestyle, environmental, and behavioral strategies to improve sleep. The content for this program was informed based on a review of insomnia-focused websites at the time of development. In some areas, content between the PE and SHUTi web programs overlap; however, SHUTi differs from the PE website in important ways. In contrast to SHUTi, the PE website (1) does not personalize or individually tailor treatment recommendations based on user input; (2) presents content in a simple, static form, without interactive assessments; and (3) delivers content all at once, meaning the user can access full site content immediately, rather than having to wait for content to be metered, or unlocked, over time. The participant will have 9 weeks to review the patient education website and at week 10 will be asked to complete post-assessment questionnaires/sleep diaries and complete the remote evaluation for post intervention assessments.

5.0 REQUIRED EVALUATIONS, TESTS, AND OBSERVATIONS

5.1. Pre-Study Evaluations

A recruitment mailing will be sent intermittently by the CCSS team to determine interest in the study. Screening questions must be completed online via DatStat to determine study eligibility.

5.2. Evaluations During Study

There are 3 assessment time points during the study: baseline (pre-intervention), post-intervention, and 6-month follow-up. At each time point, participants will complete a remote cognitive evaluation, give a blood sample using the dried

blood spot (DBS) method, wear a WHOOP wrist monitor for 7 to 11 consecutive days. Participants in the study will be asked to complete questionnaires and sleep diaries at each of these time points. All assessments will be completed remotely and study materials (DBS kits, WHOOP wrist monitors, instruction guide, charging cables) will be mailed to the participant. Prior to mailing the equipment to the study participant, all equipment will be sanitized with a product from the list of Approved Disinfectants & Cleaners available on the COVID-19 Disinfectant Guide. The appropriate contact time specific to the disinfectant will be used. We plan to use PDI Sani-Cloth® with a contact time of 2 minute but if unavailable only approved disinfectants and cleaners from the list provided by St. Jude will be used. The sanitized equipment will be packed by a study team member wearing a mask and gloves. Packages will be sent via non-contact drop-off. These measures will minimize exposure to other team members and ensure social-distancing guidelines are met for study staff. Upon return, the package with the equipment will sit for 24 hours before being opened. The study team member will wear gloves and a mask when unpacking the box. All equipment will be sanitized upon return using a product from the list of Approved Disinfectants & Cleaners available on the COVID-19 Disinfectant Guide. The appropriate contact time specific to the disinfectant will be used.

REQUIRED EVALUATIONS & OBSERVATIONS

Study Procedure	Time Point		
	Baseline	Post-Intervention	6 Month Follow-Up
Dried Blood Spot collection (DBS)	X	X	X
CNS Vital Signs remote cognitive assessment	X	X	X
Insomnia Severity Index (ISI)	X	X	X
Drug Abuse Screen Test (DAST-10)	X		
Alcohol Use Disorders Identification Test (AUDIT)	X		
FACIT-Fatigue Questionnaire	X	X	X
Epworth Sleepiness Scale (ESS)	X	X	X
Childhood Cancer Neurocognitive Questionnaire (CCSS-NCQ)	X	X	X
Patient Health Questionnaire (PHQ-9)	X	X	X
Generalized Anxiety Disorder (GAD-7)	X	X	X
WHOOP wrist monitor	X	X	X
Health-related Quality of Life Questionnaire	X	X	X
PROMIS Global Health	X	X	X

Sleep Diary	X	X	X
Work Productivity and Activity Impairment Questionnaire (WPAI)	X	X	X
Work and Social Adjustment Scale (WSAS)	X	X	X

6.0 CRITERIA FOR REMOVAL FROM PROTOCOL

6.1. Off Study Criteria

6.1.1. All protocol interventions are complete
6.1.2. Death
6.1.3. Lost to follow-up
6.1.4. Request of the Patient/Parent
6.1.5. Discretion of the Study PI, such as the following

- The researcher decides that continuing in the study would be harmful
- The participant misses so many appointments that the data cannot be used in the study
- The participant's condition gets worse
- New information is learned that the study is not in the participant's best interest

7.0 SAFETY AND ADVERSE EVENT REPORTING REQUIREMENTS

7.1. Reporting Adverse Experiences and Deaths to St. Jude IRB

7.1.1. Only "unanticipated problems involving risks to participants or others" referred to hereafter as "unanticipated problems" are required to be reported to the St. Jude IRB promptly, but in no event later than 10 working days after the investigator first learns of the unanticipated problem. Regardless of whether the event is internal or external (for example, an IND safety report by the sponsor pursuant to 21 CFR 312.32), only adverse events that constitute unanticipated problems are reportable to the St. Jude IRB. As further described in the definition of unanticipated problem, this includes any event that in the PI's opinion was:

