Sleep Treatment Education Program (STEP-1): An Online Educational Intervention for Insomnia in Cancer Survivors

Protocol and Analysis Plan

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1.0 INTRODUCTION

1.1 Background

Intensive treatments that improve cancer outcomes also place survivors at high risk for the development of medical and psychosocial late-effects.[1-5] While insomnia might initially be considered a minor symptom in the larger cancer context, it frequently develops into a debilitating chronic condition; an estimated 1 in 4 cancer survivors experience clinically significant insomnia even 10 years after cancer treatment.[6,7] Untreated insomnia is associated with significant health problems, including heart disease, obesity, hypertension, diabetes, depression, and anxiety.[4,8-16] Because of their cancer treatments, survivors are already vulnerable to many of these same health conditions, making access to effective treatment for insomnia critically important to maintaining their health.

Cognitive-behavioral therapy for insomnia (CBTI) is a well-established and empirically supported treatment for insomnia. Multiple randomized trials have demonstrated it is the most effective long-term insomnia treatment, even compared to pharmacotherapy.[17-19] A systematic review of CBTI with cancer survivors similarly concluded it "provides significant, lasting improvement in [their] sleep."[20] Unfortunately, despite compelling evidence, this empirically validated treatment is largely unavailable to the growing population of cancer survivors who need it.[21] Even among the most well-resourced cancer centers in the country, fewer than one-third provide CBTI for patients or survivors.[22] To make effective insomnia treatment available to survivors, existing barriers must be resolved, including; 1) the shortage of trained CBTI providers; >60% of the largest US cities having none;[23,24] 2) the need for more efficient treatments than standard ≥ 6 session individual CBTI;[25] and 3) the need to develop less burdensome treatments than standard CBTI, which has a drop-out rate of 20-40%.[26] Moreover, as the ongoing COVID-19 pandemic presents considerable health risk for cancer survivors,[27] it is imperative that health interventions be delivered to them in ways that minimize their risk of exposure. To address these challenges and deliver the promise of effective insomnia treatment to cancer survivors, we have developed the Sleep Treatment Education Program-1 (STEP-1), a self-management CBTI intervention which can be delivered as a single-session online educational intervention.

While many survivors with chronic insomnia may require intensive CBT-insomnia treatment, a significant number may be helped by less intensive therapies. A recent study by Dr. Recklitis (DFCI protocol 15-336), showed a sizeable minority of participants benefited from a brief single session educational intervention on sleep hygiene.[28] The STEP-1 intervention was created by expanding this existing educational session to include: 1) all core CBTI components, 2) answers to survivors' frequently asked questions about sleep and CBTI, and 3) a written sleep action plan to promote adherence.

STEP-1 has been delivered as an educational program through the Blum Center at DFCI. Based on feedback showing STEP-1 significantly reduces survivors' insomnia, we now plan to test STEP-1 in a randomized controlled trial (RCT) of 70 cancer survivors evaluating efficacy of an online STEP-1 intervention compared to a control condition.

1.2 Overview

This study will test STEP-1 in an RCT of 70 off-treatment cancer survivors. Participants will be assigned (1:1) to receive either the STEP-1 intervention or an enhanced usual care condition (relaxation training). Intervention sessions for both the STEP-1 and control groups will be delivered online using the Zoom platform, which is currently in use at DFCI for virtual patient visits and education programs. Participants will complete measures of insomnia and mood at baseline and again at 4 and 8 weeks post-intervention.

2.0 AIMS

1. To determine efficacy of the online STEP-1 intervention compared to a control condition.
2. Determine efficacy of the STEP-1 intervention to improve mood symptoms in survivors compared to control condition.

Secondary aims will be to: i) explore participant and program adherence factors associated with clinically significant response to STEP-1, ii) evaluate acceptability of the control intervention, iii) explore feasibility of delivering individualized coaching sessions for participants who do not have a significant response to the STEP-1 intervention, and iv) describe participants' satisfaction with STEP-1 and suggestions for improvement.

