Light Enhanced Cognitive Behavioural Therapy (CBT+) for Sleep and Fatigue: A Randomized Controlled Trial during Chemotherapy for Breast Cancer

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Background

Breast cancer (BC) is the most common cancer in women, with nearly 18,000 new diagnoses per year in Australia (Australian Institute of Health and Welfare, 2017). Sleep disturbances and insomnia are highly prevalent among women with BC and are reported before, during and after BC treatment in both early stage and metastatic cancer (Bower, 2008). In the general population, the prevalence of insomnia is estimated to be 10% (Howell et al., 2014) whereas prevalence estimates for insomnia in BC patients range between 30% and 60% (Garland et al., 2014). Furthermore, up to 87% of BC patients report sleep disturbances that may not meet clinical criteria for insomnia yet still yield negative consequences (Palesh et al., 2012). The experience of persistent sleep disturbance places BC patients at a higher risk for psychological and physical morbidity and reduced quality of life (Fortner et al., 2002; Otte et al., 2015). Sleep disturbances in women with BC have been linked with poor physical recovery, increased likelihood of BC recurrence, impaired cognitive functioning, decreased work productivity, medication misuse and abuse and poor interpersonal relationships (Thomas, Bower, Hoyt & Sepah, 2010; Caplette-Gingras, Savard, Savard & Ivers, 2012). In addition to the substantial physical and mental impact of sleep disturbance upon women with BC, the resultant worsened prognosis is costly to the health care system. Despite most women treated for BC experiencing significant sleep disturbances and elevated rates of insomnia, treatment of sleep is not standard and commonly inadequately managed.

Causes of Sleep Disturbance among Women with BC

The high prevalence of sleep disturbance experienced by cancer patients has been attributed to a number of factors; psychological consequences of cancer diagnosis such as anxiety, stress and depression; the direct effects of cancer treatments and their side effects, medical symptoms, and environmental changes such as hospitalization.

BC treatments and sleep disturbance.

Pain, hospitalization and common treatment side effects such as fatigue, hot flushes and nausea also cause sleep disruption. Treatments for BC have been associated with a variety of side effects that contribute to sleep disturbances in this population. Surgical treatment, radiotherapy, chemotherapy and hormonal therapy constitute the most common BC treatments and have all been associated with impaired sleep. A recent systematic review investigated the impact of BC treatments on sleep, finding that women submitted to chemotherapy and radiotherapy showed the greatest sleep impairments (Rute Costa et al., 2014). The physical impact of treatment symptoms such as nausea, vomiting, hot flashes, night sweats, diarrhoea, urinary frequency, pain, hospitalization, changes in body image and skin reactions are recognised as the main treatment-related factors perpetuating sleep disturbance. Radiation therapy has been associated with declines in sleep efficiency and increases in time spent awake during the night (Rute Costa et al., 2014). Chemotherapy and hormonal therapy have been associated with delayed sleep onset and worsened perceived sleep quality. In a study of 823 patients undergoing chemotherapy, 40% reported moderate to severe insomnia symptoms following their first chemotherapy treatment, with symptoms persisting throughout cycles in 70% of patients. A systematic review of 21 articles further suggested that sleep disturbances can persist for up to 1-year post-chemotherapy. Surgical treatments produce pain and inflammatory responses that can impair sleep yet sleep

disturbance following surgery has been reported to be significantly less severe than the disturbance associated with chemotherapy, hormonal therapy and radiotherapy (Rute Costa et al., 2014). As such, cancer treatments, particularly chemotherapy, contribute to the elevated prevalence of sleep disturbance among women with BC.

Psychological stressors and sleep disturbance.

Previous research has identified life stress, depression and anxiety to be the most prominent psychological complaints in BC patients (Palesh et al., 2007) and these stressors have been found to negatively impact sleep (Garland et al., 2014). Women with BC typically experience an ongoing series of stressors, some residual, some present and others anticipated in the future, and many of these stressors cannot be resolved. Women with BC have reported intrusive thoughts, worry and rumination surrounding diagnosis, and over the course of their illness (Burgess et al., 2005). Multiple studies have linked anxiety and stress with sleep disturbance among cancer patients in both active treatment (Fleming, Randell, Harvey, & Espie, 2014; Savard, Simard, Ivers, & Morin, 2005) and survivorship (Bower, 2008). Furthermore, up to 50% of women with BC experience clinically significant symptoms of depression throughout the course of their illness (Graci, 2005) and sleep disturbances are pathogenic in depression. Previous research has identified depression as a predictor of self-reported sleep disturbance among women with metastatic BC (Palesh et al., 2007).

Circadian disruption and sleep disturbance.

In addition to the psychological and treatment-related components of sleep disturbance in BC, previous research has implicated circadian rhythm disruption as another associated factor. Circadian rhythms are daily patterns in behaviour and physiological processes entrained to *zeitgebers* (environmental time cues), of which the most prominent is the 24-hour cycle of sunlight and darkness. Disruptions to circadian rhythms result in sleep disturbance (Savvidis & Koutsilieris, 2012) as well as depressive symptoms and worse overall quality of life (Garland et al., 2014). Circadian rhythms can be profoundly disrupted in cancer patients and research has demonstrated associations between circadian disruption and cancer incidence and progression. Mormont and colleagues (2000) found that cancer patients exhibiting dysregulated circadian rhythms were five times more likely to die within two years compared to patients with more distinguishable circadian rhythms. Core circadian genes seem to be important in tissue homeostasis and tumorigenesis such that disruption of circadian rhythms accelerates tumour progression. It has been argued that restoring circadian rhythms through sleep interventions should improve prognosis.

Several studies have shown that BC patients display more disrupted circadian rhythms compared to healthy controls (Chevalier et al., 2003; Fernandes et al., 2006; Levin et al., 2005; Pati et al., 2007) and chemotherapy has been implicated as a key contributor to circadian disruption (Ancoli-Israel etal., 2006; Berger et al., 2007). Studies that have examined disruption to circadian rhythms in women with BC have shown that circadian rhythms improve during the recovery weeks following cycle 1 chemotherapy yet by cycle 4, there is no circadian rhythm recovery (Savard et al., 2009). These findings indicate that ongoing chemotherapy is partly responsible for the deterioration of circadian rhythms among women with BC.

Treating sleep disturbance in cancer

*Cognitive Behavioural Therapy for Insomnia.*

Cognitive Behavioral Therapy for Insomnia (CBT-I) is an effective insomnia treatment, and compared to sleep medication alone, its effects are comparable at short-term, and more superior at long-term (Morin et al., 2009). Individuals with insomnia, whether or not it is comorbid with a medical condition such as cancer, typically exhibit cognitive and physiological hyperarousal, demonstrate attentional biases and endorse problematic sleep-related beliefs. CBT-I, a multicomponent intervention consisting of sleep restriction, stimulus control, sleep hygiene, cognitive restructuring and relaxation training, was developed to address these interrelated aspects of insomnia. CBT-I is considered a well-established intervention and has demonstrated efficacy for treating primary insomnia as well as sleep disturbance that does not meet the diagnostic criteria for insomnia. In primary insomnia and sleep disturbance, CBT-I has produced larger positive effects than pharmacotherapy, medication placebo, relaxation therapy, sleep hygiene education and control groups. Furthermore, the effects of CBT-I have been remarkably durable and a substantial proportion of participants continue to improve (if not reach remission) well after treatment is discontinued. Even when factors that are outside of an individual's control (such as chemotherapy and medical symptoms) interfere with sleep, CBT-I based strategies can lead to significant improvement in sleep. One reason CBT-I is effective even when factors not in one's control disrupt sleep, is that it increases the sleep drive, extinguishes conditioned arousal, and focuses on altering maladaptive behaviours and cognitions that individuals with insomnia adopt. A growing body of literature has demonstrated that insomnia and sleep disturbance comorbid with psychiatric or medical disorders is equally or more responsive to CBT-I than primary insomnia. Importantly, CBT-I has been found to be associated with clinically and statistically significant improvements in subjective sleep outcomes in patients with cancer.

The standard delivery format of CBT-I consists of eight one hour face to face sessions with a trained clinician. Despite the evidence for its efficacy, the demanding requirements of CBT-I for both patients and clinicians limit its accessibility, particularly given the medical and symptom burden cancer patients already face. Consequently, a small number of studies have trialed condensed versions of CBT-I in cancer patients. The efficacy of a nine-week internet based CBT-I program was examined in a sample of cancer survivors and compared to a control group, those receiving the intervention demonstrated significantly greater improvements in insomnia severity, sleep efficiency and sleep quality. Additionally, Savard and colleagues (2010) trialed a six-week reduced CBT-I intervention comprised of 60 minute videos and information booklets in BC patients. Findings indicated clinically significant improvements in insomnia severity, sleep onset latency and sleep efficiency. These studies provide evidence for the efficacy of CBT-I in cancer patients, even when delivered in a reduced, more accessible format.

Light therapy.

Bright light is one of the strongest cues for the synchronising of circadian rhythms and, as it is a critical factor in the regulation of sleep and wakefulness, light therapy has been developed for the treatment of sleep disorders. In addition to its circadian impact, bright light

has an alerting effect and has been associated with reduced fatigue (Van Maanen et al., 2016). Light therapy is a natural, simple form of treatment with relatively low costs and its efficacy in treating circadian disruption has been well proven (Lee et al., 1997; Thompson, 2001; Ancoli-Israel et al., 2003; Van Maanen et al., 2016). Although light therapy has been found effective in a range of populations presenting with insomnia, disturbed sleep or fatigue, to date there are no guidelines for bright light use specific to certain sleep complaints or clinical populations. The extensive research on light treatment for sleep disorders has led to varying treatment recommendations. Among these recommendations, there is consensus regarding the timing of treatment. Exposure to light in the morning shifts the biological clock rhythm to an earlier point in time, whereas light in the evening shifts it to a later time. Immediately before or after the temperature nadir is when light exposure has its greatest phase advancing effect. Light therapy in the morning should occur as early as possible without forcing individuals to wake too early resulting in day time sleepiness. Furthermore, studies using a higher light intensity or blue-enriched light have found larger therapeutic effects for sleep improvement. An example of the circadian timing advance or delay associated with timing of light relative to circadian rhythm is shown in the figure.

