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Protocol

Innovating CBT-I for cancer survivors: study protocol for a randomized controlled optimization trial

Emma G. Balkind[1], Kelcie D. Willis[1,2], Caleb Bolden[1,2], Alona Muzikansky[1], Mark J. Gorman[1], Amy H. Comander[1], Dana Haggett[1], Lynne Wagner[3], Joe Kossowsky[2,4], Elyse R. Park[1], Timur Mukhammadov[1], Tolulope Adewumi[1], Daniel L. Hall[1,2]*

[1]Massachusetts General Hospital, Boston, MA, United States
[2]Harvard Medical School, Boston, MA, United States
[3]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC, United States
[4]Boston Children's Hospital, Boston, MA, United States

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***Correspondence:**
Dr. Daniel L. Hall,
E-mail: hall@mgh.harvard.edu

ABSTRACT

Background: Insomnia is a significant issue in 30-50% of cancer survivors. Our pilot randomized controlled trial of synchronous, virtual cognitive behavioral therapy for insomnia (CBT-I) for cancer survivors suggested that a group format or booster sessions may optimize effects on insomnia and daytime functioning. The goal of this project is to conduct a factorial, randomized controlled trial to optimize synchronous, virtual delivery of CBT-I for cancer survivors.
Methods: We will conduct a 2×2 factorial trial (N=80) to evaluate the optimal combination of two intervention design components: delivery (individual vs. group) and booster sessions (0 vs 3). The primary outcome is change in insomnia severity (insomnia severity index) from T0 (week 0) to T2 (week 8). The secondary outcomes are acute (T0-T1, week 4) and sustained (T0-T3, week 16) changes in insomnia severity, emotional distress, work-related functioning, use of sleep medications, and subjective and objective sleep metrics (measured with sleep diaries and Fitbit). Exploratory aim 1 is to characterize study participation and sleep outcomes among racial and ethnic minority cancer survivors with insomnia. Exploratory aim 2 is to characterize the acceptability of design components using Likert ratings (very low=1 to very high=5, benchmarks=4 or higher) and exit interviews with open-ended responses with probes.
Conclusions: This project will yield multiple deliverables to innovate cancer survivorship care, chiefly an optimized, scalable, virtually delivered intervention that addresses chronic insomnia, one of the most deleterious concerns among the among the steadily increasing number of cancer survivors.
Trial Registration: NCT06181643.

Keywords: Insomnia, CBT-I, Survivorship, Cancer, Oncology, Optimization, MOST

INTRODUCTION

Cancer survivors are a growing population in need of treatment for chronic insomnia. The number of cancer survivors is projected to reach 19 million in the United States by 2024.[1] Notably, 30-50% of cancer survivors have clinically significant symptoms of insomnia which may be a result of late effects of cancer treatments (e.g., hot flashes, pain, fatigue) as well as physiological (e.g., circadian rhythm), psychological (e.g., fear of cancer

recurrence), and behavioral (e.g., sleep schedule disruptions) factors.[2-6] Cognitive behavioral therapy for insomnia (CBT-I) is a brief, structured, psychological intervention, recommended by the American College of Physicians as an evidence-based first line treatment for insomnia.[7-12] Meta-analyses by our team and others suggests that existing CBT-I programs for cancer survivors produce medium-sized improvements in self-reported insomnia severity, sleep efficiency, sleep onset latency, and wake after sleep onset CBT-I can also mitigate symptoms of depression, anxiety, and fatigue, which are common concerns in cancer survivors.[13-16] Despite these benefits, several studies note ongoing challenges with retention and nonadherence, suggesting room for continued optimization of CBT-I.[13-15]

Aspects of CBT-I that may be optimized for cancer survivors include the delivery method and inclusion of booster sessions. First, in accordance with the stepped care model, CBT-I may be delivered in a variety of ways (e.g., synchronously or asynchronously, in-person or virtually, individually or in a group).[17,18] Our pilot RCT (known as the "Survivorship Sleep Program") utilized an individual, 4-session, synchronous, virtual delivery of CBT-I given the time, travel, and illness burden constraints often noted in cancer survivors.[19,20]

Synchronous, virtual delivery of CBT-I was feasible and associated with large, clinically meaningful reductions in insomnia.[21,22] However, during exit interviews, we learned that cancer survivors receiving individual CBT-I via telehealth may be interested in group delivery and/or monthly booster sessions.[21,22] Group delivery may be particularly beneficial for cancer survivors as it provides additional practical and/or emotional support and problem-solving from peers. Similarly, the addition of booster sessions could address any residual concerns or nonadherence issues. Nevertheless, these suggestions have not been empirical evaluated in cancer survivors, and refining the optimal combination of these factors is important for successful implementation of CBT-I.

