Memorial University of Newfoundland

May 30th, 2023

CLINICAL STUDY PROTOCOL

VERSION 2.1 (APRIL 2021)

STUDY SUMMARY

Full Title:	**A Randomized Controlled Trial of Online Cognitive Behavior Therapy for Insomnia (CBT-I) and Perceived Cognitive Impairment (PCI) in Cancer Survivors**
Short Title:	**Online CBT-I for PCI**
Clinical Trials Information	NCT04026048
Principal Investigator:	Sheila N. Garland, PhD[1,2]
Co-Investigators:	Joshua Rash, PhD[1] Melanie Seal, MD, FRCP[2] Josée Savard, PhD[3] Robin Urquhart, PhD[4] John Thoms, MD FRCPC[2] Kara Laing, MD, FRCP[2]
Patient Co-Investigator:	Sondria Browne
Affiliations:	[1] Department of Psychology, MUN Faculty of Science [2] Division of Oncology, MUN Faculty of Medicine [3] Département d'école de psychologie, Université Laval [4] Department of Community Health and Epidemiology, Faculty of Medicine, Dalhousie University
Sponsor:	Canadian Institutes of Health Research (CIHR)

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Title	A Randomized Controlled Trial of Online Cognitive Behaviour Therapy for Insomnia (CBT-I) and Perceived Cognitive Impairment (PCI) in Cancer Survivors
Short Title	Online CBT-I for PCI
Protocol Number	HREB Application Ref No: 12843; ClinicalTrials.gov Identifier: NCT04026048
Phase	Phase IV
Methodology	Randomized controlled trial
Study Duration	4 year
Study Center(s)	Memorial University of Newfoundland (MUN)
Objectives	Primary Objective: 1: To examine whether treating insomnia using online CBT-I improves PCI in cancer survivors compared to a waitlist control group. Secondary Objectives: 1: To determine whether treating insomnia using online CBT-I can improve objective cognitive function at the end of treatment compared to a waitlist control group. 2: To evaluate whether change in insomnia better accounts for improvements in cognition than depression, anxiety, and/or fatigue. 3: To explore whether treatment of insomnia and PCI reduces work presenteeism and absenteeism. 4: To investigate associations between subjective and objective measures of cognitive function and sleep.
Number of Participants	130
Diagnosis and Main Inclusion Criteria	**For individuals with non-hematological malignancies:** • Men and women who are easily able to understand and read English • No current evidence of cancer or clinically stable/inactive disease • Received and completed all adjuvant treatments at least 6 months prior to study entry to allow for neural stabilization and recovery • Continued maintenance or hormonal therapies are acceptable • Report PCI as indicated by a score of “quite a lot” or “always” on at least one of the two items that assess concentration and memory on the EORTC [1]

	• Meet the DSM-5 criteria for insomnia disorder and have a score of 8 or greater on the Insomnia Severity Index[2] • Have an ECOG score of 0-2, indicating that they can care for themselves (working, walking), have good daily activity, and good physical ability • Have high-speed internet connection, webcam, and are fluent using the internet **For individuals with hematological malignancies:** • Men and women who are easily able to understand and read English • A diagnosis of a hematological malignancy currently in remission. • Completed cancer treatments including transplant, chemotherapy and/or immunotherapy at least 6 months prior to study entry • Report PCI as indicated by a score of "quite a lot" or "always" on at least one of the two items that assess concentration and memory on the EORTC [1] • Meet the DSM-5 criteria for insomnia disorder and have a score of 8 or greater on the Insomnia Severity Index[2] • Have good performance status as indicated by an ECOG score of 0-2 • Have high-speed internet connection, webcam, and are fluent using the internet
Study Product, Dose, Route, Regimen	Online delivered CBT-I via video-conferencing
Duration of administration	Participants will receive seven components of online CBT-I via video-conferencing over the course of 8 weeks.
Reference therapy	Waitlist control group
Statistical Methodology	Primary research question data will be analyzed using mixed-effects models. Secondary research questions will be answered using mediation/moderation analyses and/or additional mixed effects models.

1. ETHICS

The study will be approved by local research ethics boards, The Health Research Ethics Board (HREB) and the Research Proposals Approval Committee (RPAC).

The study will be conducted in accordance with the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans 2 (TCPS2) http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/Default/ and will adhere to the Memorial University Policy on Ethics of Research Involving Human Participants http://www.mun.ca/policy/site/policy.php?id=139 .

2. OBJECTIVES OF THE STUDY

Primary Objective: To examine whether treating insomnia using online CBT-I improves PCI in cancer survivors compared to a waitlist control group.

Secondary Objectives:

1: To determine whether treating insomnia using online CBT-I improves objective cognitive function compared to a waitlist control group.

2: To evaluate whether change in insomnia better accounts for improvements in cognition than depression, anxiety, and/or fatigue.

3: To explore whether treatment of insomnia and PCI reduces work presenteeism and absenteeism.

4: To investigate associations between subjective and objective measures of cognitive function and sleep.