Reproduced Figure 5 from (Revell, Molina & Eastman, 2012). DLMO = dim light melatonin onset, and is a marker of circadian rhythm. The vertical lines demarcate the sleep period. The curve shows that light blue light administered around habitual wake time modestly advances the circadian rhythm.
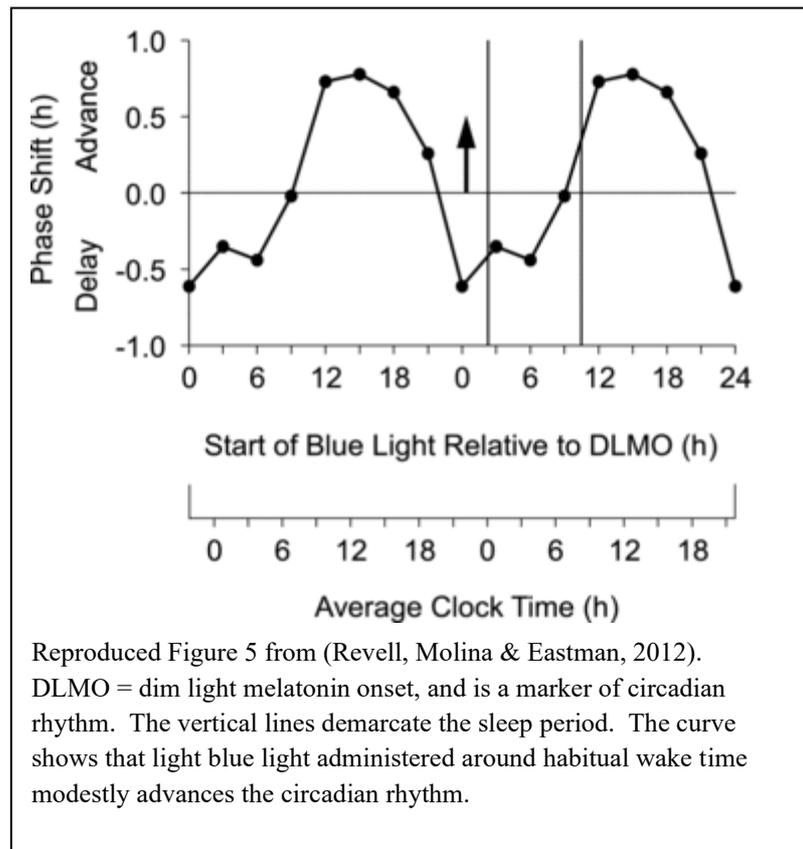
Despite the evidence for circadian disruption among women with BC and the proven efficacy of light therapy, few studies have investigated the use of light therapy in this population. Ancoli-Israel and colleagues (2012) investigated light treatment as a prevention method for fatigue in women undergoing chemotherapy. In this study, the light treatment protocol consisted of placing a 10000 lux light box approximately 18 inches from the participant's head within a 45-degree angle from the midline of the visual field. The light box was used for 30 minutes each morning upon awakening throughout the first four cycles of chemotherapy. Light therapy was found effective in preventing women from experiencing fatigue during chemotherapy (Ancoli-Israel et al., 2012). In the same study, light therapy was also found to protect women from circadian activity rhythm deterioration during chemotherapy (Neikrug et al., 2012). Redd and colleagues (2014) utilised the same light therapy protocol for four weeks in a sample of BC survivors and found light therapy to

significantly improve cancer related fatigue. Further evidencing the benefits of light for fatigue symptoms in this population, Liu and colleagues (2005) recorded daily light exposure and found a significant association between decreased light exposure and increased fatigue among women with BC during chemotherapy. To date, no studies have investigated the efficacy of light therapy in specifically treating sleep disturbance among women with BC. However, given the promising evidence for light therapy in treating fatigue in this population, as well as the efficacy of light therapy for sleep disturbance in other clinical populations (Van Maanen et al., 2016), it is expected that light therapy will improve symptoms of sleep disturbance among women with BC.

Moderators

Pain is one of the most frequently identified contributors to insomnia in cancer patients. Pain prevalence rates are 33-52% among non-metastatic BC patients and rates increase to 56-68% among women with metastatic BC (Palesh at al., 2007). Higher levels of pain have been associated with difficulties getting to sleep as well as increased night time awakenings among women with BC. Although relaxation components of CBT-I have been found to reduce pain and sleep disturbance in cancer patients (Kwekkeboom et al., 2010), experiences of pain are likely to vary between individuals and therefore pain may be a moderator in the efficacy of a sleep intervention among women with BC. An individual's sleep chronotype may also moderate the efficacy of a sleep intervention. Sleep chronotype refers to the timing of the sleep/wake cycle influenced by endogenous (circadian) and exogenous (work/social schedule) factors and is classified as a propensity for *morningness*; waking and sleeping earlier in the 24-hour cycle, or *eveningness*; waking and sleeping later. Individuals with evening chronotypes tend to experience increased sleep problems in addition to a greater degree of irregularity in their sleep/wake cycle and greater psychiatric distress (Ong, Huang, Kuo & Manber, 2007). Although CBT-I has been shown to improve sleep regardless of chronotype (Bei, Ong, Rajaratnam & Manber, 2015) studies of CBT-I in cancer populations have not included chronotype in analysis and it is possible that chronotype may moderate sleep intervention efficacy in this population. Furthermore, light therapy has been shown more effective in individuals with good sleep hygiene and regular bed times, both traits of morningness chronotypes (Van Maanen et al., 2016) that contrast with the increased irregularity in bed times associated with evening chronotypes. Chronotype may therefore also moderate the therapeutic effects of light therapy among women with BC. Finally, patients' perceived credibility of an intervention, their expectation of therapeutic outcomes and their adherence to intervention protocols can also all moderate an intervention's efficacy.

Current Study

It is clear that sleep disturbance is prevalent among women with BC and can lead to a range of negative outcomes not only relating to individual prognosis and quality of life but also increased costs to the health care system. Given the multifaceted nature of sleep disturbance in this population, it is expected that the causal factors attributed to be the most problematic for sleep may differ from one individual to another based on a number of variables such as treatment type and length, cancer stage and individual experiences of psychological distress and coping. Consequently, it is important that treatment does not target a single causal factor but is applicable to a range of possible causes. Theoretically, this more applicable approach is

achieved through the combination of condensed cognitive behavioural and bright light therapy as the behavioural, psychological and physiological causes of sleep disturbance are addressed. Furthermore, utilising cognitive behavioural strategies and light therapy targets the night time sleep disturbances and the day time fatigue that are both prevalent in the breast cancer population. The current intervention, cognitive behavioural and bright light therapy, is a combination of condensed cognitive behaviour and bright light therapy delivered over six weeks. Importantly, this intervention is designed to improve sleep with minimal burden of time and inconvenience to participants.

Aims and Hypotheses

Aim 1

Test the efficacy of cognitive behavioural and bright light therapy (CBT+) compared to relaxation audio for improving symptoms of sleep disturbance. It is hypothesised that participants receiving CBT+ will show improvements on measures of sleep disturbance compared to participants receiving relaxation audio.

Aim 2

Test the efficacy of CBT+ versus relaxation audio for psychological outcomes. It is hypothesised that participants receiving CBT+ will experience a decrease in symptoms of depression and anxiety compared to participants receiving relaxation audio.

Aim 3

To explore potential mechanisms of CBT+ and moderators of the intervention efficacy. A number of factors may potentially moderate the efficacy of CBT+, namely; pain, chronotype, perceived credibility and expectations of the intervention and adherence to the intervention protocol. Given the lack of knowledge surrounding the impact of these potential moderators in the BC population, this study aims to explore whether any of these moderators have a significant effect on intervention outcomes. Furthermore, this study aims to provide insight into the mechanisms through which CBT+ may improve sleep in women with BC. Based on the factors contributing to sleep disturbance that are targeted by CBT+, the following potential mechanisms will be investigated; pre-sleep arousal, beliefs and attitudes about sleep, vulnerability to insomnia under stress and rumination and intrusive thoughts before bed.

<center>**Research Plan**</center>

Participants

Participants will be 80 women with BC engaged in medical treatment at the Victorian Comprehensive Cancer Centre (VCCC). Women will be randomized to an intervention or control condition. Inclusion criteria include:

1. Diagnosed with any stage primary BC

2. Over 18 years of age

3. Receiving or will receive during the study period intravenous chemotherapy, with or without radiotherapy

4. Able to provide informed consent

5. Able to understand and speak English

6. Able to regularly receive and access emails

7. Able and willing to wear bright light glasses

Exclusion criteria:

1. Being male

2. Receiving only neoadjuvant chemotherapy

3. Severe psychiatric disorder

4. Severe substance use disorder

5. History of suffering migraines

6. Individuals with very advanced (habitual bedtime before 8pm and rise time before 4am)/delayed sleep timing (habitual bedtime after 3am and rise time after 11am), or have irregular or non-24 sleep/wake patterns are excluded based on the Duke structured sleep interview.

