SLEEPCARE TRIAL PROTOCOL

Scientific Title:

A Randomised, Controlled, 6-week, Parallel-group, Superiority Trial to Compare the Efficacy of Sleep Hygiene, Cognitive Behavioural Therapy, Bright Light Therapy and Their Combination on Insomnia Symptoms during Chemotherapy for Cancer: The **Sleep**, **C**ancer **a**nd **Re**st (**SleepCare**) Trial

Plain Title:

The **Sleep**, **C**ancer **a**nd **Re**st (**SleepCare**) Trial: A Randomised, Controlled Trial of Four Treatments for Sleep during Chemotherapy

ANZCTR.org.au: ACTRN12620001133921

Issue Date: 2020-06-11

Protocol Amendment Number: 08

Revision Chronology:

Date	Notes
2019-09-25	Original
2019-11-11	Amendment Number 2: At the request of the CRC the following amendments were made: • Addition of trial statistician on protocol document. • Participant inclusion criteria were restricted to a) participants undergoing chemotherapy; and b) breast and colorectal cancer diagnosis. • Revised power analysis and sample size increased. • Rationale for inclusion of participants with 'no clinically significant insomnia' provided. • Revision of primary and secondary outcome measures. • Methods of assessing fidelity and adverse event monitoring clarified. • Explanation regarding the feasibility of recruitment. • Revision of randomisation and stratification procedures. • Contrasts of baseline characteristics excluded. • A priori covariates for sensitivity analysis introduced. • Added PoCoG supported status.
2019-12-10	Amendment Number 3: In response to feedback from the Peter MacCallum Cancer Centre clinical research committee, the following amendments were made: • Clarified inclusion and exclusion criteria including further justification

	• Added more details on the assessment and planned statistical adjustments for medical and treatment related factors, including a priori covariates in Table 5 and Appendix H – Medical Record Extraction, a list of planned medical record variables to extract
2020-06-30	Amendment Number 4: • Added Monash Health as additional site including additional investigators • Added support from successful grant funding for a health economics add on including additional investigator ○ Elevated health-related quality of life to a secondary outcome to support health economic analyses • Revised to focus only on women with breast cancer • Revised inclusion and exclusion criteria to reduce heterogeneity in the sample and exclude factors that may impact trial outcomes • Added additional follow-up timepoint and one-week pre-treatment sleep diary completion • Added Glasgow Sleep Effort Scale
2020-08-26	Amendment Number 5: • Inclusion of telephone alternative for initial consultation (i.e.,face-to-face session) as well as recruitment, consent and screening procedures. • Risk management protocol amended to include off-site procedures.
2020-10-19	Amendment Number 6: • Inclusion of telehealth alternative for initial consultation. Specifically, use of virtual consultation platforms (e.g., health direct).
2020-11-18	Amendment Number 7: • Inclusion of study flyer/information video sent via email or post, to aide telehealth recruitment and minimise face-to-face contact. • Changed PeterMac site PI to Dr. Ftanou as Ms Diggens will be on secondment to the Alfred the next 9 months.
2020-06-11	Amendment Number 8: • Inclusion of introductory text message to aide telehealth recruitment and minimise face-to-face. • Addition of Associate Investigator Ms Jeanette Wong to support scoring and processing of actigraphy files under supervision of Dr Wiley.

Coordinating Principal Investigator:
Dr Joshua F. Wiley, Monash University

Peter MacCallum Cancer Centre Site Principal Investigator:
Dr Maria Ftanou, Peter MacCallum Cancer Centre

Monash Health Site Principal Investigator:
Dr. Daphne Day, Monash University and Monash Health

Study Coordinator and Student Investigator:
Mr Jordan Maccora

Trial Statistician
Dr Bei Bei, Monash University

Associate Investigators: (alphabetical by last name)
Dr Marliese Alexander, Peter MacCallum Cancer Centre and The Sir Peter MacCallum Department of Oncology, The University of Melbourne
Ms Justine Diggens, Peter MacCallum Cancer Centre
A/Prof Prudence A. Francis, Peter MacCallum Cancer Centre
Dr. Sheila Garland, Memorial University
A/Prof Duncan Mortimer, Monash University
Dr. Andrew J. K. Phillips, Monash University
Dr. Lesley Stafford, Royal Women's Hospital
Dr. Michelle White, Monash University and Monash Health
Ms Jeanette Wong, Monash University

Authors' contributions:
JFW and JM conceived of the study. All investigators contributed to the trial design and procedures. DD, PF, MW provided medical clinical expertise and oversight. BB, JD, MF, SG provided clinical psychology expertise and oversight for the intervention. JD, MA, DD, PF, and MW helped with implementation. JFW is a grant holder. AJKP provided expertise in circadian rhythms and modelling. DM provided expertise in health economic analysis and collection of health service utilisation data. BB oversaw randomisation and primary analyses.

MA provided input on collection and analysis of medication data. All investigators contributed to refinement of the trial design and protocol.

All investigators form the trial committee and are responsible for agreement of final protocol. All named investigators have had an opportunity to review and comment on the protocol.

Trial Sponsor: Monash University
Contact name: Ms. Halina Oswald, Director, Monash Research Office
Address: Clayton Campus
Telephone: +61 3 9902 4427
Email: mro.director@monash.edu

Sources and types of financial, material, and other support:
The Turner Institute for Brain and Mental Health at Monash University provided internal grant funding and funding (through in-kind time) for planning and preparation costs as well as the intervention delivery costs. Light glasses for bright light therapy (Luminette®) were manufactured and provided by Lucimed SA. Wiley is supported by a National Health and Medical Research Council Investigator Grant (APP1178487), that is also supporting incidental trial costs.
No funding or material support source had any role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.
This trial is supported by the Australian Psycho-Oncology Co-operative Research Group, Supported trial number: PoCoG-2018-15.
Conflicts of Interest:
MA, BB, JM, JFW declare no conflicts of interest related to the SleepCare Trial.

Table of Contents

1 Background and Rationale

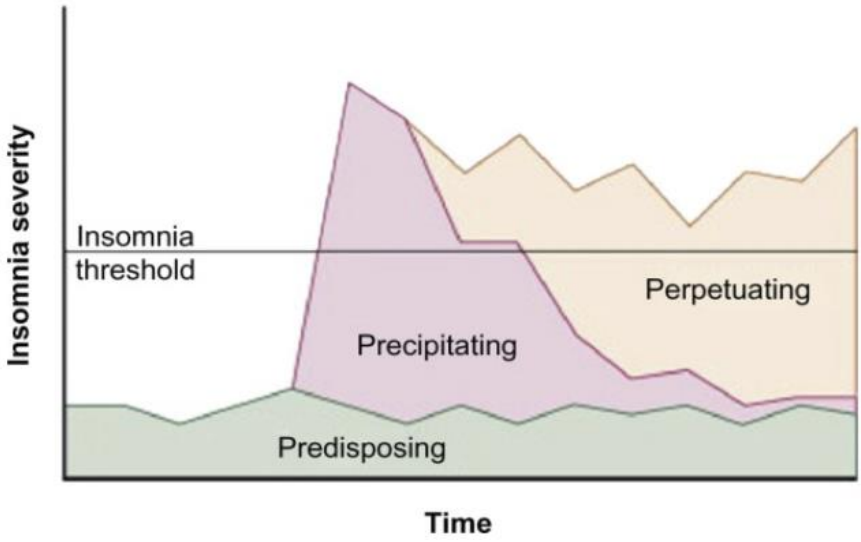
Insomnia symptoms represent a significant and widespread complaint among people with cancer, with approximately 30-60% of people with cancer reporting insomnia symptoms (Palesh et al., 2010; Savard, Ivers, Villa, Caplette-Gingras, & Morin, 2011). Further, although not achieving clinical significance, the proportion of people reporting subthreshold insomnia symptoms and associated deleterious daytime effects is even higher at up to 87% of cancer patients (Palesh et al., 2012).

Sleep disturbances in people with cancer are typically characterised by frequent night awakenings, variable sleep/wake times and recurrent daytime napping to compensate for sleep disruption (Palesh et al., 2010). Sleep disturbance is widely linked with a range of adverse consequences, including psychological and physical morbidity, and overall worse quality of life (Fortner, Stepanski, Wang, Kasprowicz, & Durrence, 2002; Otte et al., 2015). Within an oncology context, evidence suggests that sleep disturbance is associated with poorer outcomes in multiple health-related domains such as physical recovery, cancer outcomes, cognitive functioning, work productivity and interpersonal relationships (Caplette-Gingras, Savard, Savard, & Ivers, 2013; Cash et al., 2015; Filipski et al., 2003; K. S. Thomas, Bower, Hoyt, & Sepah, 2010). In addition to the substantial impact of sleep disturbance during cancer on physical and mental quality of life, important in their own right, poor sleep also is associated with a substantial economic burden (e.g. treatment costs; absenteeism). Despite its significance and pervasiveness, sleep disturbance among cancer patients is often unrecognised and inadequately managed (Kvale & Shuster, 2006).

Cancer-specific vulnerability to sleep disturbance has been attributed in part to disruption in biological (e.g., tumour growth, inflammation, pain), psychological (e.g., disease- and medical treatment-related stress and anxiety), and behavioural mechanisms (e.g., daytime sleeping, use of sleep medication) as well as environmental alterations (e.g., hospitalisations; Galiano-Castillo et al., 2017). Although these disturbances are characteristic of cancer itself, they are also exacerbated by its direct treatment, particularly chemotherapy (e.g., hot flashes, urinary incontinence, circadian disruption; Graci, 2005). The identification of etiological factors and their interactions within cancer-related sleep disturbance is an important consideration when evaluating appropriate interventions.

The Spielman model (Spielman, Caruso, & Glovinsky, 1987), is widely used to conceptualise the development and maintenance of insomnia. The theory describes three central tenets that underlay sleep disturbance trajectory: predisposing, precipitating and

perpetuating factors. Predisposing (innate vulnerability) and precipitating (acute stressors)



factors contribute to the occurrence of sleep disturbance, whereas perpetuating factors facilitate the development and maintenance of chronic symptoms even when the original stressor subsides (see Figure 1).

Figure 1. The Spielman model of insomnia (Derived from 'A behavioral perspective on insomnia treatment" by A. J. Spielman, L. Caruso, and P. Glovinsky). Precipitating factors such as medical treatment side effects or diagnosis-related stress may trigger cancer-related sleep disturbances, exceeding the insomnia threshold. During the acute phase of sleep disturbance, patients may develop unhelpful thoughts, beliefs, and behaviours about sleep. These factors may perpetuate insomnia symptoms even after the initial precipitator decreases.

With regards to people with cancer, receiving a diagnosis itself represents a significant, life threatening event which can be understood as a primary precipitating factor for sleep disturbance. Stress, depression and anxiety are also prominent psychological complaints following diagnosis (Palesh et al., 2007), all of which are highly correlated with poor sleep and insomnia symptoms (Garland et al., 2014). Multiple studies have linked anxiety and stress with sleep disturbance among people with cancer during both active medical treatment (Fleming, Randell, Harvey, & Espie, 2014; J. Savard, Simard, Ivers, & Morin, 2005), and survivorship (Bower, 2008). Additionally, common side effects of the cancer treatment procedures themselves contribute to the development of sleep disturbance. Literature suggests that chemotherapy elicits the greatest sleep impairments when compared to alternative medical treatment methods (Costa et al., 2014). For example, research has found that 40% of people receiving chemotherapy reported moderate to severe insomnia symptoms following their first chemotherapy treatment, with symptoms persisting throughout cycles in up to 70% of patients (Palesh et al., 2010). Chemotherapy effects are exacerbated

by its associated physical side effects including: nausea, vomiting, hot flashes, night sweats, diarrhoea, urinary frequency, pain, changes in body image and skin reactions, and greater risk of hospitalisation; all in which have well established roles in the disruption of sleep onset and maintenance (Galiano-Castillo et al., 2017). As such, people undergoing chemotherapy carry an enhanced vulnerability to sleep disturbance.

In response to these significant sleep disruptions, individuals may develop maladaptive behaviours and cognitions that serve as perpetuating factors. Often these responses are compensatory and appear adaptive in the short-term, particularly during illness, however, they may contribute to the development and maintenance of sleep disturbances in the long term. For instance, daytime napping and increased time spent in bed whilst awake may function to counteract the immediate effects of cancer-related sleep disruption and fatigue. When practiced regularly, however, these behaviours result in extended sleep opportunity and dysregulated sleep/wake cycles, challenging an individual's ability to achieve regular, consolidated and restorative sleep. Similarly, maladaptive cognitions that also develop in response to precipitating factors may maintain sleep disturbance. Erroneous and catastrophic thoughts related to sleep difficulties (e.g. "I will get more sick"; "I will never be able to sleep"; "I need 8 hours of sleep to function") can increase night-time arousal and in turn interfere with an individual's ability to fall asleep. Together, maladaptive behaviours and cognitions can develop early, and without intervention, perpetuate sleep disturbance after the initial precipitating factors, such as diagnosis and cancer treatment side effects, have largely remitted.

Consistent with the Spielman model, research has demonstrated that sleep disturbances are evident following a cancer diagnosis and prior to cancer treatment initiation (Ancoli-Israel et al., 2006). Sleep disturbance typically achieves peak prevalence during chemotherapy (>2/3 of patients), however, commonly persists in the long-term following treatment cessation (Palesh et al., 2012; Palesh et al., 2010). As such, vulnerability is evident at diagnosis and likely increases across cancer treatment trajectory. This can be understood within the context of developing maladaptive behaviours and cognitions, which in themselves, represent a significant precipitating and perpetuating factor in the development of more severe and chronic sleep disorders (Spielman et al., 1987). Thus, in the absence of adequate management, sleep disruption and insomnia can become chronic, leading to decreased quality of life, contributing to the development of psychological disorders, and may even increase risk of tumour progression and disease recurrence (Ancoli-Israel, 2009;

Cash et al., 2015). Given the implications if left untreated, the need for early intervention on sleep within routine cancer care is critical.