- Unexpected (in terms of nature, severity, or frequency) given (1) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document, as well as other relevant information

available about the research; (2) the observed rate of occurrence (compared to a credible baseline for comparison); and (3) the characteristics of the subject population being studied; and

- Related or possibly related to participation in the research; and

- Serious; or if not serious suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Unrelated, expected deaths do not require reporting to the IRB. Though death is "serious", the event must meet the other two requirements of "related or possibly related" and "unexpected/unanticipated" to be considered reportable.

Deaths meeting reporting requirements are to be reported immediately to the St. Jude IRB, but in no event later than 48 hours after the investigator first learns of the death.

7.1.2. The following definitions apply with respect to reporting adverse experiences:

7.1.2.1. **Serious Adverse Event**: Any adverse event temporally associated with the subject's participation in research that meets any of the following criteria:

- results in death;
- is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; or
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition (examples of such events include: any substantial disruption of the ability to conduct normal life functions, allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse), a congenital anomaly/birth defect, secondary or concurrent cancer, medication overdose, or is any medical

event which requires treatment to prevent any of the medical outcomes previously listed.

7.1.2.2. Unexpected Adverse Event:

- Any adverse event for which the specificity or severity is not consistent with the protocol-related documents, including the applicable investigator brochure, IRB approved consent form, Investigational New Drug (IND) or Investigational Device Exemption (IDE) application, or other relevant sources of information, such as product labeling and package inserts; or if it does appear in such documents, an event in which the specificity, severity or duration is not consistent with the risk information included therein; or

- The observed rate of occurrence is a clinically significant increase in the expected rate (based on a credible baseline rate for comparison); or

- The occurrence is not consistent with the expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

7.1.2.3. **Internal Events**: Events experienced by a research participant enrolled at a site under the jurisdiction of St. Jude IRB for either multicenter or single-center research projects.

7.1.2.4. **External Events:** Events experienced by participants enrolled at a site external to the jurisdiction of the St. Jude Institutional Review Board (IRB) or in a study for which St. Jude is not the coordinating center or the IRB of record.

7.1.2.5. **Unanticipated Problem Involving Risks to Subjects or Others:** An unanticipated problem involving risks to subjects or others is an event which was not expected to occur and which increases the degree of risk posed to research participants. Such events, in general, meet all of the following criteria:

- unexpected;
- related or possibly related to participation in the research; and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized. An unanticipated problem involving risk to subjects or others may exist even when actual harm does not occur to any participant.

7.1.3. Consistent with FDA and OHRP guidance on reporting unanticipated problems and adverse events to IRBs, the St. Jude IRB does not require the submission of external events, for example IND safety reports, nor is a summary of such events/reports required; however, if an event giving rise to an IND safety or other external event report constitutes an "unanticipated problem involving risks to subjects or others" it must be reported in accordance with this policy. In general, to be reportable external events need to have implications for the conduct of the study (for example, requiring a significant and usually safety-related change in the protocol and/or informed consent form).

7.1.4. Although some adverse events will qualify as unanticipated problems involving risks to subjects or others, some will not; and there may be other unanticipated problems that go beyond the definitions of serious and/or unexpected adverse events. Examples of unanticipated problems involving risks to subjects or others include:

- Improperly staging a participant's tumor resulting in the participant being assigned to an incorrect arm of the research study;
- The theft of a research computer containing confidential subject information (breach of confidentiality); and
- The contamination of a study drug. Unanticipated problems generally will warrant consideration of substantive changes in the research protocol or informed consent process/document or other corrective actions in order to protect the safety, welfare, or rights of subjects or others.

8.0 DATA COLLECTION, STUDY MONITORING, AND CONFIDENTIALITY

8.1. Data Collection

Data collection will be accomplished using online data collection tools DatStat Connect, WHOOP Platform, CNS Vital Signs and RICE. DatStat Connect has been utilized by the CCSS for consenting and online data collection. The RICE Platform includes capabilities for contacting participants, providing access to instructional and demonstration videos, collecting data and secure transmission of data to the study team. The RICE Platform allows for input constraints in the tools as well as real-time validation of data formats and ranges, providing real-time feedback to the user if "out-of-range" values are recorded. WHOOP Platform is a secure cloud-based platform hosted by WHOOP that will be used by participants to transmit heart rate data and activity/sleep data using an app on their smart phone or tablet, to the WHOOP cloud. CNS Vital Signs platform will be used to collect data for the remote cognitive assessments. Data will be downloaded and saved in a secure database. To protect the confidentiality of the participants, only participant ID and year of birth will be used and no PHI will be sent to the CNS Vital Signs for the remote cognitive assessment.