The characteristics of female, diagnosed with breast cancer and undergoing chemotherapy are relevant as the aim of this project is to evaluate a sleep and wellbeing intervention for this specific population. It is necessary for participants to have English as their primary language as the intervention materials are written in English and a significant component of the intervention consists of reading emails and engaging in a face to face session that will be conducted in English. Due to cultural and linguistic differences, translation of the intervention materials and questionnaires alone is inadequate to ensure they are comparable. Children and young people under the age of 18 are excluded as they do not come through the Peter MacCallum Cancer Centre service and the rates of breast cancer in this age group are so low that it would not be possible to evaluate the efficacy of the intervention in this younger age group. Women with severe intellectual or mental impairments are excluded from the design as the intervention requires participants to read emails and practice sleep and wellbeing strategies autonomously. Therefore, participants must be capable of undertaking and performing these requirements themselves. As this

research focuses on the Breast cancer population which is comprised of over 99% females, it is unlikely that any males will be undergoing chemotherapy at the Peter MacCallum cancer centre during the project's recruitment period. Even if there were eligible males, the age of diagnosis is typically older in men than in women and cancer is often detected at a more advanced stage leading to differences in average treatment and cancer trajectories. For these reasons, only females will be recruited to reduce variability in participant groups.

It is possible that eligible participants may be receiving additional treatment for sleep complaints (psychological treatment, prescribed sleep medication, herbal remedies etc.). These participants will not be excluded however this information will be obtained during the baseline questionnaires and medical records extraction. All medication and psychological treatment that participants may be receiving, in addition to the intervention, will be noted and taken into account during data analysis.

Design

The proposed study will utilise a randomized controlled design with two groups, one group receiving focal intervention (cognitive behavioural and bright light therapy; CBT+) and a comparison group receiving relaxation audio that will serve as the control. Substantial evidence in the literature supports the efficacy of CBT interventions, and light therapy and therefore efficacy of these components of the intervention will not be investigated individually. As light therapy and CBT impact sleep through different mechanisms, the combination of these intervention components is important, targeting multiple causal factors of sleep disturbance. Furthermore, this is a preliminary study to investigate the efficacy of a combined CBT and light intervention and given the proposed sample size, it would not be feasible to effectively evaluate these components individually as well as the combined intervention. Future research could benefit from individually evaluating intervention components; if this preliminary study shows positive effects for those women in the intervention group, a further study would be warranted with a larger sample size to evaluate the efficacy of the combined intervention in comparison to individual components.

Relaxation audio was chosen as a control so that the efficacy of the intervention is compared to a general relaxation paradigm that may offer benefits for wellbeing and stress reduction but does not specifically target sleep. Furthermore, the use of an active control will reduce the influence of placebo or expectancy effects and ensure that all women who participate in the study receive some effective support.

The CBT+ intervention lasts six weeks. Measures will be taken prior to randomization at baseline, the midpoint of the intervention (3 weeks), and post treatment (6 weeks). A follow-up assessment to evaluate sustained intervention effects on primary and secondary outcomes will be taken at a three-month follow-up.

Figure 1. CONSORT diagram. Exclusion and dropout estimated based on Savard, Simard, Ivers, and Morin (2005).
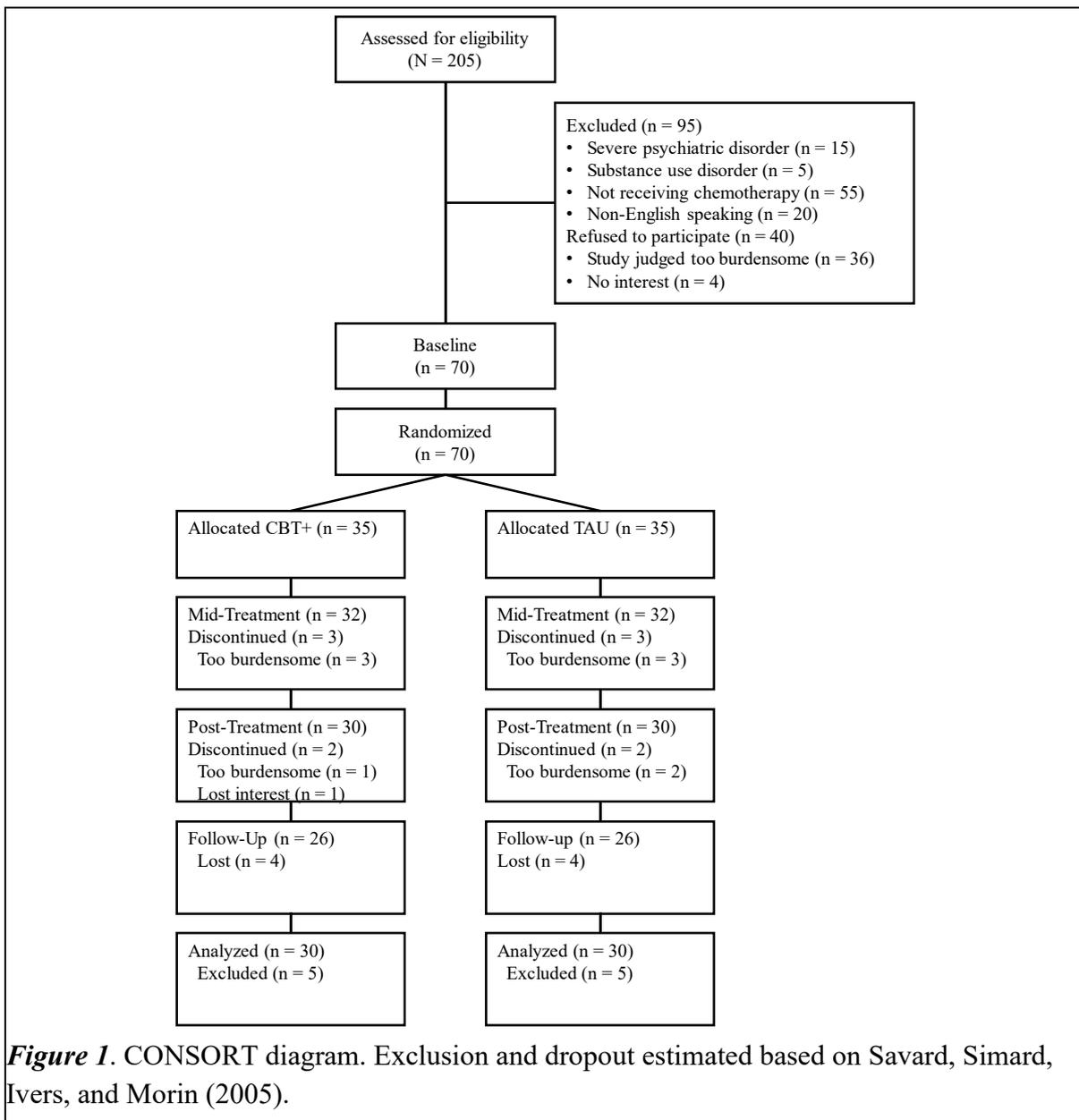
Procedures

Recruitment and Consent

Women diagnosed with BC who are or will receive intravenous chemotherapy treatment at the Peter MacCallum Cancer Centre will be recruited after diagnosis and prior to their third cycle of chemotherapy or completion of chemotherapy (if the course is less than four cycles). Eligible women will be identified by the pharmacy department at the Peter MacCallum Cancer Centre. The pharmacy department will generate a report of potentially eligible women, identified through their chemotherapy chart and accessed through CHARM. The report will detail all women with breast cancer who will be receiving chemotherapy, and the dates that they will be attending the Peter MacCallum Cancer Centre Chemotherapy Day Unit. The research team will access this report through CHARM and will attend the Chemotherapy Day Unit when each eligible woman has a scheduled appointment. Due to the stress associated with breast cancer treatment and the commencement of chemotherapy,

women will not be approached during their chemotherapy education session, or their first chemotherapy appointment. At the Chemotherapy Day Unit, a breast team nurse will advise the researcher of the time of each eligible woman's chemotherapy appointment, and the chair that the woman will be sitting in whilst she is in the day unit. Potentially eligible women will then be approached by the researcher in the chemotherapy day unit during their second or third chemotherapy session and invited to participate in "a research project that aims to improve symptoms of sleep disturbance among women with BC". Women who show interest in participating will be provided with information about sleep disturbance during BC and the study. Should they choose to participate, written informed consent will be obtained. After consenting, women will complete further screening assessments.

Screening

For participants who have given written informed consent to study participation, further eligibility will be assessed via structured interviews (the M.I.N.I International Neuropsychiatric Interview – modules C, H, I, J, K - and the Duke Structured Interview for Sleep Disorders). Generally, this screening also will take place in the Chemotherapy Day Unit, immediately after consent has been obtained. Women also may elect to have the screening completed over the telephone at a later date if they are not prepared to complete the screening immediately. Those participants who meet criteria for a severe psychiatric disorder (current for module C, current for module H (when specified that the trauma is not related to cancer diagnosis), past 12 months for modules I or J, current for module K from the M.I.N.I.), as identified through the M.I.N.I, will be excluded from study participation. Participants with very advanced (habitual bedtime before 8pm and rise time before 4am)/delayed sleep timing (habitual bedtime after 3am and rise time after 11am), or with irregular or non-24 sleep/wake patterns, as identified through the Duke, will be excluded from study participation. Participants with other existing sleep disorders, as identified through the Duke, will not be excluded yet the presence of sleep disorders will be noted and accounted for during data analysis.

Although not part of screening, ISI scores and cancer stage will be attained at this stage of involvement so that randomization of participants can be stratified by screening ISI ($\leq 7, \geq 8$) and cancer stage ($\leq 2, \geq 3$).

Randomization

Eligible participants will be randomized into group using a complete randomization scheme generated in advance. Specifically, block sizes of variable size (4, 6, or 8) will be used. Random seeds will be generated to assure allocation concealment and pre-guessing of the allocation sequence at the end of each block. Randomization will be stratified by screening ISI ($\leq 7, \geq 8$) and cancer stage ($\leq 2, \geq 3$). The randomization scheme will be generated and setup in REDCap by a member of the research staff who is (1) not involved in recruitment or delivery of intervention and (2) is not one of the study PIs, CI-Bei. REDCap is a web application and back-end database model designed to support data capture for research studies. REDCap is an open source tool developed by Vanderbilt University to build and manage online forms for data collection (www.project-REDCap.org). REDCap was developed specifically around HIPAA-security guidelines with features such as data encryption. REDCap implements role-based security, which will be used to limit access

based on user function to certain forms, reports and fields. To randomize a participant, an authorized research staff member will login to REDCap, enter eligibility and stratification data on the participant and will receive the group allocation. REDCap will only be used for participant randomization, the remaining data collection will be done on Qualtrics. Follow-up measures will either be self-completed or will be conducted by research staff who are blinded to the condition.