As many exogenous factors (precipitating factors; i.e. chemotherapy, hospitalisations) that disrupt sleep during cancer trajectory are necessary, interventions must focus on sleep-related factors that are amenable to change (i.e., the perpetuating factors). Therefore, theoretically sound therapeutic targets for early intervention are (a) maladaptive sleep-related cognitions, and (b) maladaptive sleep-related behaviours, with interventions aimed at establishing adaptive coping strategies to counteract the development, severity and persistence of symptoms.

A clear strategy for treating sleep disorders within standard oncology care is the development of accessible interventions that target factors underlying sleep disruption (Palesh et al., 2018). Cognitive behavioural therapy for insomnia (CBT) is considered the gold standard, non-pharmacological intervention for treating insomnia in a wide range of clinical populations, including cancer patients with insomnia (Johnson et al., 2016). CBT is a short term, multi-component intervention that addresses dysfunctional cognitions and behaviours surrounding sleep through behavioural recommendations, relaxation techniques and the reframing of maladaptive beliefs. Specifically, CBT comprises components of sleep restriction (i.e., consolidating periods of sleep), stimulus control (i.e., strengthening the association between bed and sleep) and cognitive restructuring (i.e., addressing dysfunctional thoughts). In addition to improving night-related sleep disturbance, CBT targets the daytime consequences of insomnia such as fatigue, which is reported by up to 60% of cancer patients (Ancoli-Israel et al., 2006).

The standard delivery format of CBT has reliably demonstrated effectiveness in treating insomnia and fatigue symptoms (See Okajima, Komada, & Inoue, 2011). CBT has proven comparable efficacy to sleep medication in the short-term and demonstrates superior outcomes with fewer side effects than medication in the long-term (Morin et al., 2009). This is reflected in the therapeutic outcomes of CBT, with a large proportion of individuals demonstrating sleep-related improvements well after the discontinuation of formal intervention (Morin, Colecchi, Stone, Sood, & Brink, 1999). This illustrates the potential for CBT strategies to ameliorate the development and impact of sleep-related disturbance when delivered earlier in the cancer trajectory.

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 than insomnia without comorbidity (Edinger et al., 2009; Smith, Huang, & Manber, 2005).

Notably, CBT has resulted in statistical and clinical improvements in subjective sleep outcomes in mixed cancer populations within the survivorship period (Johnson et al., 2016). Despite this, its utility within an oncology setting is potentially limited as it is considered cumbersome, requiring face-to-face delivery over six-to-eight sessions, presenting logistical constraints related to associated costs, availability of qualified practitioners and the medical and symptom burden cancer patients already face (Thomas et al., 2016). As a result, the development and validation of internet-delivered and accessible cognitive behavioural treatment options have become a current focus for cancer-based sleep research. A novel approach of CBT delivered in a self-administered, resource-orientated format has shown promising outcomes, and are without the limitations stated above (Ritterband et al., 2012; J. Savard, Ivers, et al., 2011; Zachariae et al., 2018). For example, a nine-week internet-based CBT program in cancer survivors produced significant improvements in subjective sleep outcomes when compared against controls (Zachariae et al., 2018). Similarly, researchers have trialed a six-week reduced CBT intervention comprised of 60-minute videos and information booklets in women with breast cancer following primary medical treatment which resulted in clinically significant improvements in insomnia severity, sleep onset latency and sleep efficiency (J. Savard, Villa, Simard, Ivers, & Morin, 2011). These studies provide evidence for the potential efficacy of CBT in cancer patients, even when delivered in a reduced, more accessible format.

A major gap in the oncology literature is a lack of considerations of circadian factors in sleep and fatigue management. The circadian rhythm is controlled by an internal pacemaker within the suprachiasmatic nucleus (SCN) of the hypothalamus that oscillates around a near 24-hour period (Czeisler et al., 1999; Ralph, Foster, Davis, & Menaker, 1990). The generated circadian cycle modulates hour-to-hour alertness levels in a number of different neurobehavioural variables, via the production of sleep and wake-promoting signals (Rogers, Dorrian, & Dinges, 2003). The circadian regulation of sleep and wake is primarily dependent on light and dark exposure (Pail et al., 2011). Environmental light or darkness is signalled to the SCN through retinal ganglion cells via the optic nerve (Buijs & Kalsbeek, 2001) and synchronises the circadian rhythm to the external environment (Duffy & Czeisler, 2009).

Literature has implicated circadian rhythm disruption as a significant factor underlying sleep disturbance among cancer patients (Savvidis & Koutsilieris, 2012). Several studies have shown that people with breast cancer display more disrupted rest-activity rhythms compared to healthy controls, with regard to circadian rhythmicity and amplitude

(Chevalier, Mormont, Curé, & Chollet, 2003; Levin et al., 2005; Pati et al., 2007). Such disruptions have been linked to negative consequences such as increased depressive symptoms and poorer overall quality of life (Garland et al., 2014). Moreover, 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.

Aspects of cancer-related sleep patterns may significantly alter circadian functioning through inconsistent regularity in light/dark exposure throughout a 24-hour period, such as through irregular sleep/wake times, night-time awakenings and exposure to light, daytime napping, and potentially reduced daytime light exposure due to time spent indoors. Additionally, chemotherapy has been implicated as a key contributor to circadian disruption (Ancoli-Israel, 2009; Berger, Farr, Kuhn, Fischer, & Agrawal, 2007). Circadian rhythms have shown a dose-dependent relationship with chemotherapy, whereby, circadian processes progressively deteriorate following sequential cycles of chemotherapy. Specifically, research has found that following the fourth cycle of chemotherapy, no autonomous circadian rest-activity rhythm recovery is evident (J. Savard et al., 2009). These findings indicate that circadian disruption among oncology populations represents a significant clinical concern, that warrants specific research during key times, specifically chemotherapy.

Bright light therapy (BLT) is regarded as a cost-effective and accessible intervention in improving circadian disruption, fatigue and mood (Johnson et al., 2018; Wu et al., 2018). BLT works to re-align the circadian rhythm by regulating light exposure across its 24-hour cycle to restore regular sleep-wake periods. Specifically, bright light is administered in the morning immediately post-wake or around habitual wake time, typically via a specialised device, and avoided in the evening via behavioural strategies (e.g., no electronic use in bed; dimmed lights). Additionally, BLT has been shown to improve mood and fatigue symptoms (Golden et al., 2005; van Maanen, Meijer, van der Heijden, & Oort, 2016). As a result, BLT may provide a useful strategy for improving sleep-related circadian disturbance in an oncology population, particularly during chemotherapy where circadian rhythm disruption is at its worst.

Current literature investigating BLT within an oncology setting is limited. Among mixed cancer types within survivorship period, BLT has been linked with improvements in cancer-related fatigue (Ancoli-Israel et al., 2012; Johnson et al., 2018; Redd et al., 2014), and symptoms of sleep disturbance (Wu et al., 2018), whilst reducing the circadian disruption effects of chemotherapy (Neikrug et al., 2012). To date, however, research within the sleep-

oncology field is limited by sample size, the utility of light devices assessed, and little research during active oncology treatment. The current proposed study intends to address these research gaps.

1.1 Gaps in the Literature

Despite a strong need to validate these emerging interventions during active oncology treatment, such as chemotherapy, this remains a clear gap in the field. Currently, literature surrounding these interventions is sparse and predominantly conducted within the survivorship period (Wu et al., 2018). No study to date has examined the combined and independent effects of online CBT and BLT among women with breast cancer undergoing chemotherapy within the same protocol. This is an important step in understanding their relative utility as an early intervention tool and capacity to provide targeted symptom management. Such interventions, with appropriate real-world validation, may provide cost-effective, symptom-focused and feasible candidates for sustainable integration within routine oncology care.

1.2 Choice of Comparator

There are many considerations when choosing an appropriate comparator. We utilised the Pragmatic Model for Comparator Selection in Health-Related Behavioural Trials created by an expert panel convened by The National Institutes of Health Office of Behavioral and Social Science Research (Freedland et al., 2019). **We defined the goal of the current trial as establishing how well CBT and BLT alone and in combination work relative to clinically relevant alternatives**. Nationally representative data from the Bettering the Evaluation And Care of Health (BEACH) program in Australia suggests that in family physician management of insomnia, about 90% of insomnia cases are treated by medication, about 20% are treated by counselling advice, such as Sleep Hygiene and Education (SHE), and about 1% of cases are referred, with these trends relatively stable from 2000 to 2015 (Miller et al., 2017). Based on these data, the two most clinically relevant alternative sleep treatments to consider as comparators were sleep medication and SHE. We evaluated both potential comparators on seven key characteristics identified in the NIH model (Freedland et al, 2019), which is summarised in ***Table 1***. Based on these considerations (Table 1), SHE was chosen as the comparator for the SleepCare Trial. In addition to being acceptable, feasible, and clinically relevant, SHE also has the benefits of being very low cost to deliver and because we can deliver it in a similar format to CBT, helping to control "nonspecific" components of CBT and BLT such as attention. SHE serves as an active comparator with high face validity that will control for placebo or expectancy effects. SHE does have some

limitations. First, the format of SHE differs from that of BLT so that it does not control nonspecific effects of BLT (e.g., wearing light glasses daily, for 20 minutes per day with glasses fixed at 1500 lux). Second, SHE does incur some costs beyond usual care. Therefore, cost-effectiveness analyses based for CBT and BLT will not reflect the true cost effectiveness of implementing CBT or BLT into usual care.

Table 1. Comparison of Potential Comparator Conditions

	Medication	**SHE**
Acceptability	*Moderate* – ethical but consumer input suggests that many prefer non-pharmacological options due to number of existing medications during oncology treatment	*High* – ethical intervention and consumer input has been positive around sleep hygiene strategies
Feasibility	*Moderate* – primarily behavioural research team would make prescribing and monitoring medication and side effects challenging	*High* – our team has delivered SHE as part of CBT for sleep and SHE can be delivered via face-to-face, telehealth and email
Formidability	*High* – while actively taking medications, medication and CBT have similar effect sizes on sleep	*Moderate* – SHE has generally shown smaller effect sizes on sleep
Relevance	*High* – sleep medication is the most common treatment for insomnia in Australia	*High* – SHE interventions and recommendations are common
Resemblance	*Low* – very little similarity between medication and either CBT or BLT	*High* – SHE has many surface similarities to CBT and CBT commonly includes some SHE.
Stringency	*Low* – medication controls expectancy/placebo effects, but not other "nonspecific" intervention effects	*Moderate* – SHE can be delivered face-to-face, telehealth and via emails matching the planned delivery of CBT and controlling for both expectancy/placebo effects and "nonspecific" intervention effects for the CBT conditions. Not high as SHE is quite different from daily light glass use in BLT
Uniformity	*High* – the same medication could be consistently used	*Moderate* – initial face-to-face or telehealth consultations will be structured but will vary some. Email SHE content will be consistent

Note. SHE = Sleep Hygiene and Education; CBT = Cognitive Behavioural Therapy for sleep and insomnia; BLT = Bright Light Therapy.

1.3 Trial Design

The SleepCare Trial is designed as a randomised, controlled, 2 x 2 factorial, superiority, parallel group trial with primary endpoints of change from baseline to immediate post-intervention in: (1) insomnia symptoms and (2) fatigue symptoms during chemotherapy for breast cancer. Randomisation will be performed as block randomisation, stratified by cancer stage (≤ 3, 4), ISI (≤ 7, ≥ 8) and site (Peter MacCallum Cancer Centre, Monash Health) with a 1:1:1:1 allocation. Participants will be randomly assigned to one of four conditions: (1) Sleep Hygiene and Education (SHE); (2) Cognitive Behavioural Therapy for insomnia (CBT); (3) Bright Light Therapy (BLT); (4) CBT+BLT combined and simultaneously delivered. A 2 x 2 factorial design was chosen as it permits the evaluation of both CBT and BLT simultaneously, which is more efficient than conducting separate trials and allows the examination of the interaction of CBT and BLT to test whether there are synergistic or antagonistic effects (McAlister, Straus, Sackett, & Altman, 2003), although we do not expect an interaction because CBT and BLT have different mechanisms of operation.

1.4 Aims and Hypotheses

1.4.1 Aim 1

Assess the main effect of cognitive behavioural therapy (CBT) on insomnia symptoms, fatigue symptoms, and health-related quality of life (HRQoL) in women with breast cancer receiving chemotherapy.

H1: It is hypothesised that there will be a main effect of CBT on insomnia, fatigue symptoms, and HRQoL, such that those randomised to CBT conditions will experience greater improvements than those not randomised to CBT conditions.

1.4.2 Aim 2

Assess the main effect of bright light therapy (BLT) on insomnia symptoms, fatigue symptoms, and HRQoL in women with breast cancer undergoing chemotherapy.

H2: It is hypothesised that there will be a main effect of BLT on insomnia and fatigue symptoms and HRQoL, such that those randomised to BLT conditions will experience greater improvements than those not randomised to BLT conditions.

1.4.3 Aim 3

Estimate CBT alone and BLT alone as compared to SHE on the incremental costs (or savings) and cost-effectiveness of from a societal perspective.

H3a: Cost savings from reduced health service utilisation under CBT alone and BLT alone will offset the additional direct cost of CBT alone and BLT alone (CBT alone and BLT alone cost-saving relative to SHE).

H3b: If not cost-saving, the effect of CBT alone and BLT alone on insomnia symptoms or fatigue symptoms or HRQoL will be sufficient to justify the additional cost (CBT alone and BLT alone cost-effective relative to SHE).