3.0 PATIENT SELECTION

3.1 Eligibility Criteria

To be determined by patient self-report from eligibility screening with potential participants. (See Appendix A for eligibility screening materials). Participants must be screened for eligibility ≤2 weeks prior to study enrollment. Participants who are screened earlier must be rescreened within this period. ISI scores are valid for 4 weeks, only rescreen with ISI if > 4 weeks since initial screening.

- Age 40-89
- History of a cancer diagnosis (except non-melanoma skin cancer) ≥ 1 year prior
- No active cancer therapy (excluding chemoprevention) in the past four months, and no further therapy planned
- Significant insomnia as evidenced by an Insomnia Severity Index score ≥12
- Regular access to the internet on a daily basis
- Able to read and write in English

3.2 Exclusion Criteria

- Survivors who report ever being diagnosed with Bipolar Disorder.
- Survivors who report ever being diagnosed with a Seizure Disorder or have experienced a seizure in the past 12 months.
- Intention to adjust (decrease or increase) use of any prescribed or over-the-counter medications taken to decrease insomnia during the study period.
- Survivors diagnosed with sleep apnea who have declined treatment or are not adherent with treatment (as assessed by screening questions, see Appendix A).
- Survivors with suspected sleep apnea who have not completed an evaluation by a sleep specialist (as assessed by screening questions, see Appendix A).
- Usual bedtime does not fall between 5:00 pm and 5:00 am.

- Employment that involves irregular sleep patterns, such as shift-work or frequent long-distance travel across time zones, or employment in a position that could impact public safety (such as air traffic-controller, operating heavy machinery)
- Any impairment (e.g., hearing, visual, cognitive) that interferes with the ability to complete all study procedures independently.
- Prior participation in a research study which provided an educational or behavioral intervention for insomnia
- Prior participation in a behavioral treatment or patient education program for insomnia delivered at the Dana-Farber Cancer Institute
- Participation in behavioral or educational interventions for insomnia in the 2 years prior to enrollment. This includes in-person as well as synchronous and asynchronous online insomnia programs, but not independent use of books, workbooks or other written self-help materials addressing insomnia.

4.0 RECRUITMENT

This study will follow procedures currently in place for other survivorship interventions at DFCI (17-515, 17-402) in order to identify potentially eligible survivors for recruitment purposes. These procedures have been developed in consultation with the disease centers and have proven to be effective and non-burdensome for clinicians and patients, while ensuring that only survivors appropriate for recruitment are approached. Study investigators will collaborate with clinicians in the clinics at Dana-Farber Cancer Institute in order to identify and recruit eligible survivors followed in these clinics. Recruitment materials and a study information sheet can be found in Appendix A. After getting permission to approach the subject from their oncology/survivorship provider, subjects will be approached, screened for eligibility, and recruited by a member of the study staff. While this could occur in person at scheduled clinic visit, as many survivorship visits are currently conducted as telehealth visits, it is anticipated that most survivors will be contacted by telephone, videoconference, email, or mail. These potential participants will receive the Study Information Sheet by email or mail. Templates for all of these recruitment methods can be found in Appendix A.

Eligible survivors will also be identified from Project REACH (DFCI #07-134), a cohort study of survivors followed at DFCI. Project REACH participants complete annual surveys of physical and emotional health and have consented to these surveys being used to determine eligibility for other survivorship studies. Potential subjects may also be referred by a Dana-Farber clinician or self-refer to the study. Additionally, study investigators will collaborate with survivorship education and support programs both affiliated with DFCI, and those in the community in order to recruit directly from these sources. Additionally, as social media has been found to be a highly successful recruitment tool in other studies of cancer survivors, we will utilize popular social media (e.g. Reddit, Facebook, Twitter, IG) to reach interested survivors. A brief advertisement (suitable for use in patient newsletters, advocacy group newsletters or websites), and a sample social media post can be found in Appendix A. A study website (STEPforSleep.com) will contain IRB-approved information about the study including contact information for the study team, the study information sheet, a link to the study on Clinical Trials.gov, and the video advertisement (see Appendix A). The study will also have a Facebook page, as well as Instagram and Twitter accounts which will direct potential subjects to the study web site. To promote the study to potentially interested cancer survivors, study staff will periodically post on these sites (see Appendix A for sample posts).