Timing and Forms of Contact

There will be six time-points when intervention materials are delivered and four time points at which measures are assessed (three during the intervention and one three-month follow-up). The intervention will be delivered via one face-to-face session to be conducted at the Peter MacCallum Cancer Centre in the Chemotherapy Day Unit, one telephone call and seven email packages. Intervention components delivered via email will use online software Mailchimp, which provides professional email templates, and automates timing of intervention delivery. The initial face-to-face session will take approximately 75 minutes and participants will be reimbursed for car parking costs. Face-to-face sessions will be scheduled around participants existing appointments in the Chemotherapy Day Unit to reduce burden of travel. The telephone session and the reading of email packages will take approximately 30 minutes each. Measures questionnaires will be primarily conducted via online surveys (Qualtrics); participants will receive a link to the surveys via email. In the event that a participant does not wish to use an online survey platform, questionnaires will be conducted via telephone by a member of the research team or a research assistant. A brief phone call, approximately 2 - 5 minute, at the end of the intervention will be conducted by study staff to ask about any adverse events.

Audio Recording

All face to face and intervention telephone contact will be recorded via Dictaphone to assess quality control. Audio recordings will be stored securely with password protection. Written informed consent from participants will be sought for obtaining these audio recordings.

CBT+ Intervention

The intervention was designed to deliver effective results whilst being as least burdensome as possible. Given that women with breast cancer are already subjected to an intensive treatment regimen, the design of the intervention was carefully considered such that the effort and time associated with each intervention component are outweighed by the likely physical and psychological benefits. The face-to-face session will be scheduled around participants' existing appointments at the Peter MacCallum Cancer Centre to reduce burden of time and travel. All other aspects of the intervention can be completed in the comfort of participants' own homes, at their leisure. The light glasses are comfortable, easy to wear, and are not likely to disrupt participant's usual morning routines. Wearing the light glasses will not impair participants' ability to move around and undertake any domestic or work related responsibilities such as preparing and consuming food, household cleaning, reading, writing or typing. Furthermore, the intervention is also economical from the perspective of the healthcare system, it is simple for clinicians to deliver and entails minimal financial expense and burden of time. These are important considerations when evaluating whether the intervention, if effective, could be implemented into routine care.

Cognitive Behavioural Therapy

Those participants allocated to the intervention group will receive 'cognitive behavioural and bright therapy' (CBT+). CBT+ is delivered via one 75-minute face to face session, one phone call lasting approximately 30 minutes and a series of 7 emails, one per week, that take approximately 15-20 minutes to read. A detailed outline of session and email content for CBT+ is provided in an attached document. Generally, the intervention group will receive sleep strategies with the following core components:

- general information and skills for better sleep (e.g., sleep hygiene, relaxation and mindfulness exercises, dealing with nighttime worries);
- fostering healthy attitudes and expectations about sleep following cancer diagnosis and during treatment;
- managing sleep challenges specific to cancer patients (e.g., physical discomfort, pain, daytime consequences of poor sleep);
- identifying and managing symptoms of insomnia (e.g., self-monitoring, stimulus control, sleep scheduling, bed restriction).

The intervention materials for the CBT+ component were adapted from the Cognitive Behavioural Treatment of Insomnia Session by Session Guide (Perlis, Jungquist, Smith & Posner, 2005). This adapted version of CBT-I is designed to maximise treatment outcomes whilst promoting sustainable integration with current oncological care at the VCCC.

Bright Light Therapy Individualised Protocol

The light therapy component will consist of daily light glasses use for the six-week duration of the intervention. Participants will receive a pair of Luminette light glasses to take home with them during the face to face CBT-I session and will be instructed to wear them for 30 minutes upon awakening each morning. Specific timing of light glasses use will be established individually with each participant during the face-to-face session.

This guide will cover key components when discussing light and dark therapy with participants during the face to face session. The goals are to:

- assess current sleep/wake patterns and individualise light/dark exposure;
- explain the functions of light therapy so participants understand *how* to apply strategies in their daily experiences; and
- discuss potential barriers to using light glasses and engaging in light therapy more generally, collaboratively brainstorming solutions.

Note: Participants with very advanced (habitual bedtime before 8am and risetime before 4am)/delayed sleep timing (habitual bedtime after 3am and risetime after 11am), or have irregular or non-24 sleep/wake patterns are excluded based on the Duke interview.

Introduction

1. Introduce yourself and describe the purpose of the session.
2. Explain that participants will get a handout of all information covered in the session, but could make notes for themselves.
3. Explain that some of this information covered will also be reinforced in the emails they will receive.

Part One: Bright Light Therapy (LT) – Daytime

1. Assess habitual bedtime, risetime, and morning fatigue and sleepiness.

- Review habitual sleep timing using information already obtained from Duke and confirm this with the participant that these still apply.
- Ask participant how they feel when wake up (e.g., morning drowsiness/fatigue). Note that LT could assist these symptoms.

2. Explain the two main functions of LT.

"*We will work out how you could apply LT based on your current experiences. But as your sleep and other experiences may change in the future, I would like you to understand how LT works, so you can adjust how you use it, just like you are your own sleep doctor.*

We all have an internal body clock that sends our body signals to determine how sleepy or awake we feel across the 24-hour day. Light helps us keep our body clocks in tune with the outside world so that we feel awake during the day and sleepy at night.

Bright light can also help reduce the feelings of grogginess and fatigue, and increase your feelings of alertness. Using bright light as soon as you wake up in the morning can make it easier to start your day and boost your feelings of energy and mood by sending a message to your brain that it's time to 'wake up'. We ask that you use the light glasses for **20 minutes** *but not more than 30 minutes at your usual wake up time. There's no need to wear glasses more than this duration each time you wear them, because after this time, there are little added benefits. You can continue doing your usual activities when you're wearing your glasses, like eating breakfast or reading the paper. It is important to keep your eyes open though, and not wear the glasses while driving, and be extra careful when the surroundings are dim – the bright light could make it difficult to see! Also, it's important* <u>not</u> *to use the glasses in the evening (after sunset or approximately 5pm) so that you're not alert when it's time for you to sleep.*"

Try to get up around the same time every day because this will help promote a consistent body clock.

3. **Develop individualised LT plan based on current sleep/wake patterns**
- Provide instructions of using the device (i.e., removing film over hologram before use, battery life, charging the device and keeping it on charge when not in use, used only in a well-lit room). Have participant try the glasses on, and instruct her the correct wearing angle. Check that she is comfortable with brightness. Do not proceed if the participant is not comfortable with brightness or the device itself.
- Explain that there is information in the Participant Guide on how to use the glasses, and that they may consult the Luminette User Manual for more detailed information and instructions.
- Discuss with the participant LT usage.
  - For most individuals (not too early in habitual rise time and do not mind potentially advancing sleep timing), bright light for 20-30 minutes upon awakening at <u>habitual bedtime</u> would be helpful.
  - Acknowledge natural fluctuation of sleep/wake timing. If she gets up much earlier than habitual rise time (e.g., > 2hrs earlier), ask to wait till their usual risetime before using the glasses.
  - For the small number of participants who have somewhat advanced sleep timing (but are not excluded via Duke) AND do not wish to further advance sleep timing AND do not have any morning grogginess/fatigue: ask them to use the glasses <u>two hours</u> after awakening, and when fatigued during the day. For example, someone who consistently gets up around 5am feeling alert and energetic, and does not wish to get up any earlier could delay light exposure.
  - To consult with Dr Bei Bei if unsure.
- Discuss **natural sources of light** which may also be beneficial during the morning and daytime:
  a. Opening shades in the morning so that sunlight may enter the house;
  b. Exercising/being outdoors after the sun has risen.

Encourage the participant to seek natural light during the morning and day. Explain to participants that the effects will be larger on a sunny vs. overcast day.

Part Two: Dark Therapy – Nighttime

1. **Explain how bright light at night affects alertness/sleep and strategies to avoid nighttime light exposure**

"*Bright light is great during the morning and day, but at night, it suppresses the important sleep hormone called 'melatonin' which is responsible for making you sleepy. Bright light at night could make you more alert, making it harder to sleep. You may have experienced this yourself, for example, when you go to the toilet in the middle of night turning bright ceiling lights on, then finding yourself fully awake and unable to get back to sleep. Remembering that light in the morning tells you to 'wake up', light at night tells you to 'stay up'.*"

- Instruct the participant to use dim lights and lamps in the evening (after 5:00pm) as this will minimise nighttime bright light exposure and reduces interference with body clock.

2. Advice for using electronic devices

- Explain to the participant that light from electronic devices may hinder sleep. "*Electronic devices such as computers, mobile phones, tablets, emit a frequency of light (blue light) that alerts us and can influence our body clocks. You might have experienced that it's harder to get to sleep after using your phone or computer in bed.*"
- Explain how the filter f.lux for computers and Android devices helps block blue light according to the time of day and should be used when using electronic devices.
- Explain how the Night Shift mode on Apple products (e.g. iPads, iPhones and laptops, using the highest setting) similarly block out blue light according to time of day
- Instruct participant to use the **lowest brightness** setting when use of electronic devices if unavoidable during the night. Ask them if they know how to turn the brightness down on their devices – if they are unsure, guide them through it.

3. Encourage adherence of LT use

- Explain that some benefits of LT use may be noticeable soon after they commence LT, however substantial benefits arise after regular and consistent usage e.g. "*You may notice that you start to feel more energised soon after you begin using the glasses, but people get the most benefits from LT when they do it consistently, every day, making it part of their routine. It is very important for you to keep this routine to improve your chances of the program working for you.*"
- Explain that they are taking part of a trial study and to give it their best shot.