3. BACKGROUND, SIGNIFICANCE, AND RATIONALE

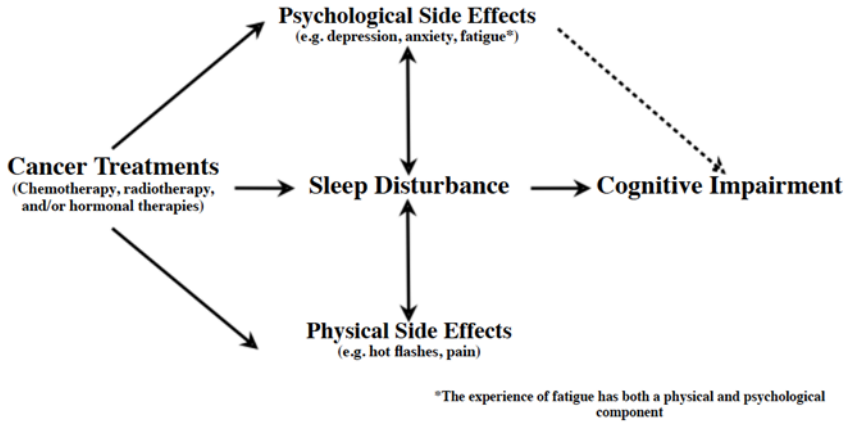
3.1 BACKGROUND: For cancer survivors, one of the biggest barriers to resuming normal functioning is perceived cognitive impairment (PCI). Approximately 75% of cancer patients report a decline in a variety of cognitive domains during chemotherapy and/or hormonal therapy, and up to 35% continue to experience cognitive difficulties for months or years post-treatment.[3] While the evidence supports the high prevalence of PCI, the research is inconclusive about how to treat these difficulties.[4] Pharmacological interventions have largely been ineffective at preventing or treating PCI.[5] The efficacy of cognitive remediation programs is also inconclusive, with some, but not all, studies reporting improved cognition.[6] Studies to date have largely ignored the possible impact of sleep, which could account for the less than impressive findings.

Sleep disturbances, primarily in the form of insomnia, are an especially important, but frequently overlooked, consequence of cancer and associated treatments.[7, 8] Several large-scale epidemiological studies demonstrate that close to 60% of people treated for cancer experience insomnia.[9, 10] When patients were asked about the development of their insomnia, most reported that it began with, or followed, their cancer diagnosis,[11] and that the effects of poor sleep were more overwhelming than the effects of cancer treatment.[12] Unfortunately, once chronic, sleep disturbances are unrelenting if not appropriately treated, and can persist for years

or even decades.[10] Sleep difficulty is one of the most frequent reasons that cancer survivors visit their general practitioners.[13] In Canada, annual indirect costs associated with insomnia-related absenteeism were estimated at $970.6 million overall, with insomnia-related productivity losses estimated at $5.0 billion.[14] The average annual per-person costs (direct and indirect combined) were $5,010 for individuals with insomnia compared to $421 for good sleepers.[14] Further, 40.6% of Canadians with insomnia reported having experienced reduced productivity compared to 12.3% of good sleepers.[15] Sleep disturbance significantly mediates the impact of cancer on healthcare expenditures and absenteeism, suggesting that addressing sleep disturbance may result in economic benefits in addition to improvements in health and quality of life.[16]

Disrupted sleep has negative consequences for cognition in the general population. Numerous experimental studies have demonstrated that both acute total and cumulative partial sleep loss lead to deteriorations in a wide range of cognitive functions such as sustained attention, executive function, and memory (for a review, see Banks and Dinges [17]). Poor sleep and insomnia are significantly associated with subjective and objective cognitive complaints in cancer populations as well.[18-20] Recent evidence challenges the conventional idea that the cancer treatment itself is responsible for the changes in cognition and places sleep in the spotlight as a potent contributor.[21] To guide the design, methods, and analyses for the proposed research, we have built a conceptual model (Figure 1) that is grounded in the current scientific understanding of how cancer and its treatment and side effects might, directly or indirectly, contribute to sleep disturbance, which can then, alone or in combination with psychological disorders, contribute to PCI.

Figure 1: Conceptual Model



Cognitive Behaviour Therapy for Insomnia (CBT-I) is specifically designed for insomnia and is recommended by the American College of Physicians and the American Academy of Sleep Medicine as a first line treatment for chronic insomnia.[22, 23] CBT-I has demonstrated efficacy in several randomized controlled trials (RCTs) in the general population.[24-27] CBT-I is also the treatment of choice in the context of cancer-related insomnia.[28] Recent evidence also suggests that CBT-I has broad effects and offers concomitant improvements in fatigue, anxiety, and depression related to cancer treatment,[29] all of which have been associated with PCI. The correlation between PCI and insomnia persists more than 18 months post-diagnosis, and there is some evidence suggesting that patients with insomnia are more likely to develop PCI.[30] Moreover, preliminary evidence from secondary analyses suggests that CBT-I may improve PCI[31] but additional research is required to investigate this question *a priori* with more refined subjective and objective measures of cognitive functioning, controlling for other factors that may explain this effect.