To identify eligible participants at DFCI, we will work directly with the administrative and clinical staff in participating clinics and programs, and we will also use administrative data sources including EPIC, OncDRS, and CORIS. We are requesting a Waiver of Authorization to identify eligible participants. Subjects will be screened in person, by telephone, or videoconference using the eligibility screen, including the ISI scale (see Appendix A).

Eligible subjects who wish to schedule a study session but are unfamiliar with Zoom or other technology aspects of this online study will be offered brief (<15 minute) technology guidance with a member of the study team prior to their intervention session. This will typically be done at the end of the eligibility screening, but could be scheduled for a different time if more convenient for the subject. This guidance will familiarize them with opening and navigating the Zoom and Qualtrics platforms.

5.0 STUDY DESIGN AND METHODS

5.1 Study Design

This study is a randomized controlled trial of 70 cancer survivors with clinically significant symptoms of insomnia, randomized to either the STEP-1 intervention group or an enhanced usual care control group. Participants will take part in a single intervention session, during which they will complete baseline measures prior to randomization and then receive their assigned intervention. Participants will complete follow-up measures 4 and 8 weeks post-intervention.

5.2 Methods

S*ee section 5.5 for descriptions of all study measures. Copies of the assessments can be found in Appendix B, and participant correspondence in Appendix C.*

Informed Consent: We are requesting a Waiver of Documentation of Informed Consent for this study, as it is a minimal risk study involving no procedures (questionnaires and educational session) for which signed consent is generally required outside of the research context. The intervention sessions in this study are similar to educational sessions currently conducted through the Blum Center at DFCI, and for which no signed consent is required. A similar online intervention currently being conducted by Dr. Recklitis (17-515) was granted a waiver of documentation of consent, and we propose to utilize those approved consent procedures for this study. Potential participants will be provided with a study information sheet which contains all the elements of informed consent (See Appendix A), and will have a consent conversation with a member of the study staff in which they can ask questions about the study or study procedures before providing verbal consent. As it is anticipated that many survivors will not have in person clinic visits at DFCI for the foreseeable future, it is expected that most of these consent versions will take place by telephone or videoconference, although they could be in person if requested.

Intervention session: After expressing interest in participating, participants will be scheduled for an individual videoconference intervention session. The intervention session consists of the following components:

1) Informed Consent: Study staff will review the study procedures and the Study Information Sheet with the participant and answer any questions they may have. They will then obtain verbal consent. (Verbal consent procedures can be found in Appendix A)

2) Baseline measures: Study staff guide participants in completing baseline measures including insomnia and mood using the Qualtrics web-based survey platform.[29] The participant will also schedule their 4-week follow-up phone appointment with study staff at this time. Additionally, participants will be asked to provider preferences for all future contact and correspondence (i.e., phone, email, send secure, text, mail) and these preferences and addresses/phone numbers will be recorded in the participant's record.

3) Randomization: Once baseline measures are completed, randomization will be performed using Sealed Envelope, a commercially available online software application for randomising patients into clinical trials. Participants will be randomized (1:1) to either: **1)** STEP-1, or **2)** an enhanced usual care control condition. No identifiable information or PHI is entered into Sealed Envelope; particpants are identified only by a study team generated ID number.

4) Intervention Delivery. Once randomized, the participant will immediately receive their assigned intervention session via videoconference. (See sections 5.3 and 5.4 for descriptions of the interventions).