Part Three: Brainstorm anticipated barriers to LT use and trouble-shoot ways to overcome them

1. Ask the participant about any obstacles they may see getting in the way of their engagement with the program

"*Now that you are aware of how to use the light glasses and strategies for both the day and night, can you think of any potential barriers or difficulties in undertaking these steps? It will be good for us to talk about these so that you're able to get the most out of the program.*"

The researcher will need to address the participant's potential concerns in a manner that motivates and empowers them to undertake the LT protocol for the duration of the project, as well as encouraging them to think of ways that they can address barriers on their own if and when they arise.

Potential barriers and ways of overcoming the may include:

1. <u>Forgetting to wear the glasses in the morning</u> – set an alarm/reminder on your phone, have a reminder note next to your bed.
2. <u>Not getting enough time in the morning to use the light glasses</u> – explain that they can still undertake their daily activities as usual and the glasses will generally not interfere with their tasks.
3. <u>Tendency to use electronic devices at night</u> (e.g., checking social media, using their phone to listen to music, reading on their ereader) – explain how this interferes with alertness and sleep, but encourage the use of appropriate settings to reduce blue light. Ask them if there is another activity that could replace this with (e.g. reading a book). Behavioural experimental, try it for a week.
4. <u>Turning on many lights during the night</u> (e.g., to care for their baby or children, go to the toilet, reading when they can't get to sleep) – explain how the use of bright lights will alert them and encourage the use of dimmable lights or lamps instead of downlights whenever possible.

Concluding the session

1. **Give a brief summary of major points covered:**
   - Bright light exposure is best in the morning, and should be avoided at night
   - LT has many benefits for improving sleep and mood
   - Opening blinds or being outside in the daylight (e.g. exercising) is great in the morning and natural light should be sought during the day
   - Electronic devices/bright light at inappropriate times 'trick' our body clocks
   - Glasses should be used immediately in the morning – 30 minutes every morning
   - Install f.lux or use Night Shift mode to block out alerting blue light
2. Thank the participant for their attention
3. At the end of the session, the researcher should explain to the participant that if they experience any negative side effects (such as nausea, headaches) at any point during the project to stop using LT immediately and let the researchers know as soon as they experience them.
4. Ask the participant if they have any questions about the program. Reinforce that they may contact us at any point during their involvement.
5. Wish them all the best with the program

Control Intervention

The control group will receive two emails containing web links to relaxation audio tracks. These emails will be received during the first and third week of the intervention. The first relaxation audio consists of abdominal breathing strategies that may assist in calming the mind and relaxing the body. The second audio consist of a body scan relaxation, both audio tracks are approximately 15 minutes and participants are instructed to listen to these audio tracks each day, whenever they feel they might be beneficial. These relaxation tracks were developed by the cancer council to assist patients in coping with a cancer diagnosis. The relaxation audio tracks do not contain any sleep specific information, instead, they include general relaxation strategies that can be used by participants at any time during the day or night. The control group will also receive a brief phone call (15 minutes) during the fourth week of their study involvement to check in with participants' and respond to any queries or

complaints. Following the final follow-up assessment, the control group will receive the set of CBT+ email packages, an additional information booklet detailing the contents of the face-to-face session and an information booklet on light therapy.

Measurements

Table 2 displays the measures for this study and the time points at which they will be administered. Women will complete sleep diaries and light therapy adherence measures using paper and pencil diaries. Prior to commencing the intervention, women will be supplied with 6 diaries, one for each week of the intervention, and six pre-paid, addressed envelopes so that at the end of each week, women can post the diary to the research team. Baseline/screening structured interviews will be conducted in person at recruitment or over the telephone. Baseline, mid-treatment, post-treatment, and follow-up questionnaires may be completed online via Qualtrics or via telephone, for women who prefer not to complete questionnaires online. If women elect to complete questionnaires over the telephone, they will be provided with an answer sheet to reference for responding to each question. Questionnaires completed via Qualtrics will be considered valid if they are within ±1 week of the planned time.

Additionally, there will be a 3 month follow up measurement. This will consist of a narrow subset of measures: the ISI and PROMIS short forms for fatigue, sleep related impairment, sleep disturbance, depression and anxiety. As per other measures, follow-up questionnaires may be completed online via Qualtrics or via telephone. Questionnaires completed via Qualtrics will be considered valid if they are within ±2 weeks of the planned time at follow-up.

Table 2. Timing of Measurements

Note. X = Measure administered at that time point; SE = sleep efficiency; SF = short form;

Name of Measure	Items/ Time	T0 Baseline (Week 0)	T1 Midpoint (Week 3)	T2 Post intervention (Week 6)	T3 follow up (3 months)
Primary Outcomes					
Insomnia Severity Index	7	X	X	X	X
Sleep Diary - Sleep Efficiency			continuous		
Secondary Outcomes					
Sleep Diary – SOL, WASO, TST			continuous		
Actigraphy – SE, SOL, WASO, TST			continuous		
PROMIS Sleep Related Impairment - SFa	8	X	X	X	X
PROMIS Sleep Disturbance – SFa	8	X	X	X	X
PROMIS Fatigue – SFa	8	X	X	X	X
PROMIS Depression - SFa	8	X	X	X	X
PROMIS Anxiety - SFa	8	X	X	X	X
Structured Interviews					
M.I.N.I. International Neuropsychiatric Interview (modules A, B, C, H, I, J, K, N)	10 min	X			
Duke Structured Interview for Sleep Disorders	20 min	X			
Other Factors					
Demographic and Cancer Information	33	X			
Current medication and supplement use	4	X			
Program evaluation	8			X	
Additional mental health and sleep treatment	6	X		X	
Medical records extraction (date of Dx, Tx, tumor staging, medications, etc.)				X	
Moderators					
PROMIS Pain intensity - SF	3	X		X	
Credibility Expectancy Questionnaire	6	X			
Morningness and Eveningness Questionnaire	5	X	X	X	
Intervention Adherence - CBT	4		X	X	
Intervention Adherence - light	3		continuous		
Mechanisms					
Dysfunctional Beliefs and Attitudes about Sleep	16	X	X	X	
Ford Insomnia Response to Stress Test	9	X	X	X	
Pre-sleep arousal	16	X	X	X	
Intrusive thoughts (IES subscale)	8	X	X	X	

SOL = sleep onset latency; WASO = wake after sleep onset; TST = total sleep time

Screening

(1) The M.I.N.I. International Neuropsychiatric Interview 7.0 (Sheehan et al., 1997) is a short, structured diagnostic interview for DSM 5 psychiatric disorders (American Psychiatric Association, 2013). The following modules will be administered for screening:
- Manic and Hypomanic Episodes (Module C),
- Alcohol Dependence/Abuse (Module I),
- Substance Dependence/Abuse (Module J),
- Post-traumatic Stress Disorder other than cancer-related (Module H) and
- Psychotic Disorders (Module K).
In addition, to characterize the sample, the following modules also will be administered:
- Major Depressive Episode (Module A),
- Suicidality (Module B),
- Generalized Anxiety Disorder (Module N).

(2) The Duke Structured Interview for Sleep Disorders (Edinger et al., 2009) will be administered in its entirety during the screening.

Primary Outcomes

The Insomnia Severity Index (ISI) and subjective sleep efficiency from sleep diary were selected as the primary outcomes, because insomnia is assessed and diagnosed via self-report and subjective sleep complaints share strong association with other psychological outcomes (Palesh et al., 2007).

(1) <u>Symptoms of insomnia</u> will be assessed via the Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001). The ISI is the gold-standard measure of insomnia symptoms and a common outcome in sleep trials.

(2) <u>Sleep efficiency</u> will be measured using a daily sleep diary (Carney et al., 2012) and based on the average across a 1 week baseline and the last week of treatment. Subjective sleep efficiency is commonly used as an indicator of progress in insomnia treatment as high sleep efficiency scores indicate consolidated sleep.

Secondary Outcomes

Secondary outcomes include additional dimensions of sleep behaviors assessed via self-reported sleep diaries and objectively via actigraphy. Additional secondary outcomes include self-reported sleep complaints, fatigue, and mental health outcomes. Secondary outcomes are:

(1) <u>Self-report and objective sleep behaviour</u> will be measured using daily sleep diaries and the ActiGraph wGT3X-BT. From the few sleep diary reports, measures of sleep onset latency (SOL), wake after sleep onset (WASO) and total sleep time (TST) can be derived. The ActiGraph wGT3X-BT records continuous activity information using a 3-axis accelerometer along with ambient light. A wear time sensor allows data collected when participants have removed the device to be excluded. Using the activity data, the wGT3X-BT provides estimates for sleep timing (bed time and rise time), sleep duration (time in bed and total sleep time), and sleep quality (sleep efficiency, sleep onset latency, wake after sleep onset). Data scoring will follow an established protocol and integrate

estimates from the automated scoring algorithm along with ambient light, and sleep diary reports of bed and rise time. Assessments are time and date stamped so that they can be matched with the self-report measures.

In sleep studies, it is common to evaluate the impact of interventions on multiple behavioural dimensions of sleep as not all dimensions may change. Furthermore, although in the insomnia literature, it is common to use self-reported sleep as the outcome, it is helpful to supplement this with an objective measure (actigraphy). Evidence suggests that often, there is only modest agreement between sleep diary and actigraphy, suggesting that these two measures capture unique information and are not redundant.

(2) <u>Sleep related complaints</u>, assessed by PROMIS Sleep Related Impairment and Sleep Disturbance (Yu et al., 2012). The PROMIS Sleep Related Impairment will capture daytime impairment due to sleep and the PROMIS Sleep Disturbance scale will capture perceived night-time sleep difficulties. Whereas sleep diary captures perceived sleep behaviours, the sleep related impairment and disturbance scales capture perceptions about nighttime sleep quality and daytime impairment or consequences of poor sleep, making them unique from each other and from the behavioural sleep diary previously measured.