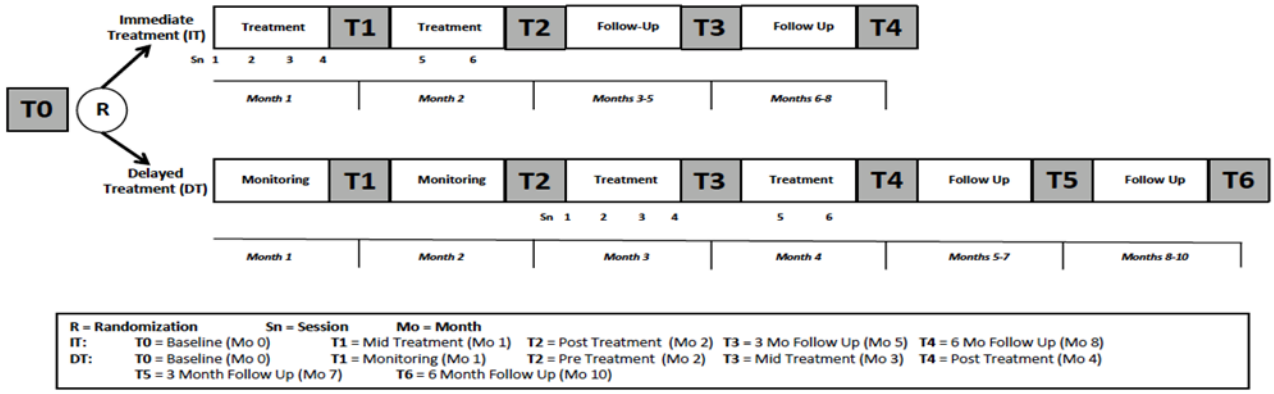
Despite the advantages of CBT-I, it is underutilized for a number of reasons such as a limited number of trained CBT-I providers, poor geographical distribution of these providers, limited insurance reimbursement, and relatively high costs of face-to-face delivered CBT-I.[32, 33]. A solution to these issues and an approach to increase access to CBT-I is the online delivery of the intervention via video-conferencing platforms. The internet is increasingly being used to deliver a wide range of behavioral and mental health programs and has had excellent success.[32]

3.2. SIGNIFICANCE: Treatment of PCI in cancer patients is a priority for clinicians, researchers, and patients, making the current trial a necessity.[34] Cognitive difficulties have a direct impact on work productivity, long-term absence, retirement intentions, and early retirement.[35] The proposed study is highly significant in that it is the first RCT specifically designed to examine whether PCI in cancer survivors can be improved using the "gold-standard" non-pharmacological intervention for insomnia.[22] This research will inform our understanding of the mechanisms of cognitive impairment associated with cancer and help determine whether CBT-I could be used alone or in adjunct to other therapies (e.g., cognitive remediation) to treat PCI.

4. STUDY DESIGN

4.1. Overall Design: The proposed trial is an RCT of immediate treatment with CBT-I compared to a waitlist control for PCI in cancer survivors with insomnia (see Figure 2). Participants will receive individual CBT-I delivered by via online video-conferencing over the course of eight weeks. Participants in the waitlist control group will be required to monitor their sleep with sleep diaries for 8 weeks. They will receive CBT-I delivered by via video-conferencing immediately after the waiting period. Both groups will complete follow up assessments three and six months after completing treatment. The total study duration for the immediate and delayed treatment groups is 8 and 10 months, respectively. We chose a waitlist, or delayed treatment, control group because it would be unethical to refuse participants with insomnia the opportunity to receive CBT-I. The use of a waitlist control is also more representative of real-world health care in Canada, where patients will often have to wait for a certain amount of time before receiving treatment and will control for the regression to the mean.

Figure 2: Trial Design



5. SUBJECT SELECTION AND WITHDRAWAL

5.1. Subject Recruitment: We plan to recruit a sample of 130 cancer survivors from across the Atlantic provinces (Newfoundland and Labrador, Prince Edward Island, Nova Scotia, and New Brunswick) who completed chemotherapy and/or radiation treatment at least 6 months prior to enrollment (for non-hematological malignancies) and completed cancer treatments including transplant, chemotherapy and/or immunotherapy at least 6 months prior to study entry (for hematological malignancies). We are confident in our ability to recruit the proposed sample. Newfoundland and Labrador has the highest age standardized incidence rate for cancer in Canada.[36] All of the oncologists providing cancer care at Eastern Health (including Co-Is Drs. Thoms and Seal) are highly committed to the successful completion of this study. Because we are recruiting cancer survivors at least 6 months after completion of cancer treatment, we will have a large pool of participants to draw from. The primary means of recruitment will be self-referral; however, we will also employ creative strategies that have been successfully used in previous studies to recruit local participants including: identification of patients with sleep problems through the Personal Well-being Checklist, a distress screening initiative used by the Dr. H. Bliss Murphy Cancer Centre; posting announcements and pamphlets available in the main areas of cancer centres and other areas where eligible patients may frequent; notification of treating physicians across areas (e.g., medical oncology, radiation oncology, hematology oncology, general oncology), nurses and allied health professionals; having new patients consent to be contacted at a later date~~;~~ notification of community support groups and posting of information on websites frequented by patients; media releases for local newspapers and television programs; paid advertising in print media, on the radio, television and/or internet; and posting advertisements on Kijiji, Buy and Sell, and Classifieds. A key recruitment method to ensure we can make patients across the province and Atlantic Canada aware of the study opportunity is to mail study invitation letters to patients through the Newfoundland and Labrador provincial cancer registry and the Atlantic Path study. Recruitment via the cancer registry will be conducted with the approval and cooperation of the NL Cancer Care Registry (NLCCR). Recruitment via the Atlantic Path study will be conducted with the approval and cooperation of Atlantic Path. Eligible patients (defined as any individual with no current evidence of cancer or clinically stable/inactive disease who completed cancer treatment at least 6 months ago) will be identified by registry cancer case and Atlantic Path records and mailed an invitation letter to participate in the study. The personal information of the individuals eligible for the invitation letter will not be made available to the researchers in this study. Study personnel will provide the stuffed envelopes and the registry or Atlantic Path will be responsible for mailing them, to ensure protection of privacy. Previous studies conducted by the principal investigator have seen successful recruitment through this strategy.