In addition, when optimizing CBT-I for cancer survivors, it is important to understand the scope of the intervention's impact, and there remains several gaps in the literature. First, few studies of cancer survivors have analyzed the effect of CBT-I on outcomes such as work functioning and use of sleep aid medication over time—two relevant variables for cancer survivors, who often report employment disturbances and may experience additional adverse effects from prescribed hypnotics.[2,23,24]

Another gap in the literature includes evaluating the feasibility, acceptability, and efficacy of CBT-I in racially or ethnically diverse cancer survivors.[25,26] While burgeoning research suggests CBT-I is similarly effective, racial and ethnic minorities may face additional barriers to accessing and/or completing CBT-I that could influence optimization.[27] Lastly, few studies in cancer survivors have utilized both subjective and objective sleep metrics simultaneously; inclusion of both measures is critical given CBT-I may have a differential impact on subjective versus objective sleep.[15,28] Overall, an examination of these additional outcomes may inform refined delivery of CBT-I for cancer survivors.

Therefore, in order to improve synchronous, virtual delivery of CBT-I for cancer survivors, we will evaluate the optimal combination of two intervention design components in a 2×2 factorial, randomized controlled trial (N=80), guided by the multiphase optimization strategy (MOST) framework.[29] Specifically, we will compare delivery method (individual vs group) and number of booster sessions (0 vs 3).

We hypothesize that the combination group delivery + 3 booster sessions will yield larger effects on insomnia severity (primary outcome) at T2 (week 8) as compared to individual delivery+ no booster sessions. Secondary outcomes of the current study include a comparison of acute (T0-T1, week 4) and sustained T0-T3 (week 16) changes in insomnia severity, emotional distress, work-related functioning, use of sleep medications, and subjective and objective sleep metrics. Lastly, we will explore the study participation and sleep outcomes among racial and ethnic minority cancer survivors as well as the acceptability of each design component to support future refinement of the survivorship sleep program (SSP).

METHODS

Study design

This trial design was preregistered (NCT06181643). As shown in Table 1, this study is a 2×2 factorial trial to evaluate change in insomnia severity utilizing the optimal combination of two intervention design components: delivery (individual vs. group) and booster sessions (0 vs 3). The 4-session survivorship sleep program (SSP) will be the used as the basis for optimization. All participants will receive SSP Sessions, delivered weekly, across 4 weeks. Content of SSP weekly sessions will be the same for group vs. individual delivery, however, group durations will be longer (90 vs 45 min) to account for group discussion and review of multiple sleep diaries. Participants will be randomized to receive either individual or group treatment delivery and 0 or 3 booster sessions. Participants randomized to booster sessions will receive booster sessions in the same format they received SSP sessions (group or individual).

SSP interventionists

Interventionists will be clinical psychology PhD and PsyD students and an MD physician who completed training in CBT-I overseen by MG. DH and MG will train the interventionists on the SSP protocol. Weekly supervision will be provided by MG, with DH as backup, both of whom supervise psychology trainees at MGH.

Table 1: Experimental conditions in a 2×2 factorial design to investigate two intervention components.

Condition	Delivery: individual	Delivery: group	Total
Booster sessions: no	n=20	n=20	n=40
Booster sessions: yes	n=20	n=20	n=40
Total	n=40	n=40	n=80

SSP fidelity

We will rigorously assess fidelity to the intervention (see Appendix A). After each session/booster, the interventionist will record information about session length, content covered, treatment fidelity, and attendance in a REDCap database. One session from each participant will be randomly selected to be reviewed with DH and EP for fidelity using a blinded, computer-generated randomized list created by the study biostatistician.