5) Session evaluation: Participants will receive a link to a questionnaire on which they will report on ease of use and acceptability, satisfaction, and credibility of the session. To promote completion of the questionnaire, participants will be encouraged to complete it while still in the Zoom session, but can choose to complete it at a later time. Participants will receive a $10 gift card upon completion of this evaluation.

Post-intervention Follow-up: At 4 and 8 weeks post-intervention, study staff will recontact participants by telephone at previously scheduled times, ask them to enter follow-up data directly into Qualtrics, and provide technical assistance if needed. Participants who cannot complete the full assessment at that time due to time constraints or logistical barriers will be asked to complete the 7-item ISI (primary outcome measure) verbally and their responses will be collected; they will then be asked to complete the full questionnaire at their earliest convenience. Participants will receive emailed reminders in advance of each phone call. At the 4-week call, participants will schedule a phone call for the next follow-up assessment.

Incentive: Participants will receive a $25 Amazon gift card upon completion of each follow-up assessment.

Optional 8-week-post ISI: At the time of their final follow-up phone call, participants will be asked if they would be willing to complete an additional sleep checklist two months later. Participants who agree will receive a Qualtrics link to the 7-item ISI 8 weeks later by email. This would take approximately 1-2 minutes to complete, and participants will not receive an incentive for this optional checklist. The link would be sent again a week later for non-responders, but participants will receive no additional reminders.

Optional post-study intervention: Once participants have completed their final follow-up questionnaire, they will be offered the chance to participate in the intervention arm to which they were not randomized. This information will be provided in the final "thank-you" correspondence. This opportunity is offered solely for the benefit of the participants, and is not part of the research study.

5.3 STEP-1 Intervention

STEP-1 is delivered in a single 75-minute synchronous videoconference session using password protected and HIPAA compliant ZOOM technology[30-32] licensed to our cancer center. The STEP-1 presentation includes presentation slides which include text and graphics. The intervention is delivered in a 1 on 1 session by a trained presenter following a structured outline. During the session, the participant is able to see and hear the presenter, view the presentation slides, and ask questions. To support participants in developing and implementing their sleep action plan, a copy of the presentation slides and sleep action plan template are provided to them by email. The presentation begins with educational information on the problem of insomnia after cancer before presenting specific suggestions for improving sleep. These suggestions are based on CBTI components of sleep hygiene, stimulus control, and cognitive restructuring. To aid comprehension, this material is presented in four sections addressing lifestyle issues, (e.g., benefits of exercise and limiting alcohol), sleep environment (e.g., importance of a dark, quiet bedroom; avoiding bed for non-sleep activities), sleep timing (e.g., regular wake time, avoiding napping) and managing expectations and challenges (e.g., sleep worry and physical symptoms). For each suggestion, an underlying rationale and potential benefit are presented. At the conclusion of each section (e.g., lifestyle), the presenter invites participant's questions. Before moving to the next section, the participant is asked to review the suggestions in the section and complete their sleep action plan using the template provided to record their current sleep

practices and behavioral changes they intend to make. This information is then shared with the presenter using a Zoom poll, while the participant retains their written copy. Action plans of this kind are central to self-management education[33] and have been shown to increase successful behavior change.[34,35] Information about how the COVID-19 pandemic may exacerbate sleep problems and what aspects of STEP-1 can address this has been noted briefly in the introduction and "managing expectations and challenges" sections. At the end of the session, the presenter offers examples of how program suggestions can be implemented in a daily routine and asks the participant to review and revise their sleep action plan, including anticipating challenges and planning strategies to manage them.