The mail out will include:

NLCCR:

- two letters
  - a letter from the NLCCR
  - a letter from the principal investigator
- two brochures
  - one about the NLCCR (http://cancercare.easternhealth.ca/wp-content/uploads/sites/2/2018/02/Cancer-Registry-NLCCR-Brochure_2017-1.pdf)
  - one about our study

Atlantic Path:

- a letter from the principle investigator
- a brochure about our study

Conservative estimates indicate that approximately 15% of patients will be both eligible and interested in participating in our research, yielding 525 potential participants per year. We aim to recruit 1-3 participants per week or approximately 5 participants per month (30 in Year 1 to allow study launch time, 58 in Year 2, and 36 in Year 3). As such, we are more than able to recruit 130 participants in the study period.

Table 1: Study Timeline

TABLE 1	YEAR 1				YEAR 2				YEAR 3				YEAR 4			
Hire/Training																
Treatment Group (n)		**7**	**11**	**12**	**14**	**14**	**15**	**15**	**15**	**15**	**6**					
Waitlist Group																
Follow Up																
Data Entry/Cleaning																
Data Analysis																
Writing/KT																

5.2. Inclusion Criteria:

5.2.1 For individuals with non-hematological malignancies:

- Men and women who are easily able to understand and read English
- No current evidence of cancer or clinically stable/inactive disease
- Received and completed all adjuvant treatments at least 6 months prior to study entry to allow for neural stabilization and recovery
- Continued maintenance or hormonal therapies are acceptable
- Report PCI as indicated by a score of “quite a lot” or “always” on at least one of the two items that assess concentration and memory on the EORTC [1]
- Meet the DSM-5 criteria for insomnia disorder and have a score of 8 or greater on the Insomnia Severity Index[2]
- Have good performance status as indicated by an ECOG score of 0-2.
- Have high-speed internet connection, webcam, and are fluent using the internet

5.2.2 For individuals with hematological malignancies:

- Men and women who are easily able to understand and read English
- A diagnosis of a hematological malignancy currently in remission.
- Completed cancer treatments including transplant, chemotherapy and/or immunotherapy at least 6 months prior to study entry
- Report PCI as indicated by a score of “quite a lot” or “always” on at least one of the two items that assess concentration and memory on the EORTC [1]
- Meet the DSM-5 criteria for insomnia disorder and have a score of 8 or greater on the Insomnia Severity Index[2]

- Have good performance status as indicated by an ECOG score of 0-2.
- Have high-speed internet connection, webcam, and are fluent using the internet

5.3. Exclusion Criteria:

5.3.1 For individuals with and without hematological malignancies:

- Another sleep disorder, besides insomnia, that is not adequately treated (ie: untreated obstructive sleep, sleep apnea)
- The presence of another psychological disorder that is not currently stable and/or would impair the ability to participate in the study
- A major sensory deficit (e.g. blindness)
- A neurologic or major medical condition known to affect cognitive function (e.g., Parkinson's)
- A history of cranial radiation
- A history of any other condition that may affect cognitive functioning (e.g., traumatic brain injury)
- Previous experience with CBT-I

Participants will not be excluded for using psychotropic medication prior to study entry (e.g. antidepressants) provided that the dose was not recently altered (stable over the previous 6 weeks). Considering the potential for prescription of medications to help with sleep (e.g. hypnotics, sedatives, and antidepressants) within the cancer population, medication use throughout the study will be tracked and adjusted for in the statistical analysis.

5.4. Early Withdrawal of Participants:

Any participant withdrawing their consent to participate in the study or their authorization to use their protected health information will be withdrawn from the study. Participants withdrawn may be replaced, at the discretion of the principal investigator.

Reasons why participants are withdrawn will be documented on the Study Termination Form. Every effort will be made to continue to collect data on every participant for the entire study duration regardless of whether the participant continues to complete assessments, assuming the participant has not withdrawn his/her authorization to obtain such information.