Community partners

To bolster recruitment of racial and ethnic minority cancer survivors from across survivorship phases, we will partner with SurvivorJourneys and Ellie Fund and will log recruitment feasibility metrics to inform a future effectiveness-implementation trial.

Inclusion criteria

Adults, ages 18 or over, with a history of non-metastatic, localized, or regional solid or blood malignancy(ies) who have completed primary cancer treatment (i.e., radiation, surgery, and/or chemotherapy) are eligible to participate in the study. Use of hormonal, maintenance, oral, and immunotherapies are permitted. Participants must have clinically significant, chronic insomnia, as indicated by DSM-5 criteria.

Exclusion criteria

Participants will be excluded if they meet the following criteria (a) self-reported inability to speak and write in English (b) an undertreated non-insomnia sleep disorder (i.e., sleep apnoea) (c) undertreated epilepsy, undertreated serious mental illness, current suicidality, and/or psychiatric hospitalization in the past year (d) inability or unwillingness to discontinue night shift work.

Participant recruitment

Participants will be identified and recruited using a variety of methods. Providers may refer patients by sharing contact information of interested patients who have given verbal permission to their provider for the study team to contact them or directly via an Epic referral queue. Participants may also learn about the study through flyers placed throughout MGH cancer center clinics. Additionally, we will collaborate with community partners who work with cancer survivors to feature and circulate the recruitment flyer throughout their networks to assist in our aspirational recruitment goal of enrolling >50% racial and ethnic minority participants. Lastly, we will use centralized data warehouses and recruitment portals within our hospital that gather clinical information and allow researchers to identify patients for clinical trials based on user-generated criteria.

Sample size

We intend to randomize 80 cancer survivors in this trial. This number was determined based on our mixed methods approach to assessing the primary aim (change in insomnia severity at T2, week 8), exploratory aim 1 (feasibility among racial and ethnic minority participants), and exploratory aim 2 (acceptability via T3 exit interviews and T3 surveys). To account for up to 10% dropout prior to randomization, we plan to obtain informed consent from up to 88 eligible patients to ensure that 80 patients enroll. Based on our pilot feasibility RCT, a sample size of N=80 (n=20/arm across 4 arms) will be sufficient to test our primary and secondary outcomes.[21]

Randomization

Using a random computer generator, the biostatistician will randomize 80 participants in a stratified block (of size 4) randomization schema. To guarantee that more that 50% of participants are of a racial/ethnic minority background, stratification by race/ethnicity will be implemented, such that the first group of 40 randomized participants could be of any race/ethnic minority category, while the second group of 40 randomized participants will be protected for those identifying as a racial and/or ethnic minority. The allocation will be concealed from the PI, who will be blinded throughout the study. Participants will be randomly assigned to 1 of 4 groups: (1) Individual SSP with 0 booster sessions; (2) Individual SSP with 3 booster sessions; (3) Group SSP with 0 booster sessions; or (4) group SSP with 3 booster sessions. All sessions will occur once weekly for 4 weeks. All individual sessions will last approximately 45 minutes. Group sessions will be approximately 90 minutes. Booster sessions will occur once monthly for 3 months in the same format as randomized (individual or group).

The SSP intervention

The SSP is a virtual, synchronous CBT-I intervention conducted across 4 weeks. Through completion of the

MOST preparation phase, SSP sessions were modelled after an evidence-based CBT-I protocol and adapted with refined content and delivery plans based on a review of the literature and findings from our qualitative study and pilot RCT.[21,29,30] As shown in Table 2, the purpose of session 1 is to introduce the survivor to the SSP and develop a sleep prescription (i.e., time in bed and time out of bed). Cancer-related factors affecting the survivor's sleep (e.g., hot-flashes, fear of recurrence) are identified, normalized, validated, and, whenever possible, problem-solved using behavioral strategies. The first session also educates the survivor on sleep habits and the 4-factor model of insomnia, introducing the survivor to the first two skills, stimulus control and efficient sleep.

Table 2: SSP intervention.