5.4 Control Condition (Relaxation)

Control group participants are provided information about how to access relaxation exercises independently during the study period, either through ***"****UCLA Mindful"* a free online app, or on YouTube. they can access.Similar to STEP-1 participants, each control participant will have an individual videoconference presentation including presentation slides delivered by a study team member. The presentation will explain the rationale behind using relaxation to help sleep, types of exercises availiable in the app and on the YouTube resource sheet, and suggest ways participants can explore how to use the exercises to improve sleep. Participants will be given the opportunity to log-on to the app during the session and given information about accessing technical support for the app, and how to access recommended relaxation videos on YouTube. Control participants who do not have a mobile device compatible with the app will be loaned a device for the study period. **Rationale:** The self-help control condition controls for attention and other non-specific factors and addresses ethical and practical problems associated with waitlist or no-treatment controls.[36] Online relaxation programs are widely used and available making it a good, pragmatic choice. Additionally, 90% of Americans use the internet[37] and the internet is very often used by cancer survivors for health information.[38]

5.5 Study Measures

Primary outcome measures were previously used with cancer survivors on DFCI 15-336. Measures can be found in Appendix B. Measures are given at all timepoints unless otherwise noted.

The Insomnia Severity Index (ISI)[39]: The 7-item ISI is the most commonly used measure in insomnia research and has been validated in cancer populations.[40] It has demonstrated adequate internal consistency, and is sensitive to detect changes in perceived sleep difficulties with treatment.

Profile of Mood States – Short Form (POMS-SF)[41]: The Profile of Mood States-Short Form is a commonly used measure of psychological distress that has been validated in cancer populations.[42] It is a 35-item measure which assesses the mood states of participants, and provides multiple scales including an overall Total Mood Disturbance (TMD) score used here.

PROMIS Sleep Disturbance Short-Form (PROMIS-SD)[43]: The 8-item PROMIS-SD will be used to assess sleep disturbances and their impact on overall sleep quality. Items include specific sleep problems (e.g., restless sleep) as well as satisfaction with sleep quality and amount of sleep. This measure is given at baseline and 8-week timepoints only.

The Consensus Sleep Diary-Morning (CSD-M)[44]: 9 items from the CSD-M will be used to assess daily sleep quality and sleep latency. Items include time of attempts to fall asleep, number and duration of awakenings, time of final awakening, final rise time, and perceived sleep quality. This measure is given at the 8-week timepoint only.

Physical Health: Physical health will be assessed with one item from the commonly-used SF-12[45] asking respondents to rate their overall health. Pain will be measured with the commonly used Pain Thermometer[46] on which participants rate their pain on a scale of 1-10, and a single item asking participants to rate whether they feel "in pain" on a five-point scale.

Sleep Treatment Change: Participants will be asked to report any changes made in sleep behaviors during the study period. This includes changes suggested or recommended in their educational session as well as those not specifically recommended by the study interventions (e.g., new sleep medications, new non-study meditation class). Control condition participants will report on their use of the control resources. This measure is only completed at post-intervention timepoints.

Demographics and Medical History: Demographic information, medical information (e.g., cancer diagnosis and treatment, recent psychiatric treatment), and insomnia history (e.g., insomnia duration, burden, past treatments) will be collected by direct patient report as well as

medical record review. This measure is only given at baseline.

Intervention Evaluations: Participants will complete evaluations at several timepoints. 1) At the end of the intervention session, participants will report on ease of use and acceptability using checklist items adapted from the Telehealth Usability Questionnaire,[47] and satisfaction will be assessed with checklist items adapted from Dr. Recklitis's previous survivorship education trials. Intervention credibility will be assessed by participant report on the six-item Credibility/Expectancy questionnaire.[48] 2) All participants will complete a brief questionnaire to provide their feedback about the intervention and how it could be improved at the 8-week post-intervention timepoint. 3) Participants who receive to the coaching sessions will complete a brief satisfaction evaluation of the coaching sessions after the second coaching phone call.

Steps to insure complete data: Participants will complete baseline measures online using Qualtrics at the intervention session prior to randomization to insure completeness. Following procedures found to be effective in Dr. Recklitis's DFCI protocols 17-515, 15-336 and 14-583, the study also makes use of scheduled telephone appointments to insure timely completion of the follow-up assessments. In previous intervention studies, telephone appointments have been highly effective for encouraging survivors to complete assessments; we have achieved 100% complete data for primary endpoints and 95% complete data overall using this method.