6. STUDY INTERVENTION

Participants will receive seven individual CBT-I delivered by via video-conferencing over the course of eight weeks. Therapists will be doctoral students in clinical psychology supervised by Drs. Garland and Rash. CBT-I is a manualized multi-component intervention that includes sleep restriction, stimulus control, cognitive restructuring, relaxation training, and sleep hygiene. Sleep restriction is designed to restrict time spent in bed to closely match the time actually spent sleeping. A sleep efficiency percentage (the amount of time spent sleeping divided by the amount of time spent in bed) is calculated, and when the individual is able to achieve 85% sleep efficiency, their sleep time is increased. This process continues until the person can achieve a restful night's sleep with few or no disturbances. Stimulus control is based on the theory that the body eventually becomes conditioned to associate the sleep time and setting with arousal (e.g.

only go to bed when sleepy and refrain from lying awake in bed). This technique is designed to break the perpetuating behaviors and re-associate the bed with sleep. Cognitive restructuring addresses the dysfunctional thoughts and beliefs that serve to maintain and exacerbate insomnia. Individuals are taught to monitor these thoughts and beliefs, challenge their validity, and replace them with adaptive cognitions conducive to the sleep process. Relaxation training targets the physiological and cognitive arousal that accompanies insomnia, and sleep hygiene promotes healthy sleep behaviors and environmental conditions.

Treatment fidelity (including adherence, competence, etc.) is critical to the successful delivery of an intervention in practice.[37] All therapists will receive training in the manualized CBT-I protocol and weekly case supervision meetings including video review throughout the duration of the trial with Drs. Garland and Rash. A checklist of the main teaching points to be covered in each treatment session will be reviewed during supervision and adherence to the CBT-I protocol will be examined by calculating a total score on the teaching checklist. Therapists with adherence ratings below 90% will be provided with additional supervision. Dr. Rash will rate twenty percent of the video recorded sessions selected at random for treatment adherence. These data will be used if needed in addition to the Credibility/Expectancy Questionnaire (CEQ)[38] to examine possible moderators of treatment effects.

7. STUDY PROCEDURES

7.1. Initial Screening: All potential participants will be identified from across Atlantic Canada. Patients will be contacted by the research coordinator and/or primary investigator to explain the study procedures in detail. A brief medical, psychological, and sleep disorders screening questionnaire will be administered to screen for the presence of other medical and/or psychological disorders that may interfere with the participant's ability to participate in the study. This will occur over the telephone.

7.2 Informed Consent: Informed consent will be obtained in two phases. In phase one, participants will be read a simplified consent form over Zoom. In phase two, participants will be given a link to the full consent form and participants will be considered consented when they check the box on the Qualtrics form. This will occur at the time of their initial screening or will be scheduled for a more convenient time prior to the baseline assessment. Once consented, participants will be considered enrolled.

7.3. Assessments: Baseline assessments will be scheduled based on participant availability and will last about 60 minutes. All of the assessments will take place over the secure video conference sessions that will take place in a secure room in the Sleep, Health, and Wellness laboratory. Assessments may also be mailed out to the participants to fill out and return, or participants will be sent a link to the assessments on Qualtrics. During the COVID-19 pandemic, all assessments will follow the usual protocol to take place over the secure video conference platform, however, now this will take place in a secure room in the research coordinator's home. Participants will also be emailed the link to the online component of the assessment which occurs on Qualtrics. No mailing of paper copies of the assessments will occur during the COVID-19 pandemic.

At the baseline assessment, we will assess cognitive function and patient reported outcomes of sleep, fatigue, anxiety, and depression. During the baseline assessment, a member of the study

team will inform the participant if they are randomized to be in the immediate treatment group or the delayed treatment group.

At the mid and post treatment assessments, the participants will also be asked to complete questions related to adverse events during the CBT-I treatment. These questions will be added to their Qualtrics assessment. The open-ended Qualtrics responses will be thematically analyzed to create a record of adverse events experienced by the participants.

7.3.1. Video-Conference Information

The CBT-I intervention and the assessments will take place over a video conference platform called Zoom (see details about privacy and security below in Section 10). Participants will be given a link to the session via email. At the end of the session the link will expire, and each new Zoom session will generate a new Zoom ID. Participants will be told to not enter their name but to enter their participant number to ensure confidentiality. We previously used telehealth systems embedded in the regional health authorities to conduct these assessments, but patients reported that this was still a barrier to participation because they had to travel (sometimes still quite a distance) to participate in the telehealth meeting. The use of Zoom will allow people to participate from the comfort of their own home and ensure privacy and equal access to treatment for Atlantic Canadians regardless of geography. Treatment sessions will be recorded to assess treatment fidelity and quality assurance.

7.4. Follow up Assessments: Both groups will complete follow up assessments three and six months after completion of treatment to investigate durability of treatment effects.

7.5. Randomization: Participants will be sequentially randomized to one of the two treatment conditions using a 1:1 allocation ratio created by the study biostatistician. The random allocation sequence will be prepared in advance and recorded on sequentially numbered, opaque, sealed and stapled envelopes to be provided to participants in order of study entrance. During the baseline assessment, the research coordinator will inform the participants which group they have been assigned to. All research personnel, including the PI, will be blind to the allocation sequence.