Session	Content	Handouts
1	Assessment: Review pertinent screening data and sleep history questionnaire Education: sleep diary Sleep drive and circadian rhythm 4 factor model of insomnia Skill: stimulus control Skill: efficient sleep Develop sleep prescription Identify and problem-solve potential barriers to adherence	1.1 Tips for sleep diary 1.2 Factor model 1.3 Stimulus control 1.4 Efficient sleep 1.5 Things to do if you feel alert
2	Identify and problem-solve barriers to adherence Review sleep diary Titrate sleep prescription Skill: Sleep Hygiene Skill: Relaxation	2.1 Sleep hygiene 2.2 Relaxation
3	Identify and problem-solve barriers to adherence Review sleep diary Titrate sleep prescription Skill: Cognitive Techniques	3.1 Thought record 3.2 Practice reframing thoughts 3.3 Worry time
4	Identify and problem-solve barriers to adherence Review sleep diary Titrate sleep prescription Education: Insomnia Relapse Prevention	4.1 Personal plan

Session 2 begins with reviewing patient sleep diaries, problem-solving barriers to adherence, and titrating the sleep prescription as needed. Session 2 skills focus on sleep hygiene and relaxation. Both session 3 and 4 follow a previous initial format to session 2. session 3 additionally focuses on cognitive techniques reframing thoughts and worry time, and session 4 includes education about insomnia relapse prevention and next steps in the study. Each of the monthly booster sessions will follow a semi-structured format to praise successes, troubleshoot barriers to adherence, review the 5 main CBT-I skills (e.g., stimulus control, efficient sleep, sleep hygiene, relaxation, and cognitive techniques), reinforce relapse prevention strategies, and discuss next steps in the study. Booster sessions are scheduled for up to 45 (individual) or 90 (group) minutes but may take less time, depending on emergent needs.

Screening measures

Demographic and medical history

During screening, the following self-reported information will be collected: date of birth, race, ethnicity, cancer diagnosis, date of cancer diagnosis, treatment types, and date of treatment completion. In the baseline assessment, the following self-reported information will be collected: education, relationship status, employment status, health insurance, and annual household income.

Primary outcome measure

Insomnia Severity Index

The Insomnia Severity Index (ISI) will be used to assess insomnia severity at each timepoint. ISI change from T0-T2 (week 8) will be evaluated as the primary outcome.[31]

Secondary outcome measures

Consensus sleep diary

Sleep diary metrics will be assessed using the consensus sleep diary. Sleep metrics to be derived include sleep efficiency, sleep onset latency, and wake after sleep onset. Discrepancy scores between subjective and objective sleep metrics (e.g., sleep onset latency) will also be examined.[32]

Objective sleep

Fitbit data will be collected during SSP sessions 1-4 and for 7 days at each timepoint (T0-T3) to derive sleep onset time, sleep wake-up (offset) time, sleep midpoint (difference between onset and offset), sleep duration, and wake after sleep onset. Discrepancy scores between subjective (i.e., sleep diary) and objective sleep metrics (i.e., Fitbit) will be examined. To increase engagement, participants may choose between a nylon and latex band. Participants may opt-out of wearing the Fitbit at any time.

PROMIS anxiety short form

The PROMIS anxiety short form is a 4-item questionnaire measuring anxiety levels. Response options range from 1 (never characteristic of me in the past seven days) to 5 (always as it applies within the past seven days).[33]

PROMIS depression short form

The PROMIS depression short form is a 4-iem self-report questionnaire measuring depression levels. Response options range from 1 (never characteristic of me in the past seven days) to 5 (always as it applies within the past seven days). [33]

PROMIS fatigue short form

The PROMIS fatigue short form is a 7-iem self-report questionnaire measuring fatigue levels. Response options range from 1 (never characteristic of me in the past seven days) to 5 (always as it applies within the past seven days).[33]

Work productivity and activity impairment: general health

The work productivity and activity impairment: general health (WPAI:GH) is a 6-item measure assessing work-related functioning including absenteeism, presenteeism, and total work impairment. Response options include 4-items that are fill in the blank and 2-items ranging from 0 (Health problems had no effect on my work) to 10 (Health problems completely prevented me from working).[34]

International physical activity questionnaire

The IPAQ is a 27-item self-report questionnaire measuring physical activity in adult populations across various domains, including occupational, transportation related, home keeping, and recreational activity. Participants are asked to input their estimate of activity in hours and minutes. The current study will use the long and short from of the IPAQ to estimate total weekly physical activity by weighting the reported minutes per week within each activity category by a metabolic equivalent of task (MET) energy expenditure estimate assigned to each category of activity.