(3) <u>Fatigue,</u> assessed by PROMIS fatigue (Cella et al., 2016). While fatigue may be related to sleep, it is a distinct construct and women may experience high fatigue despite sufficient sleep.

(4) <u>Mental health,</u> measured with PROMIS Depression and Anxiety (Pilkonis et al., 2011) symptoms. Although the intervention does not directly target mental health, previous studies (e.g., Blom, Jernelov, Kraepelien, et al, 2015) have shown that CBT for insomnia can be as effective at reducing depression symptoms as CBT for depression. Therefore, we also assess depression and anxiety symptoms using PROMIS short form measures.

Other Factors

(1) <u>Demographics,</u> will be collected via self-report at study entry with participants' consent. These will include: age, marital/co-habiting status, number of children living at home and employment.

(2) <u>Medical variables,</u> will be collected via self-report and extraction from medical records and pathology reports at T1, T2 and T3. These will include: Cancer stage, surgery type, treatment type e.g. chemotherapy or radiotherapy, treatment duration, medical comorbidities and body mass index (BMI).

(3) <u>Current medications and supplements</u>, will be collected via self-report based on recommendations from the Peter MacCallum Pharmacy Department that medical records may not reliably include a comprehensive list of both medication and supplement use. Women will be asked to write in the name, dosage, indication, and start/stop (where applicable) dates for each medication or supplement they are currently taking. This information will be used as potential covariates (e.g., women on sleep medication or mood medications may benefit less from the intervention).

Treatment Moderators

(1) <u>Pain,</u> assessed using the PROMIS pain intensity (Amtmann et al., 2010);

(2) <u>Patients' perceived credibility and expectancy of treatment</u> via the Credibility Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000);

(3) <u>Chronotype</u> via the Reduced Morningness Eveningness Questionnaire (rMEQ; Adan & Almirall, 1991);

(4) <u>CBT-I intervention adherence</u> (assessing frequency of use and usefulness of each intervention component); and

(5) <u>Light therapy adherence</u>, via a daily diary of light usage.

Treatment Mechanisms or Mediators

(1) <u>Beliefs and attitudes about sleep</u> with the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16; Morin, Vallières, & Ivers, 2007);

(2) <u>Vulnerability to insomnia under stress</u> using the Ford Insomnia Response to Stress Test (FIRST; Drake, Richardson, & Roehrs, 2004);

(3) <u>Pre-sleep arousal</u> with the Pre Sleep Arousal Scale (Nicassio, Mendlowitz, et al, 1985);

(4) <u>Intrusive thoughts</u> with the intrusive thoughts subscale from the Impact of Event Scale (Horowitz, Wilner, & Alvarez, 1979).

Data storage and confidentiality

All participants will receive a random identification number which will be used to link data from the different assessments. All direct identifiers (e.g., name, address, telephone numbers) will be stored in a separate file on computers using strong passwords. Where possible, this ID number will be used in place of personally identifying information. Survey data will be collected and stored on Qualtrics, with which Monash has a licensing agreement and data access will be secured by strong passwords.

Statistical Analysis Plan

A detailed Statistical Analysis Plan will be written and pre-registered with the clinical trial.

Sample Size and Power

Based on previous studies of CBT for insomnia (CBT-I) in cancer patients and bright white light (BWL; see **Table 3**), we expected a moderate to large effect size for the primary outcomes. We are using internet CBT combined with BWL, which each operate on different mechanisms. CBT targets behavioural and cognitive processes and BWL targets circadian processes. Given our combination of CBT + BWL and their different mechanisms of change, we expected larger effects than shown in previous studies utilizing only CBT or BWL. Specifically, we expected a standardized mean difference of d = 0.70, corresponding to a medium-to-large between-group effect at the post-treatment assessment.

Table 3. Table of Results for Power Analysis

Note. CBT-I = cognitive behavior therapy for insomnia; d = Cohen's d effect size; η^2 = eqa-squared effect size.

Citation	Treatment	Outcome / Effect Size / Required Total N
Johnson et al 2016	Meta-analysis of CBT-I	Insomnia Severity Index / d = 0.77 / N = 56 Sleep Efficiency / d = .53 / N = 114
Dozeman et al 2017	Internet CBT-I	Insomnia Severity Index / d = 1.33 / N = 20
Zacharie et al 2018	Internet CBT-I	Insomnia Severity Index / d = 1.17 / N = 26 Sleep Efficiency / d = .80 / N = 52 Fatigue / d = .42 / N = 180
Espie et al 2008	CBT-I	Fatigue Interference / d = .82 / N = 52
Wu et al 2018	BWL	Sleep Efficiency / η^2 = .28 / N = 12 Total Sleep Time / η^2 = .16 / N = 20
Johnson et al 2017	BWL	Fatigue / Within η^2 = .054 / N = 72 Fatigue / Between d = .30 / N = 352

Power analyses based on t-tests showed that 35 women in each condition will provide >80% power to detect a standardized mean difference of 0.70 at post treatment. Assuming that 85% of women randomized complete the post-treatment assessment, 40 women need to be randomized to each group to obtain a final post-treatment sample size of 35 per group.

Based on common chemotherapy rates, non-English speaking, and other exclusion criteria, we estimate that approximately 45% of women diagnosed with BC will not meet eligibility criteria. Based on adoption rates in previous CBT-I trials, of eligible women, we estimate that approximately 40% will decline. Therefore, to randomize 80 women, we expect to assess approximately 200 women for eligibility and possible inclusion. Estimated participant flow is shown in Figure 1.

Analysis Principles

All analyses will be conducted on an intention-to-treat basis. Results for all randomized women will be analysed in the group to which they were assigned regardless of protocol violations. The only exception will be women where consent to use their data in the analysis is withheld or withdrawn. All tests are two-sided, and the nominal level of α will be 5%. All statistical analyses will be unadjusted except where indicated.

Definition of Primary Outcomes

The primary outcomes for this study are the Insomnia Severity Index (ISI) and self-reported Sleep Efficiency (SE_s). The ISI is calculated as the average of 7, self-report items on insomnia symptoms. SEs is based on the ratio of self-reported total sleep time to time in bed and is expressed as a percentage.

Definition of Secondary Outcomes

Secondary outcomes include behavioural sleep measures derived from self-report and actigraphy: minutes to fall asleep (sleep onset latency; SOL), minutes spent awake after sleep onset (wake after sleep onset; WASO), and sleep duration (total sleep time; TST). Two additional sleep secondary outcomes are perceived night time difficulties (average of 8 self-rated items from the PROMIS Sleep Disturbance short form) and day time impairment due to poor sleep (average of 8 self-rated items from the PROMIS Sleep Related Impairment short form). Three other distinct, but relevant quality of life measures capturing symptoms of fatigue, depression, and anxiety also will be included as secondary outcomes. Each of these will be measured as the average of 8 self-rated items and each are based on short form PROMIS measures.

Definition of Moderators

Potential moderators of treatment efficacy will be examined. Pain is a common symptom yet women with high pain may not experience an improvement in their sleep in the intervention arm, so pain will be assessed as one potential moderator, measured as the average of 3 self-rated items from the PROMIS pain intensity short form. Treatment expectancies may impact how much women engage and the benefit they derive from the intervention. Expectancies will be evaluated as a moderator and assessed using the 6-item Credibility Expectancy Questionnaire. Chronotype may moderate treatment efficacy with later chronotypes potentially having a more difficult time benefitting from the intervention. Chronotype preference will be assessed using 5 self-rated items in the reduced Morningness and Eveningness Questionnaire. Finally, treatment adherence is a well-known moderator of efficacy and will be captured by measures of adherence to the CBT (assessed at treatment midpoint and end of treatment) and bright light (assessed as the number of minutes women wore the light glasses each day).

Definition of Mechanisms

Potential mechanisms of treatment efficacy will be examined using mediation analysis. Dysfunctional sleep beliefs and arousal are thought to contribute to symptoms of sleep disturbance and will each be measured using the average of 16 self-rated items from the Dysfunctional Beliefs and Attitudes about Sleep Scale and Pre-sleep Arousal Scale. In addition, the 9-item Ford Insomnia Response to Stress Test and 8-item Intrusive Thoughts

subscale of the Impact of Events Scale will be utilized to capture sleep impairment in response to stress and high arousal thoughts.

Statistical Analyses

Sample Profile

Statistical analyses will be conducted in R (data management, graphs, preliminary analyses) and MPlus. As a preliminary step, data will be assessed for outliers and skew and, where appropriate, transformed or winsorized. Prior to primary analyses, we will produce a thorough descriptive profile of the sample, characterize dropout and missing data. If more than 5% of data are missing on predictors, missing data will be addressed by multiple imputation using non-parametric, random forest models, which allow unknown interactions and non-linear effects. The psychometric properties of scales at each assessment wave will be assessed for reliability and if < .80, primary analyses will adjust for measurement error.

Baseline Comparisons

Participant characteristics at baseline will be presented by treatment group and statistical tests conducted to verify that randomization was successful. Discrete variables will be summarized by frequencies and percentages and baseline group differences tested using chi-square tests. Continuous variables will be summarized using mean (SD) or median (IQR) and baseline group differences tested using independent t-tests or Wilcoxon signed-rank tests for variables that evidence non normal distributions. If there are significant differences in any participant characteristics at baseline, the variable(s) will be included as covariates in final analyses.