7.6. Data Collection Schema

The data collection schema for both groups are described in Tables 1a and 1b, followed by details about the instruments. The average time to complete the patient reported outcomes and neuropsychological measures at each assessment time is approximately 45-60 minutes. Participants in both the immediate treatment group and the waitlist treatment group will complete the sleep diaries. Participants will complete the sleep diary upon waking each morning for one week at each assessment period. The time to record the previous night's sleep is approximately 2 minutes. The research team has successfully conducted previous research with similar levels of participant burden. During the COVID-19 pandemic, participants will only complete the diaries if they are able to do so electronically (print and send back electronically, or fill out on their computer and email back). Participants who require a printed copy of the diary to be mailed will not complete the sleep diary component during the pandemic.

Table 1a. Schedule of Assessments and Outcome Collection for <u>Immediate Treatment</u>

Instrument	T0 Baseline	T1 Mid-Treatment	T2 Post-Treatment	T3 3 Month Follow Up	T4 6 Month Follow Up
CEQ	X				
FACT-COG	X	X	X	X	X
ISI	X	X	X	X	X
MFSI-SF	X	X	X	X	X
HADS	X	X	X	X	X
WPAI	X		X	X	X
Sleep Diaries*	X	X	X	X	X
HLVT-R	X		X	X	X
COWAT	X		X	X	X
Digit Span	X		X	X	X
BRIEF-A	X		X	X	X
MMSE	X				
Adverse Events Protocol		X	X		

Table 1b. Schedule of Assessments and Outcome Collection for <u>Delayed Treatment</u>

Instrument	T0 Baseline	T1 Monitoring	T2 Pre-Treatment	T3 Mid-Treatment	T4 Post-Treatment	T5 3 Month Follow Up	T6 6 Month Follow Up
CEQ	X						
FACT-COG	X	X	X	X	X	X	X
ISI	X	X	X	X	X	X	X
MFSI-SF	X	X	X	X	X	X	X
HADS	X	X	X	X	X	X	X
WPAI	X		X		X	X	X
Sleep Diaries*	X	X	X	X	X	X	X
HLVT-R	X		X		X	X	X
COWAT	X		X		X	X	X
Digit Span	X		X		X	X	X
BRIEF-A	X		X		X	X	X
MMSE	X						
Adverse Events Protocol				X	X		

Medical history and demographics: A medical history and demographics questionnaire will be administered at the baseline assessment. This questionnaire will be used to obtain patient demographic information (e.g., sex, age, ethnic background, education, marital status, current employment status), medical history (e.g., type of cancer, dates of diagnosis and treatment, types of treatment received), psychiatric history, and current medication use. The Credibility/Expectancy Questionnaire (CEQ)[38] will also be used at baseline to examine possible moderators of treatment effects.

Primary Outcome - **The Functional Assessment of Cancer Therapy – Cognitive Function (FACT-Cog), version 3:** The FACT-Cog will be used as the measure of perceived cognitive impairment. It is a 37-item questionnaire with four cognitive subscales: perceived cognitive impairments, impact on quality of life, comments from others, and perceived cognitive abilities.[20, 39] Responses range from 0, ‘‘never,’’ to 4, ‘‘several times a day,’’ in the previous 7 days. A change of 10.6-points has been established as clinically meaningful change on the FACT-Cog.[39-41]

Secondary Sleep Outcomes: The Insomnia Severity Index (ISI) has 7-items designed to specifically assess the severity of insomnia symptoms, the impact on daytime functioning, and the amount of associated distress.[2] The ISI has established minimally important change values to ensure that the change is not only statistically significant, but also clinically meaningful to patients.

The Consensus Sleep Diary (CSD) provides a night-by-night, self-report of sleep duration, disruption, and perceived quality and will be used to capture more subtle variations in sleep. The sleep diary will be used to calculate sleep efficiency, sleep-onset latency, wake after sleep onset, total sleep time, time in bed, number of awakenings, sleep quality, and terminal wakefulness. Sleep diaries are considered a reliable and valid patient report of nightly insomnia symptoms.[42] Participants will complete the sleep diary for one week at each assessment point. However, during the COVID-19 pandemic, participants will only complete the diaries if they are able to do so electronically (print and send back electronically, or fill out on their computer and email back). Participants who require a printed copy of the diary to be mailed will not complete the sleep diary component during the pandemic.

Neuropsychological Measures: The use of these measures adheres to the recommendations of the International Cognition and Cancer Task Force to improve research design and facilitate between-study comparisons and meta-analyses.[43]

The Mini-Mental State Examination (MMSE) is a method used for assessing cognitive metal state in clinical practice and in research.[44] A score lower than 24 on the Mini-Mental State Examination suggesting the presence of severe cognitive impairments

The Hopkins Verbal Learning Test-Revised (HVLT-R) is a brief assessment of verbal learning and memory (immediate recall, delayed recall, delayed recognition).[45] The HVLT-R has six alternate forms available.