1.4.4 Aim 4

Estimate the incremental costs (or savings) and cost-effectiveness of CBT+BLT as compared to CBT alone, BLT alone and SHE from a societal perspective.

H4a: Cost savings from reduced health service utilisation under CBT+BLT will offset the additional direct cost of CBT+BLT (cost-saving relative to CBT alone, BLT alone and SHE).

H4b: If not cost-saving, the combined effect of CBT+BLT on insomnia symptoms or fatigue symptoms or HRQoL will be sufficient to justify the additional cost (CBT+BLT cost-effective relative to CBT alone, BLT alone and SHE).

1.4.5 Exploratory Aim 5

Assess the main effect of CBT and BLT on daytime sleep-related impairment and on rest-activity rhythms in women with breast cancer undergoing chemotherapy.

Exploratory H5: It is hypothesised that there will be a main effect of CBT and BLT on both sleep-related impairment and rest-activity rhythms such that those randomised to CBT or BLT conditions will experience greater declines in sleep-related impairment and improvements in rest-activity rhythms.

1.4.6 Exploratory Aim 6

Assess the interaction of CBT and BLT on reducing symptoms of insomnia and fatigue, improving HRQoL, reducing sleep-related impairment, and increasing rest-activity rhythms in women with breast cancer undergoing chemotherapy. We do not hypothesise an interaction between CBT and BLT; however, the interaction will be statistically evaluated on all outcomes. If an interaction is identified in this exploratory aim, analyses will be reported comparing CBT only and BLT only against SHE, as recommended for factorial clinical trials (McAlister et al., 2003).

2 Research Plan

2.1 Study Setting

The SleepCare Trial will be conducted in Melbourne, Australia. Participants will be recruited from Peter MacCallum Cancer Centre and Monash Health, two comprehensive cancer centres providing care to patients across central and southern regions of Melbourne. Research will be coordinated out of Monash University, Melbourne Australia.

2.2 Participants and Eligibility Criteria

Participants will be out-patients with a diagnosis of breast cancer who are receiving cytotoxic chemotherapy treatment. Below is a brief summary of inclusion and exclusion criteria, with more detailed criteria found in Appendix A - Inclusion and Exclusion Criteria, which also includes a detailed rationale and justification for each criteria.

Inclusion criteria:

(a) Breast cancer diagnosis;
(b) Age ≥ 18 years;
(c) Receiving oral or intravenous cytotoxic chemotherapy, with at least 6 weeks of chemotherapy treatment anticipated at the time of enrolment;
(d) Able to read and write in English;
(e) Able to provide informed consent;
(f) Have regular access to email and internet.

Exclusion criteria:

(a) History of suffering migraines;
(b) Severe psychiatric disorder including substance use disorders;
(c) Male;
(d) Daily use of sleep medications or herbal sleep aids for the previous two weeks or ongoing/planned daily use during the trial;
(e) Brain metastasis with daily steroid use;
(f) Significant symptoms of the following sleep disorders based on The Structured Clinical Interview for Sleep Disorders (SCISD-R; Taylor, Kelly, Kohut, & Song, 2017): narcolepsy, sleep apnoea, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorders.

2.3 Timing and Forms of Contact

All participants will undertake online questionnaires administered via REDCap at four time-points: baseline (t_0, prior to intervention), intervention midpoint (t_2, Week 4),

immediate post-intervention (t_3, Week 7), and 3-month follow-up (t_4, Week 18) and 6-month follow-up (t_5, Week 30). Participants will be sent personalised links to the questionnaires at each timepoint. Questionnaires will take approximately 30 minutes to complete. If a participant does not wish to use an online survey platform, questionnaires will be conducted via telephone by a member of the research team.

All conditions will operate for a duration of 6 weeks. Participants will complete an initial consultation at t_1 for a duration of approximately 30-75 minutes (will vary in duration and content depending on condition). Initial consultations will be flexibly conducted either via telehealth (phone or virtual consultation) or in-person, where safe and appropriate to do so. Telehealth consults that include video conferencing will be conducted via a password protected Monash University Zoom server or via a secure Peter Mac Health Direct server. Telehealth sessions will be scheduled at the time of screening or alternatively if preferred, participants will receive an email listing available appointment times via Calendly. All outgoing emails will be sent from a secure, project dedicated Monash University server, accessible to authorised personale only. Where consultations are conducted in-person, sessions will be scheduled around participants' existing appointments at their place of cancer treatment to reduce the burden of travel. Additionally, participants will be reimbursed for any car parking costs associated with their attendance.

Participants will receive either a phone call or meet in-person if they are already going to be in clinic, depending on their preference, with a researcher at the beginning of week four (mid-point; t_2) to provide an opportunity to answer any questions as well as to ascertain and further encourage intervention compliance, which will take approximately 15-30 minutes depending on the participants' needs. Additionally, a brief phone call (~2-5 minutes) at the end of the intervention will be conducted by study staff to review their overall experience and collect information on any adverse events. All telehealth (phone or virtual consultation) and face-to-face communication will be audio recorded, and this is described in the Participant Information Consent Form.

Intervention materials will be delivered weekly via email using the online software Mailchimp, which provides professional email templates and automates timing of intervention delivery based on predetermined time-points. In total, 12 email packages will be delivered in the CBT condition and 6 in the SHE and LT conditions.

2.4 Interventions

Interventions will be therapist-assisted with self-directed/automated components. A trained member of the research team will interact with participants in person (if appropriate)

or via phone, at the initiation of the intervention (t_1) to personalise aspects of delivery, and via phone (or in person if participants are at clinic for another appointment and prefer to meet in person) at mid-point through the intervention (t_2).

All intervention conditions were devised with the primary goal of minimising participant burden and optimising intervention efficacy. As participants will already be going through an intensive cancer treatment regimen (chemotherapy), the design of the intervention was carefully considered such that the effort and time associated with each intervention component are outweighed by the anticipated benefits.

For example, the initial consultation if conducted in-person, will be scheduled around participants' existing medical appointments 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. Similarly, the light glasses are comfortable, easy to wear, and are not likely to disrupt participant's usual morning routines. Wearing the light glasses for 20 minutes per day with glasses fixed at 1500 lux 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 has been designed to be economical from the perspective of the healthcare system, it is simple for clinicians to deliver and entails relatively low financial expense and burden of time. Taken together, the proposed interventions, if shown to be effective, have the potential to be sustainably integrated within routine oncology care.

2.4.1 Cognitive Behavioural Therapy (CBT) Intervention

Eligible participants randomised to the CBT and CBT+BLT conditions will receive an abbreviated online-based, resource-orientated variant of cognitive behavioural therapy for insomnia and sleep. The intervention will consist of an initial CBT consult (conducted in-person or via phone; ~60-75-minutes), one phone call (~30-minutes) and a series of 12 biweekly self-administered emails (~15-30-minutes). Following the initial CBT consult, participants will then subsequently engage in activities or materials by distance in a self-guided manner (i.e., by reading emails and applying recommended strategies). The primary themes targeted within the proposed adaptation of CBT include behavioural (i.e. timing, conditioning) and psychological (i.e. anxiety, rumination, stress, depression) causes of sleep disturbance and strategies for sleeping with symptoms common to cancer and its associated treatments (i.e. pain, nausea, hot flushes). Broadly, the CBT intervention groups 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 night-time worries);
- fostering healthy attitudes and expectations about sleep following cancer diagnosis and during oncology 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 adapted intervention materials were modelled on the core components described in 'Cognitive Behavioural Treatment of Insomnia Session by Session Guide' (Perlis, Jungquist, Smith & Posner, 2005). These core components have been demonstrated to improve sleep and are well-suited for use within an abridged intervention time frame (Johnson et al., 2016). Each email will address a unique theme. An outline of biweekly emails is provided in Appendix B –– CBT Cognitive Behaviour Therapy Intervention Protocol.

2.4.2 Bright Light Therapy (BLT) Intervention

Participants allocated to the CBT+BLT and BLT conditions will be provided a pair of Luminette® light therapy glasses. The BLT intervention will consist of an initial consultation (conducted in-person or via phone; ~30-45 minutes), one phone call (~30-minutes) and daily use of the Luminette® light glasses for 20 minutes at their habitual wake time for the six-week duration of the intervention. Additionally, participants will receive a brief email each week that will include reminders to promote intervention adherence as well as basic strategies to promote positive sleep habits. Participants will be provided specific instructions during the initial consultation to address both Light Therapy (e.g., seeking bright light upon waking and during the day) and Dark Therapy (e.g., avoiding electronic devices an hour before bedtime, using Nightshift mode), which will be personalised according to their individual routine. Specifically, the initial consultation session will have three objectives: (1) assess participant's current sleep-wake patterns to inform individualised timing of light glasses; (2) discuss light therapy applications and functions to promote more effective integration in daily use; and, (3) collaboratively identify and problem-solve any foreseeable difficulties concerning adherence to light therapy protocol. Please see Appendix C - Bright Light Therapy Protocol for a detailed description of the Bright Light Therapy Protocol. Additionally, pertinent information will be provided to participants in the form of a brief Light Therapy Participant Guide, including how/when to use the light glasses, as well as a summary of key Light/Dark Therapy

strategies and safety information. Participants will also receive a Luminette® guide for further detailed information regarding their light glasses. Additionally, participants in the BLT alone condition will receive basic sleep hygiene and education information (beyond light/dark therapy) to match what is delivered in SHE (described below).

2.4.3 Combined (CBT+BLT) Intervention

Participants in this condition will receive both CBT and BLT interventions simultaneously as detailed above.

2.4.4 Sleep Hygiene and Education (SHE) Intervention

The Sleep Hygiene and Education intervention group will receive similar time and attention relative to CBT and BLT interventions. Participants will receive one initial consultation covering sleep education and basic sleep hygiene (conducted in-person or via phone; ~30 minutes), a midpoint phone call (~15 minutes) and weekly emails (~10 minutes). Email modules will review positive sleep hygiene practices and general sleep education materials (e.g., stages of sleep).

2.5 Assessments and Measures

Table 2 illustrates the assessment tools for the current study and their respective administration timepoints. Questionnaires themselves are included separately. We aim to measure and monitor change in symptoms over time to assess the effectiveness of the intervention. Questionnaires will be considered valid if completed within ±1 week of the designated administration time for baseline (t_0), midpoint (t_2) and post-intervention (t_3) time-points, and within ±2 weeks of planned administration time at 3-months follow-up (t_4) and at 6-months follow-up (t_5).

Table 2. Schedule of Enrolment, Interventions, and Assessments

		Enrolment	Allocation	Post-allocation			Follow-Up
Timepoint	Items/ Time	$-t_1$	t_0	t_1	t_2	t_3	t_4 & t_5
Enrolment							
Informed consent		X					
Eligibility screen interview: Mini International Neuropsychiatric Interview (MINI)* Structured Clinical Interview for Sleep Disorders Revised (SCISD-R)	30 min	X					
Allocation (randomised)			X				
Intervention Groups							
Sleep Hygiene and Education (SHE)				———			
Cognitive Behavioural Therapy (CBT)				———			
Bright Light Therapy (BLT)				———			
Cognitive Behavioural + Bright Light Therapy (CBT+BLT)				———			
Primary Outcomes							
Insomnia Severity Index	7	X	X		X	X	X
PROMIS Fatigue (CAT)	~5		X		X	X	X
Secondary Outcomes							
HRQoL / Health Utility Score (PROMIS-29+2 Profile v2.1 (PROPr) CAT)	~30		X		X	X	X
Actigraphy – Rest Activity Rhythms	2 weeks			X		X	
PROMIS Sleep Related Impairment (CAT)	~4		X		X	X	X
Other Variables							
Demographic and Cancer Information	33		X				
Health Service Use – current medication and supplement use, mental health and sleep treatment receipt	10		X			X	X
Productivity gains – paid and unpaid home help; paid and unpaid sick leave; hours of paid employment.	5		X			X	X
Program evaluation	8					X	
Medical records extraction (date of Dx, Tx, tumour staging etc.)							X
Administrative and fidelity data – e.g., time spent delivery and receipt of intervention components, time spent using intervention					X	X	
Credibility Expectancy Questionnaire	6		X				
Reduced Morningness and Eveningness Questionnaire	5		X		X	X	
Dysfunctional Beliefs and Attitudes about Sleep	16		X		X	X	
Pre-sleep arousal	16		X		X	X	
PROMIS Anxiety (CAT)	~5		X		X	X	X
Sleep Diary & Actigraphy (SE, SOL, WASO, TST)	2 weeks	^		X		X	

Intervention Adherence – (all conditions)	~7			X	X	X	
Adverse Events				X	X	X	X
Note. X = Measure administered at that time point; SOL = sleep onset latency; WASO = wake after sleep onset; SE = sleep efficiency; TST = total sleep time; * = modules A, B, C, H, I, J, K, N; CAT = computerised adaptive test, HRQoL = health-related quality of life; CATs vary the number of items so the average number of items required are reported. ^ Three days of sleep diary completion							

2.5.1 Screening

1. Mini International Neuropsychiatric Interview 7.0 (MINI). Psychiatric and substance use disorders will be screened for by The Mini International Neuropsychiatric Interview 7.0 (MINI; Bastien, Vallières, & Morin, 2001). The MINI is a short, structured diagnostic interview for DSM V psychiatric disorders (American Psychiatric Association, 2013). For the purposes of the current screening procedures to determine eligibility/suitability of participant inclusion, the following modules will be administered: Manic and Hypomanic Episodes (Module C); Post-traumatic Stress Disorder other than cancer-related (Module H); Alcohol Dependence/Abuse (Module I); Substance Dependence/Abuse (Module J); Psychotic Disorders (Module K). In addition, to characterise the sample, the following modules also will be administered: Major Depressive Episode (Module A); Generalized Anxiety Disorder (Module N). The MINI has been validated against the Structured Clinical interview for DSM-II-R Patients, with appropriate diagnostic sensitivity and specificity (Sheehan et al., 1997), and has demonstrated good inter-rater and test-retest reliability (Lecrubier et al., 1997). Within a primary care setting the MINI is well accepted by patients and therapists (Pettersson, Modin, Wahlström, Hammarberg, & Krakau, 2018; Pinninti, Madison, Musser, & Rissmiller, 2003). The MINI has been widely used in clinical intervention literature as a screening diagnostic tool (Maranhão et al., 2015; Silverstein et al., 2017; Wigal et al., 2018).
2. Structured Clinical Interview for Sleep Disorders Revised (SCISD-R). Sleep disorders will be assessed by The Structured Clinical Interview for Sleep Disorders Revised (SCISD-R; Taylor et al., 2017). The SCISD-R will be administered in its entirety during screening. The SCISD-R is conducted as a semi-structured clinical interview. Item content was developed in line with the disorder criteria defined in both the DSM-5 and International Classification of Sleep Disorders (American Psychiatric Association, 2013). The SCISD-R has established reliability and validity (Taylor et al., 2018), and has been used previously as a screening instrument within clinical trials (Taylor et al., 2017).