Aim 1

Test the efficacy of cognitive behavioural and bright light therapy (CBT+) compared to relaxation audio for improving symptoms of sleep disturbance. Aim 1 will be tested using latent growth models. Latent growth models (LGMs) will be estimated with an intercept and two, linear slopes, representing a piecewise model. Slope 1 will have loadings constrained to 0, 0.5, 1.0, and 1.0 for times t0, t1, t2, and t3, respectively, capturing the linear change from baseline (t0) to post intervention (t2). Slope 2 will have loadings constrained to 0, 0, 0, and 1.0 for times t0, t1, t2, and t3, respectively, allowing a different slope from from post intervention (t2) to follow-up (t3) compared to from baseline to post. The means and variances of the intercept and slope factors will be freely estimated (corresponding to random effects in linear mixed models) and the intercept and slope covariances will be estimated. The residual variance will be constrained to equality across time and residuals assumed uncorrelated, corresponding to an independent, homogenous residual structure. Intercepts of indicators will be constrained to 0 to allow estimation of the latent random intercept mean.

There are two stratification factors: screening ISI ($\leq 7, \geq 8$) and cancer stage ($\leq 2, \geq 3$). These factors will be crossed creating four groups: Early Stage, Low ISI; Advanced Stage, Low ISI; Early Stage, High ISI; and Advanced Stage, High ISI. Dummy codes will be created for each strata, with Early Stage, Low ISI treated as the reference group. These dummy codes will be included as covariates to adjust for their effect on the random intercept, following recommendations that stratification factors be adjusted for in analyses of randomised controlled trials (Kahan & Morris, 2011; Kahan & Morris, 2012).

Treatment effects will be evaluated by creating a dummy code (0 = TAU+, 1 = CBT+). This dummy code will be entered as a predictor of the intercept, Slope 1, and Slope 2. However, treatment factors will be constrained to 0 for the intercept, to implement so-called "constrained longitudinal data analysis" (Coffman, Edelman, Woolson, 2016; Twisk, Bosman, Hoekstra, et al, 2018), which studies show provides a more accurate estimate of treatment effects from randomised controlled trials with repeated measures.

The primary trial results will be the effect of treatment on Slope 1 (i.e., from baseline to post-treatment). This interaction directly tests whether the change in primary outcomes over time is different in the control and intervention arm. Effect sizes of the group difference at each time point also will be calculated.

A similar process will be followed for sleep efficiency, however a continuous time model will be estimated using a mixed effects model in Mplus because up to 42 days of sleep efficiency are collected. Sleep efficiency may not follow a normal distribution. If the assumption of normality is violated, significance tests and confidence intervals will be based on non-parametric bootstrapping.

Aim 2

Test the efficacy of CBT+ versus relaxation audio for psychological outcomes. Aim 2 will be tested identically to Aim 1, but using psychological outcomes in place of the sleep and fatigue outcomes

Aim 3

To explore potential mechanisms of CBT+ and moderators of the intervention efficacy. Mechanisms will be tested using mediation conducted in path analyses. Specifically, we will examine the effect of condition on change in mechanisms from baseline to treatment mid-point, and test whether the change in mechanisms from baseline to treatment mid-point accounts for the condition effects on change in outcomes from baseline to post-treatment and follow-up. Statistical mediation will be determined by evaluating the indirect effects, calculated as the product of the paths from condition to change in mechanisms and from change in mechanisms to change in outcomes. Bootstrapping will be used to estimate the confidence interval for indirect effects and their statistical significance. Given the modest sample size, analyses will be conducted for each mechanism and outcome individually.

Treatment moderators will be evaluated by modifying the primary analyses from Aims 1 and 2 to include interactions: condition (TAU+, CBT+) x moderator, along with all lower order effects on Slope 1 and Slope 2. Individual moderators will be tested in separate models.

Human Subjects Research

We will not enroll women who are unable to consent to or complete the study (e.g., life expectancy less than 6 months, imminent plans to move out of the area, severe psychosis). Eligible women will have the study procedures and interventions explained and all questions answered fully.

Sources of research material will include data normally contained within the participant's medical record and responses to self-report surveys. Only the investigators, research staff, and the intervention team will have access to individually identifiable private information. The intervention team must be able to access participants by telephone to provide the intervention. Research staff must be able to telephone participants for scheduling.

Potential Risks

Potential risks associated with study participation include the loss of confidentiality, privacy, fatigue from completing assessments, and light-related headaches. The most likely risk associated with this study is experiencing headaches related to the bright light therapy. It is remotely possible that participants may feel psychological distress during the intervention or collection of data, but we have not seen this in our prior studies. Women will be reminded that they can stop the intervention at any time or not complete any of the assessments that they do not wish to. No other physical, financial, legal, or other risks have been identified.

We do not foresee any study-related serious adverse events. However, all serious and non-serious adverse events will be reported to the PIs and forwarded to the human research ethics committees within 72 hours of notification. Any adverse events will be reviewed quarterly for trends.

Adequacy of Protection against Risks

Recruitment and Consent

Research or clinic staff will introduce the study to women, offering the opportunity to participate to all eligible patients identified. Women will be informed about the two conditions (treatment as usual; CBT+) and that they will be randomly assigned to participate in one or the other. All participants will provide written, informed consent.

Protection against Risk

Coding all participant data with a unique identification number will minimize the risk of loss of confidentiality. The only dataset with participant identifier information will be the participant tracking system used to follow-up and contact women. All other datasets will label participant records with a unique study number and be stripped of other identifying information; specifically, clinical data will not reside with identifying data. Survey data will be kept in locked files or password-protected data files. All results will be described in aggregate without identification of individual women. All publications arising from this study will maintain the anonymity of study participants. Thus, the risk of loss of confidentiality is judged to be unlikely. If it does occur, the data collected will not be of the type to jeopardize participants, so the risk is not judged to be a serious one.

Potential Benefits of the Proposed Research

Participants of the proposed research may experience the following benefits from the sleep intervention: improved sleep quality, reduced sleep disturbance and sleep related impairment, reduced day time fatigue and improved mood and wellbeing. Based on previous findings, it is expected that participants will experience alerting effects, reduced fatigue and reduced chemotherapy related disruption to circadian rhythms through using the light glasses. It is hoped that the sleep strategies learned through this program may be of ongoing benefit to participants as they progress through their BC trajectory. Should the intervention be successful, it may be tested in a larger trial, offering potential benefits to more participants in the future. It is anticipated that the information gathered from this study and any consequent studies will be used to improve the way women are supported whilst undergoing chemotherapy and living with breast cancer.

Trial Governance

Governance and oversight of the trial will be by two committees, the Steering Committee and Data and Safety Monitoring Board (DSMB). Any problems and issues related to day-to-day management of the study and operations will be overseen and addressed by associate investigators Bean and Wiley.

Steering Committee

The Steering Committee will be composed of all study investigators and a consumer representative, Mrs. Kate Smith. This committee will be co-chaired by associate investigators Bean and Wiley, and it will serve as the primary decision-making body for the clinical trial. The committee will be responsible for execution of the study and its accurate conduct. The committee will convene monthly by conference call. In addition to any special topics, standard agenda items will include:

1. Enrolment data

2. Any protocol issues

3. Safety and adverse event data

All steering committee meetings will be recorded and these audio recordings will be stored for record keeping and be available to the full steering committee for reference. Written minutes will be distributed to the steering committee via email following meetings.

Data Safety and Monitoring Board

The Data Safety and Monitoring Board (DSMB) will be responsible for monitoring participant safety, data quality, and implementation of the protocol. The DSMB will be comprised of two study investigators, an independent member Dr. Johanna Czamanski-Cohen, and a consumer representative, Mrs. Kate Smith. The DSMB will be chaired by its independent member, Dr. Czamanski-Cohen. In the event that the DSMB cannot reach consensus regarding any safety concerns, the chair's recommendation will be final.

All participants will be monitored routinely for the occurrence of events defined as any undesirable experience or unanticipated benefit during face to face meetings, and brief phone calls with the study staff at mid-point and post-intervention. At each assessment, we will examine sleep and mental health symptoms. If any women report severe symptoms of sleep disturbance (ISI > 22) depression or anxiety (PROMIS Depression > 27; PROMIS Anxiety > 27), we will inform their clinical team and recommend that they seek a referral to a sleep specialist or clinical psychologist. Any women with previously undiagnosed severe psychiatric conditions identified during screening will also be informed and recommended to seek a referral to psychiatry or clinical psychology. Further details are outlined below in the *Brief procedure for managing project risks and participant safety*. Further, a description of all events occurring in the control or intervention arms will be recorded on case report forms. In the intervention arm, the relationship of the intervention to the event will be classified as not related, remote, possible, probable, or highly probable and the severity of an adverse event as mild, moderate, or severe. Any serious adverse events will be immediately forwarded upon identification to the DSMB, associate investigator Bean, and associate investigator Wiley. Any serious adverse events judged related to the intervention will also be

reported to the Peter MacCallum Cancer Centre human research ethics committee. Non-serious events will be reported to the DSMB via a monthly email report.

Associate investigators Bean and Wiley will support the DSMB by sending monthly reports and scheduling quarterly calls using the Zoom platform, which will allow DSMB members to call into a conference line (including local numbers for international members) or to join calls via the computer. Monthly reports will be emailed to all members of the DSMB and will include at a minimum:

1. Update on the status of the study, recruitment, and accrual

2. Summary of baseline data by randomized condition

3. A summary of study completion, missing data, and any dropout

4. Summary of any adverse events (note: serious adverse events will be sent immediately upon identification)

5. A summary of primary outcome measures

The DSMB may also request any additional information they believe is needed to monitor data quality and safety of the trial. Any requested information will be included in the next monthly report. All DSMB meetings will be recorded and these audio recordings will be stored for record keeping and be available to the DSMB and steering committee for reference.