The Controlled Oral Word Association Test (COWAT) is a measure of verbal fluency, cognitive and motor speed, cognitive flexibility, strategy utilization, suppression of interference, and response inhibition.[46] The COWAT has two alternate forms available.

The Digit Span test is a subtest of the Wechsler Adult Intelligence Scale (WAIS) and the Wechsler Memory Scale (WMS)[47]. The forward span captures attention efficiency and capacity, and the backward span is an executive task dependent on working memory[47]. The digit span is not impacted by practice effects making is suitable for repeated testing[48].

The Behaviour Rating Inventory of Executive Function-Adult (BRIEF-A) is composed of 75 items within nine non-overlapping theoretically and empirically derived clinical scales. It has 2 broad indexes (Behavioural Regulation and Metacognition), an overall summary score, and three validity scales (Negativity, Inconsistency, and Infrequency). The normative sample included 1,136 adults from a wide range of racial/ethnic backgrounds, educational backgrounds, and geographic regions. The BRIEF-A has demonstrated evidence of reliability, validity, and clinical utility as an ecologically sensitive measure of executive functioning in individuals with a range of conditions across a wide age range. A study that investigated the use of the BRIEF-A in patients with primary brain tumors suggests that measuring perceived executive dysfunction with the BRIEF-A is feasible.[49]

Work Productivity Loss Measure: The Work Productivity and Activity Impairment (WPAI) questionnaire was developed for the purpose of collecting productivity loss data within clinical trials and is suitable for direct translation into a monetary figure.[50]

Additional Patient-Reported Outcomes: Fatigue will be measured using the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF).[51] Anxiety and Depression will be measured using the Hospital Anxiety and Depression Scale (HADS) [52].

8. STATISTICAL PLAN

8.1 Data Management: A data management system will be created by the principal investigator permitting tracking of data forms, computer-based editing and error-check, generation of periodic reports, and the creation of data sets for statistical analyses. All data will be stored in a fashion consistent with patient information privacy guidelines (see below). The data analysis sets will be exported to statistical software for analysis.

8.2. Data Analysis Plan

8.2.1. Analysis Plan: To answer our primary research question, we will use mixed-effects models to determine whether treated patients had greater improvements immediately post-treatment (primary endpoint) compared with patients in the control group after their waiting period. Then, data from both groups will be pooled together to assess, with a larger sample size, the durability of any effects observed at 6 months (secondary endpoint). This statistical procedure considers within-subject correlations from repeated measurements in the same subjects and allows estimation of between-group differences without necessitating last observation carried forward or exclusion of participants with missing data. Secondary and exploratory research questions will be answered using mediation/moderation analyses and/or additional mixed effects models.

The primary analyses will occur after the treatment completion (primary endpoint) and durability analyses will occur after the 6-month follow-up (secondary endpoint).

Subsidiary analyses will be conducted to examine the role of sex, gender, and sexual orientation in participant recruitment and retention, pre-treatment symptom severity, as well as the overall efficacy of online CBT-I, and results will be reported separately.

8.2.2. Missing Data: A drawback of any study is the risk of missing data and attrition bias. Our first line of defense will be to minimize the occurrence of missing observations, using a well-constructed study design, well-trained research staff, and acceptable subject burden.[53] We will decrease barriers to recruitment/retention by scheduling study visits at a convenient time. For those who voluntarily withdraw from the study, we will record their reasons for withdrawing and use this information in a sensitivity analysis. To minimize missing data, all surveys will be checked right after completion. If needed, calls will be made to participants to complete missing data over the phone. For individuals who miss a study visit, RAs will call at least three times (morning/afternoon/evening) over the next week to try rescheduling the assessment.

Our second line of defense is to apply data analysis strategies that are as robust as possible to data losses.[54] Seeing that no universally accepted method exists for handling missing data, we will initially perform intent-to-treat analyses. We then will perform sensitivity analyses to evaluate the robustness of our results, including compete-case analysis, single imputation methods, such as last-observation and baseline carry forward analyses, and multiple imputation analyses. To avoid reporting bias, we will register our trial with ClinicalTrials.gov and follow the CONSORT recommendations for reporting randomized trials of nonpharmacological interventions.[55]

8.2.3 Sample Size Considerations: Our sample size is based on our primary outcome of PCI using the FACT-Cog immediately post-treatment. Since the primary outcome is continuous, we powered our trial using a t-test to detect the difference between two independent means for score at post-treatment. This is a conservative way to estimate sample size since the longitudinal analysis using the mixed-effects model specified in the analysis plan will provide greater power than a t-test. With power of 0.8 and two-sided alpha of 0.05, we will need at least 62 participants per treatment group and 124 in total to detect an effect size of 0.5.

9. RISKS, BENEFITS, RISK/BENEFIT RATIO

9.1. Potential Risks and Protection against Risks: Although the risks associated with participation in the proposed study are minimal, all potential risks that might occur as a result of participation will be detailed in an informed consent form and will also be fully discussed with each subject prior to enrollment.

Confidentiality Risks: Information about study participants will be kept confidential and managed according to the requirements of HREB and RPAC. The use of Zoom and Qualtrics adhere to confidentiality standards that protect participant anonymity.