2.5.2 Primary Outcomes

3. Symptoms of Insomnia will be measured via the 7-item Insomnia Severity Index (ISI; Bastien, Vallières, & Morin, 2001). Total scores are summed (range = 0-28) for interpretation – higher scores are indicative of increased insomnia severity. Clinical cut-off scores are as follows: 0-7 = '*No clinically significant insomnia*; 8-14 = '*Subthreshold insomnia'*; *15-21* = '*Clinical insomnia (moderate severity'*); 22-28 = *Clinical insomnia (severe).* The ISI has proven internal consistency within a clinical population ($\alpha = 0.91$), and good sensitivity and specificity (86.1% and 87.7%, respectively; (Morin, Belleville, Bélanger, & Ivers, 2011). The ISI has been validated within cancer populations (Savard, Savard, Simard, & Ivers, 2005), and via online delivery (Thorndike et al., 2011), and is widely used within oncology sleep research (See Garland et al., 2014)
4. Symptoms of Fatigue will be assessed by PROMIS Fatigue – Computerised Adaptive Test (Cella et al., 2016). While fatigue may be related to sleep, it is a distinct construct and oncology patients may experience high fatigue despite sufficient sleep, particularly when undergoing chemotherapy. The Patient Reported Outcome Measurement Information System (PROMIS; The National Institutes of Health, 2015; NIH, 2015) is a measurement system comprising item-banks developed based on item-response theory (Cella et al., 2007), to provide highly precise, psychometrically sound, easy-to-use, self-report unidimensional measures across a range of health and well–being domains (Bartlett et al., 2015) and are extensively validated. PROMIS-Cancer (PROMIS-Ca) measures were developed through expert consensus and informed by focus groups to include items most applicable to a cancer population. PROMIS-Ca measures will be used within the present study. Computerised adaptive tests (CATs) are tailored to the individual patient and can achieve comparable measurement using only a subset of the entire bank of items. PROMIS CATs provide standardized measurement with results reported using a T-score, which has a mean of 50 and standard deviation of 10 (NIH, 2015).

2.5.3 Secondary Outcomes

5. Health-related Quality of Life / Health Utility Score. An overall health utility score will be calculated using preference-based weights developed for PROMIS using the PROMIS-29+2 Profile v2.1 (PROPr) based on computer adaptive testing. The Health Utility Score is a composite of the following seven domains captured by PROMIS: Physical Function, Pain Interference, Cognitive Function, Depression (Pilkonis et al.,

2011), Fatigue, Sleep Disturbance (Yu et al., 2012), and Ability to Participate in Social Roles and Activities.

6. Daily Rest-Activity Rhythms (RAR) reflect the change in an individual's activity levels across a 24-hour period to provide a marker of circadian function. Periods of activity and in-activity will be monitored objectively using a wrist-worn Actigraph wGT3X BT monitor (ActiGraph Corp, Pensacola, FL). RAR will be averaged across two 2-week monitoring periods that will immediately upon starting the intervention and in the final 2 weeks of the intervention. RAR has been used previously as a circadian assessment tool within oncology research (Innominato et al., 2018; Ortiz-Tudela, Innominato, Rol, Lévi, & Madrid, 2016). Cosinor analysis is commonly used to calculate RAR (fitting a cosine curve for a 24 hr period). However, as 24 hr RAR do not typically follow a sinusoidal waveform, a non-parametric approach will be used in the present study.
7. Sleep-related impairment measured using the PROMIS Sleep Related Impairment - Computerised Adaptive Test (Yu et al., 2012), a validated measure that captures daytime impact due to poor sleep.

2.5.4 Other Factors

8. Demographics, will be collected via self-report at study entry with participants' consent. These include: age, marital/co-habiting status, number of children living at home and employment.
9. Medical variables, will be collected via self-report and extraction from medical records and pathology reports at t_1, t_2 and t_3. These include: cancer stage, surgery type, cancer treatment type e.g. chemotherapy or radiotherapy, cancer treatment duration, medical comorbidities and body mass index (BMI).
10. Health Service Use, will be collected via a combination of self-report and administrative data and overseen by **AI Mortimer**. We are not exclusively relying on medical records 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 and standard procedures (**AI Alexander**). We obtain permission to access medical records and these will be cross-referenced with self-report use of health services (e.g., primary care; prescription and over the counter medications; allied health care; community care; paid and unpaid home-help) both to quantify access and use of health services as well as for costing and health economic analyses. Detailed medication information will include the name, dosage, indication,

and duration of use for each medication or supplement they are taking. Where self-reported medication use is ambiguous, a member of the research team will conduct a brief phone call (~3-5 min) with the participant to clarify their responses. This information will be used as potential covariates (e.g., participants on sleep medication or mood medications may benefit less from the intervention).

11. Patients' perceived credibility and expectancy of SHE, CBT, BLT, or CBT+BLT treatment via the Credibility Expectancy Questionnaire (CEQ; Devilly & Borkovec, 2000); a brief 6-item measure with high internal consistency, within each factor (i.e., "Credibility" Cronbach's $\alpha = 0.81$ to 0.86, "Expectancy" $\alpha = 0.79$ to 0.90) and good one-week test retest reliability "Credibility" = 0.82, and "Expectancy" = 0.75 (Devilly & Borkovec, 2000).
12. Sleep. Measured using both self-reported sleep behaviours (Consensus Sleep Diary; Carney et al., 2012) and objective, wGT3X BT actigraphy derived sleep parameters over the past two weeks (ActiGraph Corp, Pensacola, FL). Specific sleep parameters examined from both subjective and objective measures include: time in bed (TIB) sleep efficiency (SE), sleep onset latency (SOL), wake after sleep onset (WASO), terminal wakefulness (TWAK), and total sleep time (TST).

$$SE = \frac{TST = (TIB - SOL - WASO - TWAK)}{TIB} \times 100$$

SE scores below 85% are suggested to reflect clinically significant insomnia (Schutte-Rodin, 2008; Spielman et al., 1987). SE is utilised within assessment, sleep treatment formulation and to monitor clinically important therapeutic effects (Morin, 2003; Riemann et al., 2017). SE has shown moderate correlations with polysomnography and actigraphy recordings (Edinger, Means, Stechuchak, & Olsen, 2004), whilst the Consensus Sleep Diary has established convergent validity against objective sleep instruments and existing sleep diaries (Maich, Lachowski, & Carney, 2018).

13. Chronotype via the Reduced Morningness Eveningness Questionnaire (rMEQ; Adan & Almirall, 1991); a validated tool to assess preferred timing for mental and physical activities that correlates with biological circadian phase (Chelminski, Petros, Plaud, & Ferraro, 2000).
14. Intervention adherence and feedback assessing frequency of use and usefulness of each component for CBT, BLT and SHE interventions. At post-intervention, will answer questions regarding intervention adherence and usefulness (e.g., how helpful was each component (0= "not useful at all", 3= "very useful") and will report how

many days in a typical week they have used different components of the intervention emails. Feedback regarding any additional benefits or challenges in applying CBT strategies will be collected.

15. Satisfaction. Adapted from the original 18-item version (CSQ-18), the brief 8-item Client Satisfactory Questionnaire (CSQ-8; Attkisson & Zwick, 1982) is a commonly preferred measure of client satisfaction (Attkisson & Zwick, 1982). Items (e.g., "*to what extent has our program met your needs*", are rated on a 4-point scale. The CSQ-8 has high internal consistency (Cronbach's $\alpha = 0.93$).
16. Light therapy adherence is measured via a daily diary of light glasses usage (20 minutes per day with glasses fixed at 1500 lux).
17. Beliefs and attitudes about sleep with the Dysfunctional Beliefs and Attitudes about Sleep Scale (DBAS-16; Morin, Vallières, & Ivers, 2007), a 16-item measure of sleep-related beliefs and attitudes in insomnia, designed to both evaluate, and monitor change. The DBAS-16 is suitable for clinically translatable sleep research, with adequate reliability and good concurrent validity (Morin et al., 2007).
18. Pre-sleep arousal with the Pre-Sleep Arousal Scale (PSAS; Nicassio, Mendlowitz, Fussell, & Petras, 1985). The PSAS is a 16-item measure that evaluates cognitive and somatic symptoms prior to sleep. The PSAS has demonstrated appropriate psychometric properties (Nicassio et al., 1985).
19. Anxiety will be measured using the PROMIS Anxiety using Computer Adaptive Testing (Pilkonis et al., 2011), a validated measure of anxiety symptoms.
20. Sleep effort will be assessed via the Glasgow Sleep Effort Scale (GSES; Broomfield & Espie, 2005).

2.5.5 Sleep Treatment Fidelity and Audio Recording

All initial consultations and intervention telehealth contact will be recorded for quality control and to assess CBT and SHE treatment fidelity. Audio recordings will be stored securely on the Monash Google Drive, which is secured by two-factor authentication. Written informed consent from participants will be sought for obtaining these audio recordings. Recordings will be listened to by trained and experienced clinical sleep psychologists routinely throughout the trial (**PI Diggens**, **AI Garland**). Inconsistencies with CBT or SHE treatment protocol will be addressed through discussion with and supervision of trial interventionists.

2.5.6 Adverse Events

Adverse events will be tracked in the following ways.

1. A >10 point worsening (relative to t_{-1}) in patient reported outcome T Scores on any of the following PROMIS domains: (a) depression symptoms, (b) anxiety symptoms, (c) physical function, (d) pain interference, (e) cognitive function, (f) fatigue symptoms, (g) sleep disturbance, (h) ability to participate in social roles and activities, or (i) sleep-related impairment.
2. Two questions asked in surveys
    a. General side effects, based on responses to:
    "Have you experienced any side-effects because of using the strategies outlined in this program?"
    answered yes/no -- if yes,
    "Please describe what side-effects you experienced." [open ended]
    b. Negative treatment experience, based on responses to:
    "Sometimes people find programs are not what they expected, are unhelpful, or inappropriate and result in a negative experience or even losing trust in whether similar programs in the future could help. Did you experience anything like this because of our program?"
    answered as yes/no -- if yes,
    "Please describe what happened." [open ended]

Monitoring for any unsolicited reports of adverse events or serious adverse events (e.g., mental health-related hospital admissions) will be monitored at all surveys following the baseline (i.e., t_2, t_3, t_4, & t_5). Staff will follow-up any survey reports of adverse events where further information is needed or unsolicited reports and record them in case report forms (CRFs) in REDCap.

2.6 Sample Size and Power Analysis

Current literature surrounding CBT and BLT in oncology populations has yielded positive therapeutic outcomes (see ***Table 3***). Specifically, standard and internet-based CBT has demonstrated moderate-to-large effect sizes on the insomnia severity index and fatigue symptoms. Similarly, BLT has exhibited moderate to large effect sizes on sleep efficiency (strongly related to insomnia symptoms) and fatigue. Given that the combined intervention condition will include both CBT and BLT, intervention effect sizes are likely to be equal or greater than those stated above. Research evaluating rest activity rhythms as an outcome measure is sparse. Emerging literature, however, has shown that CBT and BLT have promising effects (Bernatchez, Savard, & Ivers, 2018; Palesh et al., 2018).

Table 3. Intervention Effect Sizes within Cancer Populations

	Intervention	*N*	Outcome/Effect Size
Standard CBT-I			
Johnson et al 2016	Meta-analysis	*N* = 752	Insomnia Severity Index / d = 0.77
Espie et al 2008	5, weekly, 50-minute sessions	*N* = 150	Fatigue Interference / d = .82

Self-administered CBT-I			
Dozeman et al 2017	6-week, internet self-help program, therapist-assisted	*N* = 100	Insomnia Severity Index / d = 1.33 Fatigue / d = .24
Zachariae et al 2018	6-week, internet self-help program	*N = 255*	Insomnia Severity Index / d = 1.17 Fatigue / d = .42
Ritterband et al 2012	6-week, Internet self-help program	*N* = 28	Insomnia Severity Index / d = 1.85 Fatigue / d = 1.16
Casault et al 2015	6-week, self-help booklets, therapist-assisted	*N = 242*	Insomnia Severity Index / d = 1.62 Fatigue / d = .56
Savard et al 2014	6-week, self-help booklets, video-assisted	*N* = 38	Insomnia Severity Index / d = 1.40 Fatigue / d = .21
Savard et al 2011	6-week, self-help booklets, video-assisted	*N* = 11	Insomnia Severity Index / d = 1.29 Fatigue / d = .29
Bright Light Therapy			
Wu et al 2018	30-minute morning administration	*N* = 44	Sleep Efficiency / η^2 = .28 Total Sleep Time / η^2 = .16
Johnson et al 2018	30-minute morning administration	*N* = 81	Fatigue / Within η^2 = .054
Redd et al 2014	30-minute morning administration	*N* = 36	Fatigue / Between d = .30 Fatigue / d = .98

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

Based on these previous studies, data from our previous sleep trial in women with breast cancer treated with chemotherapy (Bean et al, 2020), and clinical judgement, we set the minimally important difference (MID) for the insomnia severity index at 3 and for the PROMIS Fatigue at 4 (Yost, Eton, Garcia & Cella, 2011). These represent approximately half a standard deviation on both measures in our SleepWell trial or a between group Cohen's d of approximately 0.50. For the insomnia severity index, a 3-point change also is about half a "category" shift based on common cut offs. In addition to representing a minimally important difference, previous trials (***Table 3***) demonstrate that these or larger magnitude changes may be expected following CBT-I or BLT.