5.6 Exploring Feasibility of Individualized Coaching (post-RCT)

Participants randomized to the STEP-1 condition who did not have a ≥ 6-point decrease in their ISI score[49] at 8-week follow-up data will continue on the study and receive 2 individualized coaching sessions to explore feasibility of delivering individualized coaching sessions to them (secondary aim iii). (Participants randomized to the STEP-1 condition who **did** have a ≥ 6-point decrease in their ISI score continue on the study until the final sleep checklist measure is collected as described below, and participants assigned to the control condition end participation after week 8 data are collected). Optimal timing for the first coaching session is within 7 days after the 8-week follow-up, and the second session should be 7 days after the first. However they may be scheduled any time within 23 days after the 8-week follow-up with at least 5 days between coaching sessions. Paraprofessional coaches trained and supervised by psychologists with CBTI expertise will deliver the coaching sessions remotely by following a structured outline adapted from Dr. Recklitis's insomnia study for young adult cancer survivors (DFCI 21-

613). During 30-minute sessions, participants will review progress and challenges in following their sleep action plan. Coaches will offer support and encouragement and may refer participants to the on-hand materials to help answer questions and reinforce program goals and suggestions. Following principles of self-care management,[50-54] coaching sessions are not prescriptive, but promote survivors' self-management skills (e.g., goal-setting, problem solving) to implement their sleep action plan. At the end of the 4-week period, participants complete a questionnaire assessing acceptability and satisfaction with the coaching sessions, and will complete the ISI and Sleep Change measure. Participants will receive a $25 gift card upon completion of this questionnaire. Administrative data on coaching session duration, and sessions missed, interrupted, or rescheduled will be collected.

5.7 OnCore Registration

As per DF/HCC SOP REGIST-101A, with the approval of the Director of the Office of Data Quality, retrospective registration will be utilized for this minimal risk study.

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore as required by DF/HCC SOP REGIST-101. When required by REGIST-101, registration must occur prior to the initiation of protocol-specific procedures or assessments.

Registration requires a signed informed consent document and a completed eligibility checklist according to DF/HCC SOP REGIST-104.

Specific procedure for registering a participant in OnCore for a minimal risk study with a waiver of documentation of informed consent:

When registering a participant on OnCore, under consent form tab the "Consent for Research (1)" choose "Study Brochure," confirming that the participant has received the approved study brochure with the elements of informed consent and has verbally consented to the study.

6.0 RISKS AND ADVERSE REACTIONS AND THEIR MANAGEMENT

Potential for some participants to experience increased daytime fatigue from the study intervention

The primary risk of this minimal risk study for participants randomized to the STEP-1 intervention is a brief (1-2 week) period of daytime fatigue, which is the result of sleep scheduling (i.e., reducing daytime sleep). Consequently, participants may experience some physical and mental side effects associated with sleepiness. However, these side effects should be similar to the effects of sleepiness they have previously experienced due to their insomnia. In order to address and mitigate this risk, the STEP-1 intervention provides information about anticipating and planning management strategies to cope with increased symptoms of fatigue that may occur. In particular, instructions will be provided to maintain personal safety by avoiding driving at times when participants are likely to become sleepy, and taking appropriate steps if they become sleepy while driving. Specifically, participants are instructed that they should immediately pull over to a safe area, stop driving and sleep if they become fatigued while driving. Additionally, participants will be provided with the contact information of the PI, Dr. Christopher Recklitis, a licensed psychologist with extensive clinical experience with cancer survivors and insomnia treatment. Participants who have any concerns about the study are encouraged to contact him for assistance.