Fear of cancer recurrence short form

The FCRI-short form is a 9-item measure assessing intrusive thoughts around fear of cancer recurrence. Each item is assessed on a Likert scale ranging from 0 (Not at all) to 4 (a great deal). Higher scores indicate higher fear of cancer recurrence.[35]

Perceived weight changes

Cancer survivors will be asked about their perceived weight changes because of cancer treatment and their intention to change their weight. Participants will choose from the following options: lose weight, gain weight, stay about the same, or not applicable.

Smoking

Smoking habits (frequency, method, time from sleep) will be assessed using a self-report questionnaire developed by the study team.

Sleep aid medications

Use of sleep aid medications (frequency, dose) will be evaluated via self-report in surveys and sleep diaries using questions developed by the study team.

Exploratory outcome measure

Approximately half of all participants randomized to group and/or booster sessions will be randomly assigned to complete exit interviews at T3 to characterize acceptability of the SSP design components. Participants randomized to receive individual treatment with no boosters will not be interviewed, since this intervention combination has previously been studied in our pilot RCT. Exit interviews will be held virtually via Zoom and conducted by a trained interviewer using a semi-structured interview guide to assess intervention acceptability using open-ended responses with probes. Additionally, a survey at T3 will assess acceptability using 5-point Likert ratings (1=Very low to 5=Very high) in terms of intervention enjoyableness, convenience of telehealth sessions, helpfulness for insomnia, odds of future skills use, and overall satisfaction.

Statistical analysis

Our statistical design accounts for use of mixed methods (qualitative and quantitative) to obtain a comprehensive understanding of the optimal efficacy, feasibility, and acceptability of the intervention content and procedures. Outcome assessments will be conducted by assessors blinded to treatment allocation.

Sample size analysis

Sample size was determined based on our mixed methods approach to assessing optimization (primary aim), feasibility benchmarks among racial and ethnic minority participants (exploratory aim 1), and acceptability via exit interviews (T3) and surveys (T3) (exploratory aim 2). Based on our pilot feasibility RCT, a sample size of N=80 (n=20/arm across 4 arms) will be sufficient to test our primary and secondary outcomes.[21] With n=20 participants in each of the 4 factorial arms, the study will have 80% power to detect an effect size of d=0.92 between any two arms, using a two-sided t-test with a significance level of 0.05. Notably, this effect size is 27.5% smaller than the effect we observed in our pilot trial, which did not include components of group delivery or booster sessions.

Primary aim

We hypothesize that SSP delivered to groups with booster sessions (n=20) will similarly yield large effect size reductions in ISI scores as compared to the SSP program delivered to individuals with no booster sessions (n=20). With n=20 participants in each of the 4 factorial arms, the study will have 80% power to detect an effect size of d=0.92 between any two arms, using a two-sided t-test with a significance level of 0.05. In addition to this interaction effect, main effects will be compared at the marginal levels; with n=40 participants in each level of both main factors, the study will have at least 80% power to detect an effect size of 0.63 using two-sided t-test with a significance level of 0.05. Because our primary hypothesis is directly comparing two conditions (group boosters vs individual +no boosters), significance is not adjusted for multiple comparisons. Nevertheless, we expect to be adequately powered to detect significant differences between any two factors (for instance, comparing delivery to group vs. individual) post multiple comparison adjustment since the effect size targeted for this study is quite smaller than the one, we observed in our pilot RCT.

Secondary outcomes

Linear mixed models with repeated measures will be utilized to model acute (T0-T1, week 4) and 3-month (T0-T3, week 16) changes in insomnia severity (ISI), anxiety and depression symptoms (PROMIS anxiety and depression scores), daytime fatigue (PROMIS fatigue), work-related absenteeism, presenteeism, and total work impairment (work productivity and activity impairment, general health), use of sleep aids (frequency, dose), and sleep diaries and actigraphy scores as measured by Fitbit (sleep efficiency, sleep onset latency, and wake after sleep onset; and discrepancy scores between subjective and objective measures). Adjusted and unadjusted linear mixed effects models will be conducted with repeated measures from T0 (week 0) to T1 (week 4), T2 (week 8), and T3 (week 16). Additionally, effect sizes will be calculated to assess standardized change in ISI and secondary outcome variables across each timepoint. ISI scores will be examined separately as a continuous variable and categorical variable (below/at or above clinical cutoff=15).