Following recommendations for analysing longitudinal data from randomised controlled trials, we plan to use so-called "constrained longitudinal data analysis" (Coffman, Edelman, Woolson, 2016; Twisk, Bosman, Hoekstra, et al, 2018) and to adjust for stratification factors used in randomisation (Kahan & Morris, 2011; Kahan & Morris, 2012). In addition, we anticipate dropout throughout the trial due to illness and burden from other cancer treatment including chemotherapy. Appropriate power analysis for constrained longitudinal analyses (Coffman, Edelman, Woolson, 2016; Twisk, Bosman, Hoekstra, et al, 2018) adjusted for stratification factors and with missing data is not readily calculated using fixed formula. Therefore, a Monte Carlo study was conducted in Mplus using MplusAutomation (Muthen & Muthen, 2002; Hallquist & Wiley, 2018). Extensive details are

in Appendix G – Power Analysis and code to reproduce the Monte Carlo study is publicly available at: https://github.com/behavioralmedicinelab/SleepCarePlanning. This trial is powered to detect a main effect of BLT and main effect of CBT for the primary outcomes, insomnia severity index and fatigue symptoms at alpha = .05, assuming the minimally important differences previously noted (3 for insomnia severity index and 4 for fatigue symptoms) and little to no interaction between conditions, given that they operate on very different mechanisms. In our previous SleepWell trial, over a quarter of participants had metastatic cancer resulting in high attrition rates. We estimated that there would be 35% missing data by the post intervention assessment, a very conservative estimate. The BLT x CBT interaction (the combination sleep treatment) is an exploratory aim of this trial and the trial is not powered for this.

Tests for the primary trial aims (main effect of BLT and CBT on ISI and Fatigue) will be adjusted for multiple comparisons using a false discovery rate to control for type 1 error (Benjamin & Hochberg, 1995; Verhoeven, Simonsen & McIntyre, 2005), with FDR set at 0.05. While this method is less conservative than other methods, it has been used previously in sleep research (Maccora, Manousakis & Anderson., 2018; Lee et al., 2015).

Randomising N = 210 participants will provide ≥ 80% power for the main effect of BLT and CBT on the insomnia severity index and fatigue symptoms (Aims 1 and 2) under the conditions specified based on results from the Monte Carlo simulation study. For the exploratory aim to examine the BLT x CBT interaction, as expected this trial will generally not have adequate power. There will be 80% power to detect the interaction for the insomnia severity index, if it reaches the minimally important difference of 3. However, interactions often are smaller in magnitude than main effects and theoretically given the different mechanisms of operation we expect only a small interaction.

2.7 Recruitment and Consent

Individuals with a breast cancer diagnosis who are or will receive intravenous chemotherapy treatment will be recruited after diagnosis and prior to completing chemotherapy. The process of recruitment and consent will differ slightly at each site due to variation in site-specific processes of patient care.

Peter MacCallum Cancer Centre recruitment process:

Participants will be recruited via reports generated via EPIC, a specialist oncology eHealth system utilised by Peter MacCallum Cancer Centre. Reports will outline the appointment times for all breast patients scheduled to receive chemotherapy within a given period. Participants identified through pre-screening via EPIC will receive an introductory

text message and study advertisements (e.g., flyer, brief informational video) via email and/or post to provide an overview of the project and study contact details. Also, a researcher will make contact with potential candidates either in-person (e.g., at the Chemotherapy Day Unit), or via phone or telehealth. Participants will not be contacted during their chemotherapy education session due to the psychological stress and information overload associated with this session. If approaching in person at the Chemotherapy Day Unit, a team nurse will advise researchers of each patient's confirmed appointment time and their allocated chair.

Monash Health recruitment process:

Eligible participants at Monash Health will be informed about the study and provided information sheets in medical oncology breast clinics at Moorabbin, Dandenong and Casey Hospitals. Interested patients will be connected with a researcher where available or have their contact details passed onto a study coordinator. Providing further information about the study, consent and final screening will be conducted by a study researcher with patients at a mutually convenient time either in-person (e.g., at the Chemotherapy Day Unit) or via phone or telehealth.

Patients at both sites will be invited to participate in "a research project that aims to improve symptoms of sleep disturbance among individuals with breast cancer". Interested participants will receive general information pertaining to sleep disturbance in cancer as well as the proposed research project. Should a person choose to participate, written informed consent will be obtained where recruitment is conducted in-person, and verbal informed consent will be obtained in the instance recruitment occurs via phone or telehealth. As participants will not have access to the PICF when recruited via phone, a researcher will discuss each section of the PICF with the patient to ensure informed consent. All verbal consent will be recorded and participants will receive a copy of PICF via email. Participants will then undergo subsequent screening to confirm eligibility.

Our team has used a similar recruitment method for a trial of combined CBT and BLT in women with breast cancer undergoing chemotherapy, the SleepWell Trial (Bean et al, 2020). In SleepWell, between July 2018 and November 2019, we approached 237 women and consented 101 eligible women with breast cancer to the trial, at an average rate of 1.5 per week, recruiting 2 days on a typical week. The success of the SleepWell Trial shows that this approach is feasible both for participants and for staff in the Chemotherapy Day Unit. In the current SleepCare Trial, we are including two sites and have support to recruit more days per week if needed, making recruitment feasible.

2.8 Screening

Following informed consent, participant eligibility will be further evaluated via structured interviews for psychopathology (the MINI) and sleep disorders (the SCISD-R). Screening will be conducted immediately after written or verbal informed consent where possible or at a follow-up telephone call depending on participant preference and availability.

The following modules of the MINI will be administered for screening: Manic and Hypomanic Episodes (Module C); Post-traumatic Stress Disorder other than cancer-related (Module H); Alcohol Dependence/Abuse (Module I); Substance Dependence/Abuse (Module J); Psychotic Disorders (Module K). Participants will be excluded from study participation if they currently meet the criteria for Modules C, H or K or have met the criteria of Modules I or J within the past 12 months. Participants who meet exclusion criteria due to a severe psychiatric condition will be referred to site specific psychological support services or provided contact information of relevant professionals/services (e.g., Lifeline, Beyond Blue). See Appendix D - Risk Management Protocol for further details on the management of high-risk participants. The SCISD-R will be administered in its entirety for screening. Participants will be excluded in the event a pre-existing sleep disorder is identified, including narcolepsy, sleep apnoea, periodic limb movement disorder, restless legs syndrome, or a circadian rhythm sleep disorder (See Appendix A - Inclusion and Exclusion Criteria). Participants who meet exclusion criteria due to a sleep disorder will be encouraged to discuss with their physician for further support.

2.9 Randomisation and Blinding

Eligible participants will be randomised into group using a complete randomisation scheme generated in advance. Specifically, variable block sizes (4 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. Randomisation will be stratified by site (Peter MacCallum Cancer Centre, Monash Health), cancer stage (≤ 3, 4) and screening ISI (≤ 7, ≥ 8). The randomisation scheme will be generated and set up in REDCap by **AI 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 randomise 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. Follow-up measures will either be self-completed or will be conducted by research staff who are blinded to condition.

2.10 Data Management and Storage

For security of information collected, each participant will be assigned an identification (ID) number. Participants' identifiable information will be stored in Monash University REDCap, which has role-based secure access, and researchers working on this project will have different levels of access (e.g., full access, de-identifiable information only). Access also can be revoked at once if required (e.g. if a member of the team were to leave the project). Outside REDCap (e.g., dataset for analyses), participants will only be identified using the numeric ID. Any hard copies of data collected will be kept in secure locked filing cabinets at Monash University or at one of the sites. Only the researchers involved in the project will have access to the data. 7 years after the final publication, data will be de-identified (e.g., by removing names, date of birth, addresses/contact details), and any information that may link the data to individual participants. Any other rare categories that may be easily re-identifiable will be recoded (e.g., rare cancers collapsed into "other"). These personally identifying data will be completely erased and destroyed. The de-identified database will be made publicly available through Monash Figshare to maximise the potential benefit to the scientific and research community.

3.1.1 Data Cleaning

All descriptive and inferential statistics will be computed using R (R Core Team, 2018). Preliminary analysis will be conducted to screen for outliers and skew within the data set. Where applicable, data abnormalities will undergo appropriate transformations or will be winsorized to their respective group's next highest non-outlier value, in accordance with Field's (2013) recommendations. For Actigraphy data, prior to analysis all off-wrist intervals (omissions in activity data) will be excluded. Any 24 hr periods containing less than 75% data will be excluded from analysis.

3.1.2 Baseline Characteristics

*A thorough descriptive profile of b*aseline characteristics for each intervention condition and the overall sample will be presented as a table. Discrete variables will be summarised by frequencies and percentages, while continuous variables will be represented using mean (SD) and median (IQR). These descriptive analyses will facilitate evaluation of the external validity and generalisability of the findings.

3.1.3 Primary Intervention Effects (Aims 1 and 2)

To assess the intervention-dependent changes on each primary outcome (Aim 1 & 2) an intention-to-treat analysis will be conducted in R and Mplus using MplusAutomation (Hallquist & Wiley, 2018). Primary analyses will match those used in the Monte Carlo simulation study for power analysis (see Appendix G – Power Analysis) and are available online: https://github.com/behavioralmedicinelab/SleepCarePlanning and summarised in ***Table 4***.

Latent growth models (LGMs) will be estimated with an intercept and a linear slope with loadings constrained to 0, 0.5, and 1.0 for times t_0, t_2, and t_3, respectively. 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 covariance 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 three stratification factors: site (Peter MacCallum Cancer Centre, Monash Health), cancer stage (≤ 3, 4) and insomnia severity index at screening (≤ 7, ≥ 8). These factors will be crossed creating eight groups. Dummy codes will be created for each strata.

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).

Intervention effects will be evaluated by creating dummy codes for BLT, CBT, and the BLT x CBT interaction. These will be entered as predictors of the random intercept and slope. However, intervention factors will be constrained to 0 for the random 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 intervention effects from randomised controlled trials with repeated measures. To calculate the overall main effects, estimates will be averaged across conditions to average out the interaction (for non-primary analyses, the interaction and simple effects will be tested). We anticipate missing data and dropout over time. Missing data will be addressed using full information maximum likelihood estimation (Enders & Bandalos, 2001).

An alpha level of .05 will be used to assign significance. All comparisons will be made using a false discovery rate to control for type 1 error (Benjamin & Hochberg, 1995; Verhoeven, Simonsen & McIntyre, 2005). While this method is less conservative than other methods, it has been used previously in sleep research (Maccora, Manousakis & Anderson., 2018; Lee et al., 2015).

For each outcome measure, a Cohen's d effect size at post-intervention (t_3) will be computed as well as a "within" standardised mean difference based on the change from baseline (t_0) to post-intervention (t_3). To assess comparative treatment effects, post hoc pairwise comparisons of each condition's computed effect size will be conducted on all primary outcomes.

In the event normality cannot be assumed for an outcome variable, as can occur with sleep measures (Carney et al., 2012), bootstrapping will be employed for significance testing and calculation of confidence intervals (Field, 2013).

Table 4. Variables, Measures, and Statistical Analyses

Variable/Outcome	Hypothesis	Measure	Statistical Analysis
Primary Outcomes			
Insomnia symptoms	Main effects of CBT and BLT in reducing from t_0 to t_3	Insomnia Severity Index (ISI) at t_0, t_2, & t_3 [primary endpoints are the change over t_0, t_2 and t_3]	Latent Growth Models (LGMs) with appropriate time & condition interactions
Fatigue symptoms		PROMIS Fatigue at t_0, t_2, & t_3 [primary endpoints are the change over t_0, t_2 and t_3]	LGMs with appropriate time & condition interactions
Secondary Outcomes			

Health-related quality of life	Main effects of CBT and BLT in reducing from t_0 to t_3	PROMIS QoL at t_0, t_2, & t_3 [primary endpoints are the change over t_0, t_2 and t_3]	LGMs with appropriate time & condition interactions
Sleep related impairment	Main effects of CBT and BLT in reducing from t_0 to t_3	PROMIS SRI at t_0, t_2, & t_3 [primary endpoints are the change over t_0, t_2 and t_3]	LGMs with appropriate time & condition interactions
Rest activity rhythms	Main effects of CBT and BLT at t_3	Dichotomy Index (I<O) at t_3 [primary endpoint is t_3]	Linear regression
Subgroup Analyses	Intervention effects will be stronger in those with initially high symptoms		
Baseline high/low insomnia symptoms		ISI at t_0, t_2, t_3	LGMs with appropriate time, condition, and group interactions
Baseline high/low fatigue symptoms		PROMIS Fatigue at t_0, t_2, t_3	LGMs with appropriate time, condition, and group interactions
Sensitivity Analyses	Main effects of CBT and BLT in reducing from t_0 to t_2 to t_3	All outcomes	LGMs and linear regressions as defined for primary analyses
Per protocol analysis			
Adjusting for covariates^			

Note. t_0 = baseline, prior to start of intervention; t_1 = 2-week diaries and actigraphy data collected from the start of the intervention; t_2 = intervention midpoint; t_3 = immediate post-intervention;. ^ Covariates are described in ***Table 5***.