8.2. Study Monitoring

Lowest Risk:
This study is considered lowest risk for monitoring purposes. The Principal Investigator (PI) and study team are responsible for ensuring protocol and regulatory compliance. The St. Jude monitoring group will not monitor this study. The study team is responsible for data quality and will meet as needed to review case histories or quality summaries on participants and will generate minutes which are signed by the PI.

Protocol continuing reviews by the Institutional Review Board (IRB) and Scientific Review Committee (CT-SRC) will occur at least annually. In addition, Unanticipated Problems and/or Serious Adverse Event reports are reviewed by the IRB.

8.3. Confidentiality

Study numbers will be used in place of an identifier such as a medical record number. No research participant names will be included in the final data set. The list containing the study number and participant name will be included in a secure database only accessible to the St. Jude study team.

The medical records of study participants may be reviewed by the St. Jude IRB, FDA, clinical research monitors, etc.

9.0 STATISTICAL CONSIDERATIONS

Anticipated Primary Completion Date: January 1, 2022
Anticipated Study Completion Date: July 1, 2023

9.1. Summary of Primary and Secondary Objectives

Statistical Analysis
A randomized controlled design will be employed for the proposed study. We plan to enroll a total of 352 survivors (176 of each sex), and assuming 10% drop out by the post-intervention 9-week assessment, we will have a total of 320 survivors (160 of each sex) remaining for evaluation. Balance of patient characteristics between study arms will be evaluated and if necessary, adjusted comparisons will be carried out.

The primary endpoint of the study will be the ISI measure of insomnia severity represented as described above. The difference in score from baseline to post-intervention (10 weeks) and baseline to 6 months post-intervention will be calculated and the mean of these differences compared between study arms using linear regression (adjusted for stratification factors). The primary time point of interest will be at 10 weeks, with a secondary endpoint evaluating maintenance at 6 months after intervention. Due to potential sex differences in insomnia and cognition, *a priori* we plan to carry out all analyses and report results separately by sex. Our study is not powered to detect meaningful interaction effects, but if we deem that the effects are reasonably comparable between sexes we will consider presenting combined analysis to increase precision of the estimate. Because this is a randomized trial we expect analyses to be simple and directed towards ascertaining controlled and generalizable intervention effects. The primary endpoint will be considered significant at the two-sided 0.05 level. Estimates of intervention effects (mean differences) will be presented along with associated confidence intervals and two-sided p-values.

Because mean scores do not reflect the number of survivors who have clinically significant insomnia symptoms, secondary analyses of sleep will compare the proportion of survivors who no longer meet the clinical criteria for insomnia (ISI ≤ 7) between study arms post-intervention (10 weeks) and at 6 months (noting that 100% of eligible participants will meet the criteria at randomization), using logistic regression models. Additional measures of sleep will also be summarized and compared (sleep diary, actigraphy, fatigue, daytime sleepiness) from baseline, post-intervention, and 6 months. Using the same analytic framework as above, we will evaluate the effect of study intervention on the secondary endpoints of neurocognitive impairment: patient reported (Task Efficiency, Memory, Emotional Regulation) and directly assessed (attention, memory, and executive function) with continuous outcome measures. Additional analyses relevant to secondary objectives focus on better understanding the associations and mediating relationships between the CBTi intervention, insomnia, neurocognition, emotional distress, cardiovascular risk indices and HRQoL (see Figure 2 for theoretical framework). We will evaluate