Exploratory aims

We will primarily compare cancer survivors who identify as racial and ethnic minorities relative to cancer survivors who identify as non-Hispanic, white using descriptive statistics (Mean, Median, Range) and data visualization. We estimate this categorization to be approximately n=36 per group (racial and ethnic minorities vs non-Hispanic, white). We will also explore differences across all races (American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Black or African American, Multiracial, White) and ethnic (Hispanic, Non-Hispanic) groups using descriptive statistics (mean, median, range) and data visualization. Chi-square tests will be used to compare frequencies of reasons for ineligibility, refusal, dropping out, the ratio of screened-to-eligible, attendance in intervention sessions, self-reported adherence to skills practice, and supervised clinicians' fidelity by participant race and ethnicity. Distributions of feasibility metrics will be explicated by study condition, as well as by race and ethnicity categories, to characterize optimally feasible design features (i.e., individual vs group delivery, 0 vs 3 booster sessions).

Exit interviews will undergo directed content analysis of exit interviews using NVivo software and two independent coders to identify the most and least acceptable aspects of the intervention. Distributions of acceptability ratings and most/least acceptable aspects will be explicated by study condition to characterize optimally acceptable design features (i.e., individual vs. group delivery; 0 vs. 3 booster sessions).

Data management and sharing plan

Data sharing will be conducted in accordance with the Mass General Brigham (MGB) health care office for Human research studies, which has published specific guidelines for data sharing for investigator-initiated research, and the Dana-Faber/Harvard cancer center IRB. All data will be entered into a study-specific database using participant study numbers, rather than participant names. Only the investigators and the study team will maintain the password-protected, secure log linking participant study identifiers to participants. Thus, we will have the ability to de-identify the data for conversion into Microsoft Excel to enable data sharing with outside individuals and institutions. Depending on the planned analysis, we will withhold components of the data when sending to outside institutions to prevent participant identification. The SSP facilitator's guide and participant handouts will be available upon request to the corresponding author.

Data monitoring and independent monitoring committee

Study recruitment, enrolment, and retention will be reviewed by the PI and RA weekly and monthly in study team meetings. An Independent Monitoring Committee (IMC) will perform an independent review of ongoing study progress and safety. The IMC will be comprised of three members with prior experience with monitoring clinical trials: a clinical oncologist with expertise in cancer survivorship, a biostatistician, and an expert in CBT-I. The IMC will meet biannually and in the event of a serious adverse event related to the study, though this is not anticipated.

DISCUSSION

Chronic insomnia is a common sleep disorder and is associated with several adverse outcomes, including, impaired social and work functioning.[2-6] Cancer survivors, a growing population, have a high prevalence of chronic insomnia and need an accessible, evidence-based treatment.

Sleep aids are often prescribed and may have heightened adverse effects in cancer survivors. CBT-I, which improves emotional distress and insomnia severity, has been shown to be effective with cancer survivors. However, in-person CBT-I may not be accessible for cancer survivors, due to travel limitations and cancer-related constraints.[36-40]

Synchronous, virtual CBT-I for cancer survivors across 4 weekly sessions is associated with clinically significant reductions in insomnia severity and increases treatment accessibility across geographic regions. This trial aims to further optimize synchronous CBT-I by evaluating the combination of delivery and booster sessions to best address cancer-related factors impacting sleep. This trial represents the next critical step in behavioral intervention refinement: the MOST optimization phase.[29]

CONCLUSION

The current study is unique in its assessment of both subjective and objective sleep markers via self-reported sleep-diaries and Fitbit. Given that individuals with insomnia may be prone to recall bias when reporting sleep metrics, the use of both sleep diaries and actigraphy allows for a more comprehensive understanding of insomnia in this population.

The current study also leverages community-based organizations to reach ethnically diverse cancer survivors who have been previously underrepresented in CBT-I trials. Findings from this trial have the potential to inform future guidelines for delivering CBT-I in cancer survivors.

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