3.1.4 Economic Evaluation

Overseen by **AI Mortimer**, cost-effectiveness and cost-utility analyses will be conducted to summarise health gains, health care costs and productivity gains associated with (i) replacing SHE with CBT+BLT, CBT alone or BLT alone, (ii) adding CBT to BLT alone, and (iii) adding BLT to CBT alone. Analyses will be conducted from a societal perspective and will be limited to costs and consequences within the trial period.

Health gains will be captured by primary clinical outcomes (ISI at t_3 and t_4; PROMIS Fatigue at t_3 and t_4) and total quality adjusted life-years (QALYs) from baseline to trial-end. Total QALYs to trial-end will be calculated using an area-under-the-curve approach based on PROPr utility scores at t_0, t_2, t_3, t_4, and t_5 and assuming a linear time-trend between time-points. Intervention effects with respect to QALYs will be estimated using one-part generalized linear models (GLM) specifying appropriate variance and link functions, controlling for strata variables and PROPr utility scores at baseline (t_0). Intervention effects with respect to the primary clinical outcomes will be estimated as for the main effectiveness analysis (described above).

Total cost per patient from baseline to trial-end will be calculated as the sum of intervention costs (i.e. direct cost of SHE, CBT, BLT or CBT+BLT), cost of 'related' health service utilisation (e.g. prescription and OTC medicines for sleep problems, anxiety, low

mood and depression; visits to primary, specialist and allied health care providers for sleep problems, anxiety, low mood and depression) and productivity gains (e.g. use of paid and unpaid home help; change in employment status hours; paid and unpaid sick leave). Patient-level estimates of intervention costs will be based on administrative records and fidelity analysis regarding delivery of intervention components and adherence data regarding receipt of intervention components. Patient-level estimates of the cost of 'related' health service utilisation will be based on patient self-report at t_3 (for the period t_0 to t_3), t_4 (for the period t_3 to t_4), and t_5 (for the period t_4 to t_5). Patient-level estimates of productivity gains will be based on patient self-report at t_3, t_4, and t_5 with respect to use of paid and unpaid home help, paid and unpaid sick leave and hours of paid employment. Intervention effects with respect to total cost will be estimated using one-part GLM models with gamma variance function and a log link (rather than transformed OLS or two-part models), controlling for strata variables.

Results will be expressed as (1) cost per point improvement on the primary clinical outcomes (ISI at t_3, t_4, t_5; PROMIS Fatigue at t_3, t_4, and t_5), and (2) cost per QALY gained to t_5. We will summarise sampling error and parameter uncertainty using the bootstrap acceptability to calculate confidence intervals and generate cost-effectiveness acceptability curves.

3.1.5 Analyses for Exploratory Aims

Similar analyses to the primary analyses will be conducted for sleep-related impairment. Daily rest activity rhythm will be compared at post-treatment (t_3) only using linear regression models with a main effect of CBT, main effect of BLT and the interaction of CBT and BLT. Only t_3 is compared for daily rest activity rhythms because it can only be computed on several days of data and the first assessment begins after intervention, so that change over time is less relevant for this measure.

Although not part of the primary trial aims, the CBT x BLT interactions will be tested in the primary analysis models. If these are significant, simple effects will be calculated by examining each condition against the control Sleep Hygiene and Education (SHE) condition. These analyses are exploratory as many studies show that interaction effects often are smaller in magnitude than main effects and this trial is not powered to detect likely smaller CBT x BLT interaction.

3.1.6 Planned Secondary Analyses

Planned secondary analyses will report the intervention effects at follow-up (t_4; 3-month follow-up and t_5; 6-month follow-up) to evaluate maintenance of any gains at post-treatment (t_3). These will be conducted for all primary and secondary outcomes. These

analyses will replicate the primary analyses, but adding a second, linear slope in the latent growth models for the period from t_3 to t_5.

3.1.7 Heterogeneity, Covariates and Sensitivity Analyses

Primary analyses are adjusted for stratification and blocking factors, specifically chosen as they are likely to account for a significant portion of the heterogeneity in patient-reported insomnia and fatigue symptoms, our primary outcomes. However, sleep and fatigue are complex and multi-factorial so it is likely that other factors will be related to our outcomes. We carefully assess, evaluate, and adjust for the *a priori* covariates in ***Table 5*** in follow-up sensitivity analyses in addition to our stratification factors. For categorical covariates (e.g., whether or not women are taking hypnotic medications), we will first conduct descriptive analyses. If more than 90% of women fall into a single category, the covariate will be omitted. If any category has less than 5% prevalence in the sample, categories will be collapsed prior to analysis. Sensitivity analyses will be conducted and reported in addition to the primary analyses. Exploratory analyses will evaluate covariates individually as effect modifiers to assess whether any strong signals emerge that intervention efficacy varies by these factors. For these exploratory effect modifier analyses, given the number of tests and two primary outcomes, we will use $\alpha = .005$ to control for multiple comparisons.

Table 5. A priori covariate list and coding

Variable	Coding
Prior history of intravenous chemotherapy	yes; no
Chemotherapy cycle	time-varying, the cycle number
Hospitalisation	time-varying: yes; no
Whether further cancer treatment after chemotherapy planned (e.g., further surgical/radiation)	yes; no
Psychosocial treatment use (e.g., psychotherapy, support groups)	time-varying: yes; no
Time since diagnosis	continuous in months
Menopausal status, based on self-report	post-menopausal prior to chemo; pre- or peri-menopausal at chemotherapy
Anxiety or depressive disorder, based on semi-structured clinical interview at screening	yes; no
Age	continuous in years
Sleep impact of physical symptoms and side effects: pain, nausea/vomiting, hot flushes/night sweats, nocturia, recorded in daily sleep diaries over 4 weeks	continuous, the number of days women report their sleep being impacted
Hormone replacement therapy	current; none
Sleep medications (i.e., benzodiazepines, benzodiazepine-like medications, suvorexant, melatonin, evidence-based herbal sleep aids)	time-varying: yes; no
Dexamethasone/steroids with chemotherapy, recorded in daily sleep diaries	none; 1 day per cycle; multiple days per cycle
Stimulant medications or medications with a significant stimulant side effect (besides dexamethasone)	time-varying: yes; no
Psychotropic medications (e.g., anti-depressants, anxiolytics)	time-varying: yes; no

4 Research Ethics Approval

This protocol, questionnaires, intervention materials, and the informed consent forms attached will be reviewed and approved by the Human Research Ethics Committee at each site with respect to scientific content and compliance with applicable research and human subjects' regulations. The coordinating PI will make safety and progress reports to the ethics committee at least annually and within three months of study termination or completion including summaries of the number of participants enrolled, randomised and completed.

Any significant modifications of this protocol which may impact on the conduct of the study (e.g., changing objectives, design, sample size, significant procedures) will be approved by the investigator team and reviewed by the ethics committee. Minor modifications (e.g., corrections, clarifications, typographical errors) will be documented in a revision note and only re-reviewed by the ethics committee if more significant changes are made.

5 Dissemination Plan

In the final stages of data collection, the research team will develop a strategic plan for presentation and publication of trial results. All investigators will be included as authors on the trial protocol manuscript and manuscript detailing results of the trial on the primary outcomes. As this project is used for Mr Jordan Maccora's PhD dissertation, Jordan 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 behavioural 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 analysed. Primary modes of dissemination will be:

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

Simultaneous to peer-reviewed publications, we will work with communications and media teams at each site and Monash University to develop press releases and a social media dissemination plan. We will reach out particularly to popular websites and blogs for people with cancer and provide them with summaries of key findings and implications written for a general audience. This will help to ensure that findings reach a general public audience. Team members will be available for media interviews.

To reach local stakeholders and "close the loop", we will develop a series of presentations intended for a general audience to be presented at each site, with our trial participants, interested groups of cancer consumers, and members of the cancer advocacy community. For all materials developed for release to a general audience and particularly those intended for cancer consumers, we will work with a consumer advisory group comprising people who

have or have had cancer to provide input on whether materials are understandable, appropriate, and sensitive. These efforts will help to ensure that media releases, newsletters, and presentations intended for cancer consumers have the best chance of successfully and impactfully disseminating the important findings from this trial.

5.1 Paper 1: Trial Protocol & Lessons Learned

Paper 1 will be submitted to a journal that publishes trial protocols (e.g., *Trials*, *Contemporary Clinical Trials)* and will detail the trial design, rationale, and summarize lessons learnt from recruitment. Mr. Maccora will be first author. Dr. Wiley will be senior author. All investigators will be co-authors.

5.2 Paper 2: Intervention Efficacy on Primary and Secondary Outcomes

This paper will report the primary outcomes. It will focus on the main effects of CBT, BLT and a test of their interaction on insomnia severity, fatigue symptoms, sleep-related impairment, rest activity rhythms, and health-related quality of life from baseline to post-treatment. Mr. Maccora will be first author. Dr. Wiley will be senior author. All investigators will be co-authors.

5.3 Paper 3: Follow-Up Intervention Efficacy

This paper will report on secondary analyses. It will focus on evaluating the primary effects identified in Paper 2 on the primary and secondary outcomes at follow-up. All investigators will be co-authors. First and last author are to be determined.

5.4 Paper 4: Economic Evaluation

This paper will report on the economic evaluation. It will focus on (i) the cost effectiveness of replacing SHE with CBT alone, BLT alone and CBT+BLT, (ii) the cost effectiveness of adding CBT to BLT alone, and (iii) the cost effectiveness of adding BLT to CBT alone. A/Prof Mortimer and a member of his team will be first and senior author. All investigators will be co-authors.

Additionally analyses and papers will be planned, discussed and approved by the investigator team with authorship as agreed by the team and following recommendations of the International Committee of Medical Journal Editors (ICMJE; http://www.icmje.org/) recommendations for who is an author.

Finally, if our hypotheses regarding the efficacy of CBT and BLT are supported by this study and are shown to be cost effective, we intend to engage an expert in Implementation and Dissemination studies to move toward the next phase of this program of research.

6 Data Sharing Plan

6.1 Data Availability

Data will be available publicly seven years after completion of the final publication.

6.2 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.

6.3 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. All date information will be categorised into study day and month/season as dates may be used to potentially re-identify participants. This process follows best practices used in data de-identification and is informed by national and international privacy laws, including the EU General Data Protection Regulation (GDPR) and good practice including on publishing and sharing sensitive data by the Australian National Data Service. The goal is to balance strong protections of privacy while recognising the significant benefit that individual data can provide to the community through inclusion in individual data meta-analyses allowing questions to be answered about subgroups of participants who most benefit from specific therapies that are impossible to answer without very large clinical trials. Prior to release, we will carefully process all variables, consult with cancer consumers, legal experts from Monash University Office of the General Counsel, and information technology experts from Monash University.

6.4 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.

6.5 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 will be licensed under a CC BY-NC-SA, which prohibits resharing the data commercially.

6.6 Data Access

Seven years after the final publication of the current study, the data and documentation will be shared publicly via Monash Bridges (currently powered by figshare located at: https://bridges.monash.edu/), Monash University's data repository.

6.7 Additional data sharing requirements

None

7 References

Adan, A., & Almirall, H. (1991). Horne & Östberg morningness-eveningness questionnaire: A reduced scale. *Personality and Individual Differences*, *12*(3), 241–253. https://doi.org/10.1016/0191-8869(91)90110-W

Ancoli-Israel, S. (2009). Recognition and Treatment of Sleep Disturbances in Cancer. *Journal of Clinical Oncology*, *27*(35), 5864–5866. https://doi.org/10.1200/JCO.2009.24.5993

Ancoli-Israel, S., Liu, L., Marler, M. R., Parker, B. A., Jones, V., Sadler, G. R., … Fiorentino, L. (2006). Fatigue, sleep, and circadian rhythms prior to chemotherapy for breast cancer. *Supportive Care in Cancer : Official Journal of the Multinational Association of Supportive Care in Cancer*, *14*(3), 201–209. https://doi.org/10.1007/s00520-005-0861-0

Ancoli-Israel, S., Rissling, M., Neikrug, A., Trofimenko, V., Natarajan, L., Parker, B. A., … Liu, L. (2012). Light treatment prevents fatigue in women undergoing chemotherapy for breast cancer. *Supportive Care in Cancer*, *20*(6), 1211–1219. https://doi.org/10.1007/s00520-011-1203-z

Attkisson, C. C., & Zwick, R. (1982). The client satisfaction questionnaire: Psychometric properties and correlations with service utilization and psychotherapy outcome. *Evaluation and Program Planning*, *5*(3), 233–237. https://doi.org/10.1016/0149-7189(82)90074-X

Australian Institute of Health and Welfare. (2019). *Cancer data in Australia* (No. CAN 122). Retrieved from https://www.aihw.gov.au/reports/cancer/cancer-data-in-australia

Bartlett, S. J., Orbai, A.-M., Duncan, T., DeLeon, E., Ruffing, V., Clegg-Smith, K., & Iii, C. O. B. (2015). Reliability and Validity of Selected PROMIS Measures in People with

Rheumatoid Arthritis. *PLOS ONE*, *10*(9), e0138543. https://doi.org/10.1371/journal.pone.0138543

Bastien, C. H., Vallières, A., & Morin, C. M. (2001). Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Medicine*, *2*(4), 297–307. https://doi.org/10.1016/S1389-9457(00)00065-4

Bean, H. R., Stafford, L., Little, R., Diggens, J., Ftanou, M., Alexander, M., ... & Wiley, J. F. (2020). Light-enhanced cognitive behavioural therapy for sleep and fatigue: study protocol for a randomised controlled trial during chemotherapy for breast cancer. Trials, 21, 1-14.