direct relationships between change in ISI (baseline to post-intervention) with emotional distress and cardiac health indices at postintervention time points and with HRQoL measures. To establish whether a mediation relationship exists, we will follow standard methodology[68-70] by 1) establishing that there is an association between the causal variable (e.g. CBTi intervention) and the outcome (e.g. neurocognitive impairment), 2) establishing the association between the causal variable and the mediator and 3) showing that the mediator is associated with the outcome variable in a model with the causal variable included and 4) in the same model as used to evaluate step 3, determine that the relationship between the causal variable and the outcome variable is attenuated by inclusion of the mediator in the model. We do not expect to observe complete mediation in any of our investigations. Specifically, the above methodology will be used to test hypothesis 1.2.2.b with the causal variable defined as CBTi intervention, mediator as change in insomnia (ISI) and outcomes as neurocognitive indices. Hypothesis 1.2.2.c will consider change in insomnia as the causal variable, neurocognitive function indices, emotional distress symptoms and cardiovascular risk indices as mediators for the outcome HRQoL at 6 months. In addition to the stepwise model-based approach outlined above, we will also evaluate relationships using Structural Equation Modelling (SEM) approaches to evaluating mediation, which would allow simultaneous evaluation of the multiple pathways and classes of variables together in a single model, with improved power, allowing estimates of direct and indirect effects calculated from each.[71, 72] All effects size estimates (mean differences and/or odds ratios) will be presented along with associated confidence intervals and two-sided p-values, both unadjusted and adjusted for multiple comparisons. Primary therapies for childhood cancer have been associated with insomnia and study outcomes (neurocognitive morbidities, emotional distress, cardiovascular risk). Because our study inclusion criteria require that survivors have observed neurocognitive deficits we do not expect differential responses to SHUTi by previous childhood cancer treatment exposures. However, chemotherapy exposures and radiation doses are abstracted from medical records and cumulative doses of methotrexate (high dose and intrathecal), cytarabine, and cranial radiation will be included as covariates in relevant analyses. In addition, we will conduct sensitivity analyses to examine their contributions to treatment response.

We have planned for 20% attrition over the course of the 6-month study. However, if there is a substantial amount of missing data at 9 weeks or 6 months we will examine the characteristics of survivors who have complete data with those who do not. Depending upon the pattern of missing data, we will conduct sensitivity analyses to assess the impact of missing data on the results. We will consider factors such as demographic and treatment variables as well as premorbid baseline functioning in our sensitivity analyses.

Power and sample size

We plan to enroll a total of 352 subjects, 176 of each sex), and assuming 10% drop out by the post-intervention 9-week assessment, we will have a total of 320 subjects (160 of each sex) remaining for evaluation. Therefore, within each sex

stratum, with 80 survivors per study arm, 80% power and α of 0.05 for the primary endpoint comparison of the ISI, we will be able to detect a minimum effect size of 0.45. We will continue to enroll participants until we have 320 evaluable at 9 weeks. Assuming a total dropout of 20% by 6 months post-intervention, there will be approximately 70 survivors within each sex per study arm available for assessment, allowing detection of a 0.48 minimum effect size. If sex specific intervention effect estimates are comparable with each other, a combined analysis among the 320 survivors evaluable at 10 weeks will be sufficient to detect an effect size of 0.31, with 80% power and two-sided α of 0.05. Secondary endpoints of neurocognition will have ability to detect the same effect sizes; secondary endpoint p-values will be presented using both a nominal significance level of 0.05 and adjustments for multiple comparisons using a false discovery rate methodology.[73]

10.0 OBTAINING INFORMED CONSENT

10.1. Informed Consent Prior to Research Interventions

CCSS participants are recruited via email, telephone, and mail. Recruitment materials for this study will be included in the initial mailing and follow-up recruitment emails sent. Interested participants will be sent an email that contains a link to the study website. Participants will be presented with informed consent and will have the opportunity to provide an affirmative indication to enroll in the study. In addition to the on-line option to consent to participate in this study, participants will also have the opportunity to provide verbal consent while speaking with a representative from the CCSS Call Center.

11.0 REFERENCES

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APPENDICES

APPENDIX I: Schedule of Evaluations

Study Procedure	Time Point		
	Baseline	Post-Intervention	6 Month Follow-Up
Dried Blood Spot (DBS) Collection	X	X	X
Remote cognitive Assessment CNS Vital Signs	X	X	X
Drug Abuse Screen Test (DAST-10)	X		
Alcohol Use Disorders Identification Test (AUDIT)	X		
Insomnia Severity Index (ISI)	X	X	X
FACIT-Fatigue Questionnaire	X	X	X
Epworth Sleepiness Scale (ESS)	X	X	X
Childhood Cancer Neurocognitive Questionnaire (CCSS-NCQ)	X	X	X
Patient Health Questionnaire (PHQ-9)	X	X	X
Sleep Diary	X	X	X
WHOOP wrist monitor	X	X	X
Health-related Quality of Life Questionnaire	X	X	X
PROMIS Global Health	X	X	X
Work Productivity and Activity Impairment Questionnaire (WPAI)	X	X	X
Work and Social Adjustment Scale (WSAS)	X	X	X