Risk of psychological discomfort: It is possible that participants may be upset by some of the questions or by their performance on the neurocognitive testing. If the participant demonstrates clinically significant distress, he or she will be referred for psychosocial counseling. Dr. Garland, the PI, is a registered clinical psychologist and has extensive clinical experience in treating physical and psychological distress related to cancer or cancer

therapy. During the study period, if the research staff identifies any patients who are psychologically distressed they will notify Dr. Garland immediately to facilitate appropriate evaluation and treatment.

9.2. Potential Benefits:

Participants may experience an improvement in their insomnia and/or other cancer-related co-morbidities (e.g. cognition, fatigue, mood disturbance). Improving insomnia and other problematic symptoms often leads to an improvement in overall physical and emotional well-being.

10. DATA HANDLING AND RECORD KEEPING

10.1. Confidentiality

Information about study participants will be kept confidential and managed according to the requirements of the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans 2 (TCPS2) and will adhere to the Memorial University Policy on Ethics of Research Involving Human Participants.

Data from the online assessments will be downloaded from Qualtrics and stored on a secure and locked drive. Information collected from the video-conference assessments will be stored in a locked office in the Department of Psychology at Memorial University of Newfoundland. Dr. Sheila Garland is the person responsible for keeping it secure. Information collected during the COVID-19 pandemic will be stored in a sealed envelope in a secure room in the research coordinator's home. Only the research coordinator will have access to this. Upon returning to the lab, these documents will be transferred to the secure locked office in the Department of Psychology at Memorial University of Newfoundland.

Use of Zoom Video-Conferencing: Communication (CBT-I intervention, assessments) via Zoom will be kept confidential as Zoom is a secure and confidential video platform. Zoom offers end-to-end encryption which is an added layer of application security that prevents third-parties from accessing data while it's transferred from one end system or device to another. Zoom can encrypt all presentation content at the application layer using TLS 1.2 with Advanced Encryption Standard (AES) 256-bit algorithm. Zoom sessions will be recorded for quality assurance and treatment fidelity and deleted immediately after review.

Use of Qualtrics Online Survey Tool: Assessments from Qualtrics will be kept confidential as Qualtrics is ISO 27001 certified with industry standard encryption. They have been approved by security compliance and health information protection such as FedRAMP and HIPAA. Qualtrics' servers are protected by high-end firewall systems, and scans are performed regularly to ensure that any vulnerabilities are quickly found and patched. All data collected from this study will be stored in Canada in Qualtrics' Toronto data centre.

In the event that a subject revokes authorization to collect or use personal health information, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization.

There are not currently plans to destroy the data. The data will be kept in a password protected and encrypted file and all identifiers will be stripped after completion of the trial.

11. TRIAL STEERING COMMITTEE:

We will convene a Trial Steering Committee (TSC) that consists of an independent chair and at least two other independent members, the nominated principal applicant, and the patient collaborator in the project. The TSC will meet quarterly throughout the study period to review: 1) the study protocol and any amendments and deviations: 2) rates of recruitment and retention; 3) any adverse events; 4) completeness of data collected; and 5) any other organizational problems or trial issues. The TSC will meet on an as needed basis to discuss adverse events, serving as the data safety monitoring board (DSMB). We deemed the TSC an appropriate DSMB given that adverse events associated with CBT-I are rare.

12. STUDY FINANCES

12.1. Funding Source

This study is supported by a grant from Canadian Institutes of Health Research (CIHR).

12.2. Conflict of Interest

None of the study investigators have any conflicts of interest to disclose.

12.3 Subject Stipends or Payments

To encourage retention and adherence to the study procedures, each participant will be paid $100 in total if in the immediate treatment group or $140 in total if in the delayed treatment group ($20 per assessment). The participants will be given a choice to receive one of the four following e-gift-cards: Amazon, Tim Hortons, Home Hardware, or Esso. Each gift-card is available online and will be delivered to the participants through e-mail. A number of participants have peers who may be eligible for the study and we will compensate participants for their referrals. To compensate participants for their time and effort, they will receive an additional $10 to their gift cards for each eligible person they refer to the study and can receive a maximum of $20 (2 referrals).

13. PUBLICATION PLAN

The Principal Investigator will be responsible for publishing the primary results of this study. All subsequent publications will be at the discretion of the Principal Investigator.

14. AMENDMENTS

May 2023 – Increased sample size to 130 participants; added recruitment of qualitative exit interviews after trial completion.

May 2021 – Added study invitation mailout letters to patients from Atlantic Path study.

October 2020 – Eligibility criteria adjusted to allow individuals who have finished their cancer treatments 6 months prior to participate; added adverse event questionnaire at mid- and post-treatment.

September 2020 - Removal of participants wearing actigraphy watches (due to COVID-19).

June 2020 – Increased referrals from all Atlantic provinces instead of only Newfoundland and Labrador.

December 2019 – Added new recruitment strategy (local media and newspaper); added treatment fidelity (adherence, competence, etc.) as a component of the trial.

October 2019 – Added eligibility criteria for participants with hematological malignancies.

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