Potential for some participants to be disappointed with being randomized to a particular intervention

In recognition of the fact that some participants may be disappointed in the arm of the study to which they are randomized, after completing the final assessment, all participants will be offered access to the intervention they did not receive as part of the study.

Privacy and Confidentiality

We have taken steps to protect the privacy of participants during all aspects of intervention delivery and data collection.

The Zoom videoconferencing technology which will be used to conduct eligibility screening conversations and deliver the online intervention is fully HIPAA compliant. The platform is licensed to our cancer center, and is currently used for telehealth visits, research visits, educational webinars, and study meetings. As of June 2020, Zoom is encrypted using AES 256-bit GCM encryption standard, the strongest and most robust encryption standard that is currently commercially available. For additional security, our institution has locked the password function so that passwords are required for all Zoom meetings. A new individual password is created for

each session, which is then embedded into the link sent to the participant. This enables the participant to access the session securely without having to enter a password, while ensuring that only the participant has access to the meeting. Once the participant enters the meeting, the meeting will be locked which provides further protection against any other person entering the meeting either accidentally or intentionally.

The Qualtrics web-based survey platform that will be used to collect study data remotely has been used successfully by Dr. Recklitis for other online intervention studies. Qualtrics is the leading global provider of data collection and analysis for academic research, serving over 5,000 customers in 75 countries. The Qualtrics platform can deliver web and mobile surveys, embed videos in a larger survey, send email and mobile reminders, and automate the data collection procedures. Qualtrics provides secure collection of survey data using encrypted data transfer and complies with HIPAA protections for privacy of patient information. In our application for this study, the Qualtrics program will identify participants only by study ID, and will contain no identifiers. Participants will access the Qualtrics platform through a unique link connected only to their study ID, and email addresses will not be stored in Qualtrics, so that no protected health information is stored on the Qualtrics platform.

We will use standard IRB-approved and HIPAA compliant measures to maintain patient confidentiality, privacy and data security. Data privacy and security procedures will include: a) training staff on data sensitivity and protocols for safeguarding confidentiality; b) storing and processing sensitive hardcopy in a secured, centralized location; c) securing sensitive hardcopy in locked files when not in use; d) removing names, addresses, and other direct identifiers from hardcopy and computer readable data after they are not necessary for patient tracking and then using encrypted codes for subsequent identification of subjects; e) destroying all identifiable linkages to data after data accuracy has been verified and final analyses have been completed; f) using restricted logon identification and password protection computer protocols for all computerized entry, retrieval, and analysis.

7.0 STATISTICAL ANALYSIS

Primary Aim: *Evaluate the efficacy of the online STEP-1 intervention to improve insomnia and mood symptoms in cancer survivors.*

This is a randomized 2-arm trial comparing the STEP-1 intervention to an enhanced usual care control condition. Immediately after completing baseline assessment subjects will be randomized (1:1 by the Sealed Envelope platform) to the Experimental group which will receive the STEP-1 intervention, or the Control group which will receive the relaxation based intervention. Randomization, with block size of 4, will be stratified by age category (40-64 years vs. 65-89 years). Primary endpoint is change in Insomnia Severity Index score from baseline to 8-weeks post-intervention. Secondary endpoint is change in mood symptoms on the Profile of Mood States-Short Form at 8-weeks. Changes in Total Sleep Time and Sleep Efficiency (calculated from the CSD-M), and Total Sleep Disturbance score from the PROMIS-SD will also be evaluated Data analysis for these variables will follow methods used for our recently completed clinical trial of in-person insomnia interventions delivered to cancer survivors (R03CA201459). Change scores will be treated as continuous variables and primary analyses will compare the arms using 2-way analysis of variance with one between-subjects factor (STEP-1 vs. Control) and one within-subjects factor (time). Cohen's d will be used to quantify within-group effect sizes and Hedges' g adjustment will estimate between-group effect sizes. Primary and secondary endpoints are change at 8 weeks; data collected at 4-week post-assessment timepoints will be analyzed using similar methods.