Berger, A. M., Farr, L. A., Kuhn, B. R., Fischer, P., & Agrawal, S. (2007). Values of Sleep/Wake, Activity/Rest, Circadian Rhythms, and Fatigue Prior to Adjuvant Breast Cancer Chemotherapy. *Journal of Pain and Symptom Management*, *33*(4), 398–409. https://doi.org/10.1016/j.jpainsymman.2006.09.022

Bernatchez, M. S., Savard, J., & Ivers, H. (2018). Disruptions in sleep–wake cycles in community-dwelling cancer patients receiving palliative care and their correlates. *Chronobiology International*, *35*(1), 49–62. https://doi.org/10.1080/07420528.2017.1381615

Bower, J. E. (2008). Behavioral symptoms in breast cancer patients and survivors: Fatigue, insomnia, depression, and cognitive disturbance. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *26*(5), 768–777. https://doi.org/10.1200/JCO.2007.14.3248

Broomfield, N. M., & Espie, C. A. (2005). Towards a valid, reliable measure of sleep effort. *Journal of Sleep Research*, *14*(4), 401-407. doi:10.1111/j.1365-2869.2005.00481.x

Buijs, R. M., & Kalsbeek, A. (2001). Hypothalamic integration of central and peripheral clocks. *Nature Reviews Neuroscience*, *2*(7), 521–526. https://doi.org/10.1038/35081582

Caplette-Gingras, A., Savard, J., Savard, M.-H., & Ivers, H. (2013). Is Insomnia Associated With Cognitive Impairments in Breast Cancer Patients? *Behavioral Sleep Medicine*, *11*(4), 239–257. https://doi.org/10.1080/15402002.2012.672940

Carney, C. E., Buysse, D. J., Ancoli-Israel, S., Edinger, J. D., Krystal, A. D., Lichstein, K. L., & Morin, C. M. (2012). The Consensus Sleep Diary: Standardizing Prospective Sleep Self-Monitoring. *Sleep*, *35*(2), 287–302. https://doi.org/10.5665/sleep.1642

Cash, E., Sephton, S. E., Chagpar, A. B., Spiegel, D., Rebholz, W. N., Zimmaro, L. A., … Dhabhar, F. S. (2015). Circadian disruption and biomarkers of tumor progression in breast cancer patients awaiting surgery. *Brain, Behavior, and Immunity*, *48*, 102–114. https://doi.org/10.1016/j.bbi.2015.02.017

Cella, D., Lai, J.-S., Jensen, S. E., Christodoulou, C., Junghaenel, D. U., Reeve, B. B., & Stone, A. A. (2016). PROMIS Fatigue Item Bank had Clinical Validity across Diverse Chronic Conditions. *Journal of Clinical Epidemiology*, *73*, 128–134. https://doi.org/10.1016/j.jclinepi.2015.08.037

Cella, D., Yount, S., Rothrock, N., Gershon, R., Cook, K., Reeve, B., … Rose, M. (2007). The Patient-Reported Outcomes Measurement Information System (PROMIS). *Medical Care*, *45*(5 Suppl 1), S3–S11. https://doi.org/10.1097/01.mlr.0000258615.42478.55

Chelminski, I., Petros, T. V., Plaud, J. J., & Ferraro, F. R. (2000). Psychometric properties of the reduced Horne and Ostberg questionnaire. *Personality and Individual Differences*, *29*(3), 469–478. https://doi.org/10.1016/S0191-8869(99)00208-1

Chevalier, V., Mormont, M.-C., Curé, H., & Chollet, P. (2003). Assessment of circadian rhythms by actimetry in healthy subjects and patients with advanced colorectal cancer. *Oncology Reports*, *10*(3), 733–737. https://doi.org/10.3892/or.10.3.733

Coffman, C. J., Edelman, D., & Woolson, R. F. (2016). To condition or not condition? Analysing 'change' in longitudinal randomised controlled trials. *BMJ Open*, *6*, e013096. doi:10.1136/bmjopen-2016-013096

Costa, A. R., Fontes, F., Pereira, S., Gonçalves, M., Azevedo, A., & Lunet, N. (2014). Impact of breast cancer treatments on sleep disturbances – A systematic review. *The Breast*, *23*(6), 697–709. https://doi.org/10.1016/j.breast.2014.09.003

Devilly, G. J., & Borkovec, T. D. (2000). Psychometric properties of the credibility/expectancy questionnaire. *Journal of Behavior Therapy and Experimental Psychiatry*, *31*(2), 73–86. https://doi.org/10.1016/S0005-7916(00)00012-4

Dozeman, E., Verdonck-de Leeuw, I. M., Savard, J., & van Straten, A. (2017). Guided web-based intervention for insomnia targeting breast cancer patients: Feasibility and effect. *Internet Interventions*, *9*, 1–6. https://doi.org/10.1016/j.invent.2017.03.005

Duffy, J. F., & Czeisler, C. A. (2009). Effect of Light on Human Circadian Physiology. *Sleep Medicine Clinics*, *4*(2), 165–177. https://doi.org/10.1016/j.jsmc.2009.01.004

Edinger, J. D., Means, M. K., Stechuchak, K. M., & Olsen, M. K. (2004). A Pilot Study of Inexpensive Sleep-Assessment Devices. *Behavioral Sleep Medicine*, *2*(1), 41–49. https://doi.org/10.1207/s15402010bsm0201_4

Edinger, J. D., Olsen, M. K., Stechuchak, K. M., Means, M. K., Lineberger, M. D., Kirby, A., & Carney, C. E. (2009). Cognitive Behavioral Therapy for Patients with Primary Insomnia or Insomnia Associated Predominantly with Mixed Psychiatric Disorders: A Randomized Clinical Trial. *Sleep*, *32*(4), 499–510. https://doi.org/10.1093/sleep/32.4.499

Enders, C. K. & Bandalos, D. L. (2001). The relative performance of full information maximum likelihood estimation for missing data in structural equation models. *Structural Equation Modeling, 8*(3), 430-457.

Espie, C., Fleming, L., Cassidy, J., Samuel, L., M Taylor, L., White, C., … Paul, J. (2008). Randomized Controlled Clinical Effectiveness Trial of Cognitive Behavior Therapy Compared With Treatment As Usual for Persistent Insomnia in Patients With Cancer. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *26*, 4651–4658. https://doi.org/10.1200/JCO.2007.13.9006

Filipski, E., King, V. M., Li, X., Granda, T. G., Mormont, M.-C., Claustrat, B., … Lévi, F. (2003). Disruption of circadian coordination accelerates malignant growth in mice. *Pathologie Biologie*, *51*(4), 216–219. https://doi.org/10.1016/S0369-8114(03)00034-8

Fleming, L., Randell, K., Harvey, C.-J., & Espie, C. A. (2014). Does cognitive behaviour therapy for insomnia reduce clinical levels of fatigue, anxiety and depression in cancer patients? *Psycho-Oncology*, *23*(6), 679–684. https://doi.org/10.1002/pon.3468

Fortner, B. V., Stepanski, E. J., Wang, S. C., Kasprowicz, S., & Durrence, H. H. (2002). Sleep and Quality of Life in Breast Cancer Patients. *Journal of Pain and Symptom Management*, *24*(5), 471–480. https://doi.org/10.1016/S0885-3924(02)00500-6

Freedland, K. E., King, A. C., Ambrosius, W. T., Mayo-Wilson, E., Mohr, D. C., Czajkowski, S. M., … Riley, W. T. (2019). The selection of comparators for randomized controlled trials of health-related behavioral interventions: Recommendations of an NIH expert panel. *Journal of Clinical Epidemiology, 110,* 74–81. https://doi.org/10.1016/j.jclinepi.2019.02.011

Galiano-Castillo, N., Arroyo-Morales, M., Ariza-Garcia, A., Fernández-Lao, C., Fernández-Fernández, A. J., & Cantarero-Villanueva, I. (2017). Factors that Explain

the Cancer-Related Insomnia. *The Breast Journal*, *23*(4), 387–394. https://doi.org/10.1111/tbj.12759

Garland, S. N., Carlson, L. E., Stephens, A. J., Antle, M. C., Samuels, C., & Campbell, T. S. (2014). Mindfulness-based stress reduction compared with cognitive behavioral therapy for the treatment of insomnia comorbid with cancer: a randomized, partially blinded, noninferiority trial. *Journal of Clinical Oncology, 32*(5), 449-457.

Garland, S. N., Johnson, J. A., Savard, J., Gehrman, P., Perlis, M., Carlson, L., & Campbell, T. (2014). Sleeping well with cancer: A systematic review of cognitive behavioral therapy for insomnia in cancer patients. *Neuropsychiatric Disease and Treatment*, *10*, 1113–1124. https://doi.org/10.2147/NDT.S47790

Golden, R. N., Gaynes, B. N., Ekstrom, R. D., Hamer, R. M., Jacobsen, F. M., Suppes, T., … Nemeroff, C. B. (2005). The Efficacy of Light Therapy in the Treatment of Mood Disorders: A Review and Meta-Analysis of the Evidence. *American Journal of Psychiatry*, *162*(4), 656–662. https://doi.org/10.1176/appi.ajp.162.4.656

Graci, G. (2005). Pathogenesis and Management of Cancer-Related Insomnia. *The Journal of Supportive Oncology*, *3*(5), 11.

Hallquist, M. N. & Wiley, J. F. (2018). MplusAutomation: An R Package for Facilitating Large-Scale Latent Variable Analyses in Mplus. *Structural Equation Modelling: A Multidisciplinary Journal, 25*(4), 621-638. doi: 10.1080/10705511.2017.1402334

Innominato, P. F., Komarzynski, S., Palesh, O. G., Dallmann, R., Bjarnason, G. A., Giacchetti, S., … Lévi, F. A. (2018). Circadian rest-activity rhythm as an objective biomarker of patient-reported outcomes in patients with advanced cancer. *Cancer Medicine*, *7*(9), 4396–4405. https://doi.org/10.1002/cam4.1711

Johnson, J. A., Garland, S. N., Carlson, L. E., Savard, J., Simpson, J. S. A., Ancoli-Israel, S., & Campbell, T. S. (2018). Bright light therapy improves cancer-related fatigue in

cancer survivors: A randomized controlled trial. *Journal of Cancer Survivorship*, *12*(2), 206–215. https://doi.org/10.1007/s11764-017-0659-3

Johnson, J. A., Rash, J. A., Campbell, T. S., Savard, J., Gehrman, P. R., Perlis, M., … Garland, S. N. (2016). A systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy for insomnia (CBT-I) in cancer survivors. *Sleep Medicine Reviews*, *27*, 20–28. https://doi.org/10.1016/j.smrv.2015.07.001

Kahan, B. C. & Morris, T. P. (2011). Improper analysis of trials randomised using stratified blocks or minimisation. *Statistics in Medicine, 31*, 328-340. doi: 10.1002/sim.4431

Kahan, B. C. & Morris, T. P. (2012). Reporting and analysis of trials using stratified randomisation in leading medical journals: review and reanalysis. *BMJ, 345*, e5840. doi: 10.1136/bmj.e5840

Kvale, E. A., & Shuster, J. L. (2006). Sleep Disturbance in Supportive Care of Cancer: A Review. *Journal of Palliative Medicine*, *9*(2), 437–450. https://doi.org/10.1089/jpm.2006.9.437

Lecrubier, Y., Sheehan, D., Weiller, E., Amorim, P., Bonora, I., Harnett Sheehan, K., … Dunbar, G. (1997). The Mini International Neuropsychiatric Interview (MINI). A short diagnostic structured interview: Reliability and validity according to the CIDI. *European Psychiatry*, *12*(5), 224–231. https://doi.org/10.1016/S0924-9338(97)83296-8

Levin, R. D., Daehler, M. A., Grutsch, J. F., Quiton, J., Lis, C. G., Peterson, C., … Hrushesky, W. J. M. (2005). Circadian function in patients with advanced non-small-cell lung cancer. *British Journal of Cancer*, *93*(11), 1202–1208. https://doi.org/10.1038/sj.bjc.6602859

Maich, K. H. G., Lachowski, A. M., & Carney, C. E. (2018). Psychometric Properties of the Consensus Sleep Diary in Those With Insomnia Disorder. *Behavioral Sleep Medicine*, *16*(2), 117–134. https://doi.org/10.1080/15402002.2016.1173556

Manber, R., Buysse, D. J., Edinger, J., Krystal, A., Luther, J. F., Wisniewski, S. R., ... & Thase, M. E. (2016). Efficacy of Cognitive-Behavioral Therapy for Insomnia Combined With Antidepressant Pharmacotherapy in Patients With Comorbid Depression and Insomnia: A Randomized Controlled Trial. *The Journal of Clinical Psychiatry*, *77*(10), e1316-e1323.