Adverse Event Reporting

A description of all undesirable and unanticipated events during the intervention phase (adverse events) will be recorded on Qualtrics. Adverse events will be collected from any ad hoc reporting, and during the mid-treatment phone call, and during a brief phone at the end of the intervention by one of the study staff. During calls, participants will be asked if they have experienced any change in health conditions, new or worsening of symptom severity, or other unexpected events. After the implementation of study protocols, the relationship of the study protocol to the event will be classified as follows:

- **Not related**: The event is clearly related to factors such as the participant's clinical state, not with therapeutic interventions associated with the study protocol.
- **Remote**: The event was most likely related to factors such as the participant's clinical state, not with therapeutic interventions associated with the study protocol.
- **Possible**: The event follows a reasonable temporal sequence from initiation of the intervention and/or is consistent with known events related to intervention components but is possibly related to factors such as the participant's clinical state.
- **Probable**: The event follows a reasonable temporal sequence from initiation of the intervention and/or is consistent with known events related to intervention components and cannot be reasonably explained by factors such as the participant's clinical state.
- **Highly Probable**: The event follows a reasonable temporal sequence from initiation of the intervention and/or is consistent with known events related to intervention components and cannot be reasonably explained by factors such as the participant's

clinical state. In addition, the event occurs immediately following a clinical intervention or is consistent with known events related to intervention components.

The severity of an adverse event in both groups is defined as a qualitative assessment of the degree of intensity of an adverse event as determined as follows:

- **Mild**: Does not impact (in any way) the participant's course of illness.
- **Moderate**: Impacts the participant's course of illness but is not life-threatening or incapacitating.
- **Severe**: Fatal, life threatening, permanently disabling; severely incapacitating; requires/prolongs inpatient hospitalization.

Brief Procedure for Managing Project Risks and Participant Safety

Initial screening questionnaires and follow-up questionnaires administered throughout the study include questions about sleep disorders, as well as current and past mental health. Face to face and telephone contact with participants may also include discussion around sleep and mental health concerns. When physical or mental health concerns arise, the following procedures will be undertaken to ensure appropriate care and safety of participants:

- Recruitment, screening and intervention components of the study will be administered only by the study coordinator (SC).

- Informed consent will be obtained prior to administration of any questionnaires.

- All screening questionnaires will be administered by the SC in the PMCC chemotherapy day unit. The SC will read through each question with the participant and address any questions or concerns as they arise. The SC will allow enough time for questionnaire completion, so the participant does not feel rushed.

- All other questionnaires will be completed by the participant at home. The participant has access to a study contact number and can contact the SC if they require assistance or have any queries/ concerns.

Identification of sleep disorders:

- During screening for eligibility, participants will be screened on site at PMCC for the following sleep disorders: restless leg syndrome, sleep apnoea, advanced or delayed circadian phase. The Study coordinator will also monitor online survey responses through the four time-points (baseline, midpoint, endpoint and three-month follow-up) to identify severe symptoms of sleep disturbance (ISI > 22).

- If sleep disorders are identified, participants will be encouraged to discuss results and referral options with their oncologist or GP if necessary.
- The participants' PMCC medical team, and the study PI, will be notified by email (participant will be made aware of this), and a Verdi note will be made on the participant's medical file.

Identification of physical health concerns:
- In the event that participants report any physical problems to members of the research team (such as: worsening of cancer treatment side effects, pain), the Study coordinator will speak to the participant to discuss and clarify their concerns and whether the participant would like to / is able to continue study participation.
- The participants' PMCC medical team, and the study PI, will be notified by email (participant will be made aware of this), and a Verdi note will be made on the participant's medical file. The relevant medical consultant can then take what they consider the necessary course of action, if any.
- In the event that a participant decides to withdraw from study participation, all study investigators and the participant's medical oncologist will be notified by email.

Identification of mental health concerns:

<u>When psychiatric disorder identified during screening:</u>

Any women with psychiatric condition/s identified during screening will have their screening results discussed with them. Options available to the participant will be discussed including:
- That they discuss their concerns with their medical oncology team (doctor, nurse) and seek input/advice/ referral to appropriate services.
- Informing the patient of the PMCC Psychosocial Oncology (POP) service, and options of self-referral (by calling 8559 5265).
- Options of direct referral by the SC to PMCC Psychosocial Oncology (POP) services when deemed appropriate, for intake of their needs. (See attached POP Triage Protocol document).
- That they discuss their concerns with their GP.

- The Study coordinator will email the participant's treating team (medical oncologist and nurse coordinator), and the study PI, regarding symptoms disclosed and outcomes. The Study coordinator will document outcomes in Verdi. The relevant medical consultant can then take what they consider the necessary course of action.

<u>Identification of mental health issues during other time points in the study:</u>

Participants may disclose distress or other mental health concerns during their face-to-face appointment, their 30-minute mid-point phone call, during completion of survey responses or telephone administration of surveys.

- In all these situations, the Study coordinator will discuss the reported distress with the participant and follow appropriate steps as outlined above (informing the treating team, and documentation in Verdi).

<u>When immediate action is required:</u>

If there is any indication of thoughts of suicidal ideation, risk or harm to self or others, the Study coordinator will take the following steps.

- When on site : call / page the Psychosocial Oncology PCLN/ intake worker, requesting urgent and immediate (same-day, as soon as possible) assessment of the participant on the CDU. PI Justine Diggens or Investigator Dr Maria Ftanou will also be notified. The participant's case will then be managed as required by the psychosocial oncology service, and this will be documented accordingly on participant's medical file by the attending member of the POP team.

- During phone contact: the Study coordinator will encourage the participant to seek additional supports/assistance (e.g., calling Lifeline, calling an ambulance, attending the Emergency Dept) and the Study coordinator will immediately contact the PI or alternative Investigators for consultation. Referral to PMCC POP services may be initiated as above.

Proposed timeline of the study

Tasks to be completed	2018			2019		
	Apr.-Jun.	Jul.-Sep.	Oct.-Dec.	Jan.-Mar.	Apr.-Jun.	Jul.-Sep.
Ethics application and approval	▓					
Recruitment and intervention	▓	▓	▓	▓		
Intervention and follow-up measures		▓	▓	▓	▓	
Data cleaning and management		▓	▓	▓	▓	
Manuscript preparation: Writing of introduction + methods			▓	▓	▓	
Data analysis					▓	▓
Manuscript preparation: Writing of results + discussion					▓	▓

Dissemination Plan

The results of this trial will be important to disseminate. In the final stages of data collection, the Steering Committee will develop a strategic plan for presentation and publication of trial results. All investigators will be included as authors on the primary manuscript detailing results of the trial on the primary outcomes. As this project represents Helena Bean's doctoral dissertation, Helena will be the first author on manuscripts and abstracts testing the primary aims and hypotheses of this study. Other publications resulting from the collaborative work will include at least a subset of the key collaborators. The investigator team also will plan additional topics, authorship and timing for abstracts and conference presentations, as well as review and approve additional manuscript plans not covered in the primary study aims. A copy of all abstracts or manuscripts will be sent to relevant study personnel for evaluation and approval prior to submission or publication. We anticipate secondary publications in sleep and behavioral medicine journals. Final data sets and statistical analyses will be archived for safe-keeping.

Dissemination will begin after the intervention periods have been completed and primary results analyzed. Primary modes of dissemination will be:

- **Internet communication for press releases from Monash University**;

- **Peer-reviewed, scientific publications** (e.g., submitted to *Sleep*, *Journal of Consulting and Clinical Psychology*, *Journal of Clinical Sleep Medicine*, or *Psycho-Oncology*);

- **National and international conferences** (e.g., *SLEEP*, the annual meeting of the Associated Professional Sleep Societies; *Sleep Down Under*, the annual meeting of the Australasian Sleep Association; *COSA*, the Clinical Oncology Society of Australia Annual Scientific Meeting; and *APS*, the annual meeting of the American Psychosomatic Society).

Paper 1: Trial Protocol & Lessons Learned

The first paper will be submitted to a journal that publishes trial protocols, such as *Trials*. This paper will detail the trial design, rationale, and summarize any lessons learnt around recruitment and adherence. The full study team will be authors on this paper.

Paper 2: Treatment Efficacy on Primary and Secondary Outcomes

This paper will report the primary efficacy outcomes. It will focus on the group differences over time between women randomized to CBT+ vs Relaxation Audio and the results on primary and secondary outcomes at post-treatment and whether these effects are sustained at the three-month follow-up. The full study team will be authors on this paper.

Paper 3: Treatment Moderators and Mechanisms

This paper will report whether intervention effects are moderated by the proposed moderators and also examine whether the proposed mechanisms significantly mediate the treatment effects on study outcomes. Authorship will be based on interest and contribution.

<center>**Data Sharing Plan**</center>

Data Availability

Data will be available publicly five years after completion of data collection.

Data File Formats

Data will be available in as a compressed R data file (.RDS) and as a comma separated values file (.CSV). These formats were selected as R is a free and open source software package for data analysis that is widely available. A number of variables, such as dates and times, can be formally marked as date/time variables in R datasets. CSV was chosen as an additional format as it is a plain text format and is widely accessible across many platforms and programs. Including both formats should ensure that everyone is able to access the data in some format.

Transformations for Preservation and Data Sharing

Prior to sharing, data will be de-identified, including procedures the following procedures, at a minimum:

Removing original ID variables, email addresses, and any other names or contact details. Original ID variables will be replaced with a new, random, ID. Converting date of birth to age categories and removing all date of birth data. Careful assessment of all other variables to evaluate whether any other data may reasonably be sensitive or allow individual identification. Any such variables will be re-coded (e.g., top or bottom coded, categories collapsed to, etc.).

Metadata and Documentation

A codebook describing the raw data will be available alongside the data. If resources permit, created variables (e.g., scale scores) will also be included in the data and documented, along with basic descriptive statistics and psychometric results. If resources permit, documentation will follow the Data Documentation Initiative standard.

Data-Sharing Agreement

No data-sharing agreement will be required once the data are publicly released. We do request that anyone who uses the data acknowledge the source (e.g., by citing original articles).

Data Access

Five years after completion of the study (data collection), the data and documentation will be shared publicly via Monash Figshare (currently located at: https://monash.figshare.com/).

Additional data sharing requirements

None.

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