Sample Size/Power: To meet our aims we require 60 participants with evaluable data, but will enroll 70 as a hedge against attrition. As is common for most CBTI interventions, STEP-1 has demonstrated large effects of $d \geq 1.00$ in our pilot testing). Using this effect size as a reference, the study is conservatively powered to detect an effect size of 0.6 (Primary Aim). With sample size of 60 (30 per arm) the study will have 90% power to detect an effect of this size (two-sided test with a =.05). Even in the highly unlikely event that the sample size is reduced to 50 (25 per arm), the study will retain >80% power to detect an effect of this size.

Missing Data: Participants will be randomized after completing a baseline so complete baseline data are assured. Primary analysis will be an intent-to-treat analysis of randomized subjects. Based on experience using similar data collection methods (Clinical Trials document 2.5), we anticipate minimal missing data (<10%). If needed, we will use multiple imputation to account for missing data. Potential factors in the imputation model include baseline sleep and mood variables. Sensitivity analysis will impute missing change scores with values sampled from an estimated distribution of change scores from the control group participants.

Secondary Aims:

i) Explore participant and program adherence factors associated with clinically significant response to STEP-1. Logistic regression will be used to identify participant demographic and sleep factors (e.g., age, severity of insomnia symptoms) associated with a reduction of ISI scores ≥ 6 points. Variables identified in univariate analysis ($p<.10$) will be entered in a multivariable model estimating STEP-1 response from baseline variables. This analytic approach will also be used to explore how patient adherence factors (e.g., adherence to specific program strategies, number of strategies employed, consistency of adherence) are associated with a reduction of ISI scores ≥ 6 points. Depending on results of these exploratory logistic regression analyses, mediation and moderation analyses can be applied to determine how demographic and sleep variables may themselves be associated with patient adherence factors and clinically significant response to STEP-1 (i.e., reduction of ISI scores ≥ 6 points).

ii) Evaluate feasibility and acceptability of the control intervention. Descriptive statistics will be used to summarize data on duration of the control intervention sessions, as well as sessions missed, interrupted, or rescheduled. Fidelity information from the adherence checklist used to evaluate audiotapes of the control sessions will also be described using descriptive statistics. Scores on the Telehealth Usability Questionnaire, the Credibility/Expectancy Questionnaire, and a study-specific satisfaction checklist will also be summarized. While the focus will be on describing usability and acceptability of the control intervention, comparisons between the control and STEP-1 sessions on these metrics will also be explored using parametric (e.g., t-test) and non-parametric methods (e.g., chi-square, Mann-Whitney).

iii) Explore feasibility of delivering individualized coaching sessions for participants who do not have a significant response to the STEP-1 intervention. Similar to methods used for secondary aim ii, descriptive statistics will be used to summarize data on duration of the coaching sessions, as well as sessions missed, interrupted, or rescheduled. Fidelity information from the coaches' self-report checklists and the adherence checklist used to evaluate audiotapes coaching sessions will also be summarized and descriptive statistics reported, as will participants questionnaires reporting their perceived acceptability and satisfaction with the coaching sessions.

iv) Describe participants' satisfaction with the STEP-1 program and their suggestions for improving it. Similar to methods used for secondary aims ii & iii, descriptive statistics will be

used to summarize data from the final program satisfaction questionnaire. The measurement properties of the rating scale items will be explored for consistency and reliability (e.g., item-scale correlations, alpha with item deleted) and summarized in a total satisfaction score as appropriate. Closed-ended items asking participants to rate usefulness of STEP-1 program elements will be summarized. To explore how participants' ratings of usefulness may be associated with their treatment response, the difference in these ratings between participants with and without a reduction of ISI scores ≥ 6 points between baseline and week-8 will be explored using non-parametric statistics (e.g., Mann-Whitney). Finally, closed- and open-ended items capturing participants' report of additional program elements that would improve the STEP-1 program will be summarized.

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