Maranhão, M. F., Estella, N. M., Cury, M. E. G., Amigo, V. L., Picasso, C. M., Berberian, A., … Claudino, A. M. (2015). The effects of repetitive transcranial magnetic stimulation in obese females with binge eating disorder: A protocol for a double-blinded, randomized, sham-controlled trial. *BMC Psychiatry*, *15*(1), 194. https://doi.org/10.1186/s12888-015-0569-8

McAlister, F. A., Straus, S. E., Sackett, D. L., & Altman, D. G. (2003). Analysis and Reporting of Factorial Trials: A Systematic Review. *JAMA*, *289*(19), 2545–2553. https://doi.org/10.1001/jama.289.19.2545

Miller, C. B., Valenti, L., Harrison, C. M., Bartlett, D. J., Glozier, N., Cross, N. E., … Marshall, N. S. (2017). Time Trends in the Family Physician Management of Insomnia: The Australian Experience (2000–2015). *Journal of Clinical Sleep Medicine*, *13*(06), 785–790. https://doi.org/10.5664/jcsm.6616

Morin, C. M. (2003). Measuring outcomes in randomized clinical trials of insomnia treatments. *Sleep Medicine Reviews*, *7*(3), 263–279. https://doi.org/10.1053/smrv.2002.0274

Morin, C. M., Belleville, G., Bélanger, L., & Ivers, H. (2011). The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. *Sleep*, *34*(5), 601–608. https://doi.org/10.1093/sleep/34.5.601

Morin, C. M., Colecchi, C., Stone, J., Sood, R., & Brink, D. (1999). Behavioral and Pharmacological Therapies for Late-Life Insomnia: A Randomized Controlled Trial. *JAMA*, *281*(11), 991–999. https://doi.org/10.1001/jama.281.11.991

Morin, C. M., Vallières, A., Guay, B., Ivers, H., Savard, J., Mérette, C., … Baillargeon, L. (2009). Cognitive Behavioral Therapy, Singly and Combined With Medication, for Persistent Insomnia: A Randomized Controlled Trial. *JAMA*, *301*(19), 2005–2015. https://doi.org/10.1001/jama.2009.682

Morin, C. M., Vallières, A., & Ivers, H. (2007). Dysfunctional Beliefs and Attitudes about Sleep (DBAS): Validation of a Brief Version (DBAS-16). *Sleep*, *30*(11), 1547–1554. https://doi.org/10.1093/sleep/30.11.1547

Mormont, M.-C., Waterhouse, J., Bleuzen, P., Giacchetti, S., Jami, A., Bogdan, A., … Lévi, F. (2000). Marked 24-h Rest/Activity Rhythms Are Associated with Better Quality of Life, Better Response, and Longer Survival in Patients with Metastatic Colorectal Cancer and Good Performance Status. *Clinical Cancer Research*, *6*(8), 3038–3045.

Muthen, L. K. & Muthen, B. O. (2002). How to use a Monte Carlo study to decide on sample size and determine power. *Structural Equation Modelling: A Multidisciplinary Journal*, *9*(4), 599-620. doi: 10.1207/S15328007SEM0904_8

Neikrug, A. B., Rissling, M., Trofimenko, V., Liu, L., Natarajan, L., Lawton, S., … Ancoli-Israel, S. (2012). Bright Light Therapy Protects Women from Circadian Rhythm Desynchronization During Chemotherapy for Breast Cancer. *Behavioral Sleep Medicine*, *10*(3), 202–216. https://doi.org/10.1080/15402002.2011.634940

Nicassio, P. M., Mendlowitz, D. R., Fussell, J. J., & Petras, L. (1985). The phenomenology of the pre-sleep state: The development of the pre-sleep arousal scale. *Behaviour Research and Therapy*, *23*(3), 263–271. https://doi.org/10.1016/0005-7967(85)90004-X

Okajima, I., Komada, Y., & Inoue, Y. (2011). A meta-analysis on the treatment effectiveness of cognitive behavioral therapy for primary insomnia: CBT for insomnia: a meta-analysis. *Sleep and Biological Rhythms*, *9*(1), 24–34. https://doi.org/10.1111/j.1479-8425.2010.00481.x

Ortiz-Tudela, E., Innominato, P. F., Rol, M. A., Lévi, F., & Madrid, J. A. (2016). Relevance of internal time and circadian robustness for cancer patients. *BMC Cancer*, *16*(1), 285. https://doi.org/10.1186/s12885-016-2319-9

Otte, J. L., Carpenter, J. S., Manchanda, S., Rand, K. L., Skaar, T. C., Weaver, M., … Landis, C. (2015). Systematic review of sleep disorders in cancer patients: Can the prevalence of sleep disorders be ascertained? *Cancer Medicine*, *4*(2), 183–200. https://doi.org/10.1002/cam4.356

Pail, G., Huf, W., Pjrek, E., Winkler, D., Willeit, M., Praschak-Rieder, N., & Kasper, S. (2011). Bright-Light Therapy in the Treatment of Mood Disorders. *Neuropsychobiology*, *64*(3), 152–162. https://doi.org/10.1159/000328950

Palesh, O., Peppone, L., Innominato, P. F., Janelsins, M., Jeong, M., Sprod, L., … Mustian, K. (2012). Prevalence, putative mechanisms, and current management of sleep problems during chemotherapy for cancer. *Nature and Science of Sleep*, *4*, 151–162. https://doi.org/10.2147/NSS.S18895

Palesh, O., Scheiber, C., Kesler, S., Janelsins, M. C., Guido, J. J., Heckler, C., … Mustian, K. M. (2018). Feasibility and acceptability of brief behavioral therapy for cancer-related insomnia: Effects on insomnia and circadian rhythm during chemotherapy: a phase II

randomised multicentre controlled trial. *British Journal of Cancer*, *119*(3), 274–281. https://doi.org/10.1038/s41416-018-0154-2

Palesh, Oxana G., Roscoe, J. A., Mustian, K. M., Roth, T., Savard, J., Ancoli-Israel, S., … Morrow, G. R. (2010). Prevalence, Demographics, and Psychological Associations of Sleep Disruption in Patients With Cancer: University of Rochester Cancer Center–Community Clinical Oncology Program. *Journal of Clinical Oncology*, *28*(2), 292–298. https://doi.org/10.1200/JCO.2009.22.5011

Palesh, Oxana Gronskaya, Collie, K., Batiuchok, D., Tilston, J., Koopman, C., Perlis, M. L., … Spiegel, D. (2007). A longitudinal study of depression, pain, and stress as predictors of sleep disturbance among women with metastatic breast cancer. *Biological Psychology*, *75*(1), 37–44. https://doi.org/10.1016/j.biopsycho.2006.11.002

Pati, D. A. K., Parganiha, A., Kar, A., Soni, R., Roy, S., & Choudhary, V. (2007). Alterations of the Characteristics of the Circadian Rest-Activity Rhythm of Cancer In-Patients. *Chronobiology International*, *24*(6), 1179–1197. https://doi.org/10.1080/07420520701800868

Pettersson, A., Modin, S., Wahlström, R., Hammarberg, S. af W., & Krakau, I. (2018). The Mini-International Neuropsychiatric Interview is useful and well accepted as part of the clinical assessment for depression and anxiety in primary care: A mixed-methods study. *BMC Family Practice*, *19*(1), 19. https://doi.org/10.1186/s12875-017-0674-5

Pilkonis, P. A., Choi, S. W., Reise, S. P., Stover, A. M., Riley, W. T., & Cella, D. (2011). Item Banks for Measuring Emotional Distress From the Patient-Reported Outcomes Measurement Information System (PROMIS®): Depression, Anxiety, and Anger. *Assessment*, *18*(3), 263–283. https://doi.org/10.1177/1073191111411667

Pinninti, N. R., Madison, H., Musser, E., & Rissmiller, D. (2003). MINI International Neuropsychiatric Schedule: Clinical utility and patient acceptance. *European Psychiatry*, *18*(7), 361–364. https://doi.org/10.1016/j.eurpsy.2003.03.004

Redd, W. H., Valdimarsdottir, H., Wu, L., Winkel, G., Byrne, E. E., Beltre, M. A., … Ancoli-Israel, S. (2014). Systematic Light Exposure in the Treatment of Cancer-Related Fatigue: A Preliminary Study. *Psycho-Oncology*, *23*(12), 1431–1434. https://doi.org/10.1002/pon.3553

Riemann, D., Baglioni, C., Bassetti, C., Bjorvatn, B., Groselj, L. D., Ellis, J. G., … Spiegelhalder, K. (2017). European guideline for the diagnosis and treatment of insomnia. *Journal of Sleep Research*, *26*(6), 675–700. https://doi.org/10.1111/jsr.12594

Ritterband, L. M., Bailey, E. T., Thorndike, F. P., Lord, H. R., Farrell-Carnahan, L., & Baum, L. D. (2012). Initial evaluation of an Internet intervention to improve the sleep of cancer survivors with insomnia. *Psycho-Oncology*, *21*(7), 695–705. https://doi.org/10.1002/pon.1969

Rogers, N. L., Dorrian, J., & Dinges, D. F. (2003). Sleep, waking and neurobehavioural performance. *Frontiers in Bioscience : A Journal and Virtual Library*, *8*, NaN-NaN. https://doi.org/10.2741/1174

Savard, J., Ivers, H., Villa, J., Caplette-Gingras, A., & Morin, C. (2011). Natural Course of Insomnia Comorbid With Cancer: An 18-Month Longitudinal Study. *Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology*, *29*, 3580–3586. https://doi.org/10.1200/JCO.2010.33.2247

Savard, J., Liu, L., Natarajan, L., Rissling, M. B., Neikrug, A. B., He, F., … Ancoli-Israel, S. (2009). Breast Cancer Patients have Progressively Impaired Sleep-Wake Activity

Rhythms during Chemotherapy. *Sleep*, *32*(9), 1155–1160. https://doi.org/10.1093/sleep/32.9.1155

Savard, J., Simard, S., Ivers, H., & Morin, C. M. (2005). Randomized Study on the Efficacy of Cognitive-Behavioral Therapy for Insomnia Secondary to Breast Cancer, Part I: Sleep and Psychological Effects. *Journal of Clinical Oncology*, *23*(25), 6083–6096. https://doi.org/10.1200/JCO.2005.09.548

Savard, J., Villa, J., Simard, S., Ivers, H., & Morin, C. M. (2011). Feasibility of a self-help treatment for insomnia comorbid with cancer. *Psycho-Oncology*, *20*(9), 1013–1019. https://doi.org/10.1002/pon.1818

Savard, M.-H., Savard, J., Simard, S., & Ivers, H. (2005). Empirical validation of the Insomnia Severity Index in cancer patients. *Psycho-Oncology*, *14*(6), 429–441. https://doi.org/10.1002/pon.860

Savvidis, C., & Koutsilieris, M. (2012). Circadian Rhythm Disruption in Cancer Biology. *Molecular Medicine*, *18*(9), 1249–1260. https://doi.org/10.2119/molmed.2012.00077

Schutte-Rodin, S. (2008). Clinical Guideline for the Evaluation and Management of Chronic Insomnia in Adults. *Journal of Clinical Sleep Medicine*, *4*(5), 18.

Sheehan, D., Lecrubier, Y., Harnett Sheehan, K., Janavs, J., Weiller, E., Keskiner, A., … Dunbar, G. (1997). The validity of the Mini International Neuropsychiatric Interview (MINI) according to the SCID-P and its reliability. *European Psychiatry*, *12*(5), 232–241. https://doi.org/10.1016/S0924-9338(97)83297-X

Silverstein, M. J., Faraone, S. V., Alperin, S., Biederman, J., Spencer, T. J., & Adler, L. A. (2017). How Informative Are Self-Reported Adult Attention-Deficit/Hyperactivity Disorder Symptoms? An Examination of the Agreement Between the Adult Attention-Deficit/Hyperactivity Disorder Self-Report Scale V1.1 and Adult Attention-Deficit/Hyperactivity Disorder Investigator Symptom Rating Scale. *Journal of Child*

and Adolescent Psychopharmacology, *28*(5), 339–349. https://doi.org/10.1089/cap.2017.0082

Smith, M. T., Huang, M. I., & Manber, R. (2005). Cognitive behavior therapy for chronic insomnia occurring within the context of medical and psychiatric disorders. *Clinical Psychology Review*, *25*(5), 559–592. https://doi.org/10.1016/j.cpr.2005.04.004

Spielman, A. J., Caruso, L. S., & Glovinsky, P. B. (1987). A Behavioral Perspective on Insomnia Treatment. *Psychiatric Clinics of North America*, *10*(4), 541–553. https://doi.org/10.1016/S0193-953X(18)30532-X

Taylor, D. J., Kelly, K., Kohut, M. L., & Song, K.-S. (2017). Is Insomnia a Risk Factor for Decreased Influenza Vaccine Response? *Behavioral Sleep Medicine*, *15*(4), 270–287. https://doi.org/10.1080/15402002.2015.1126596

Taylor, D. J., & Pruiksma, K. E. (2014). Cognitive and behavioural therapy for insomnia (CBT-I) in psychiatric populations: a systematic review. *International Review of Psychiatry*, 26(2), 205-213.

Taylor, D. J., Wilkerson, A. K., Pruiksma, K. E., Williams, J. M., Ruggero, C. J., Hale, W., … Peterson, A. L. (2018). Reliability of the Structured Clinical Interview for DSM-5 Sleep Disorders Module. *Journal of Clinical Sleep Medicine*, *14*(03), 459–464. https://doi.org/10.5664/jcsm.7000

Thomas, A., Grandner, M., Nowakowski, S., Nesom, G., Corbitt, C., & Perlis, M. L. (2016). Where are the Behavioral Sleep Medicine Providers and Where are They Needed? A Geographic Assessment. *Behavioral Sleep Medicine*, *14*(6), 687–698. https://doi.org/10.1080/15402002.2016.1173551

Thomas, K. S., Bower, J., Hoyt, M. A., & Sepah, S. (2010). Disrupted sleep in breast and prostate cancer patients undergoing radiation therapy: The role of coping processes. *Psycho-Oncology*, *19*(7), 767–776. https://doi.org/10.1002/pon.1639

Thorndike, F. P., Ritterband, L. M., Saylor, D. K., Magee, J. C., Gonder-Frederick, L. A., & Morin, C. M. (2011). Validation of the Insomnia Severity Index as a Web-Based Measure. *Behavioral Sleep Medicine*, *9*(4), 216–223. https://doi.org/10.1080/15402002.2011.606766

Twisk, J., Bosman, L., Hoekstra, T., Rijnhart, J., Welten, M., & Heymans, M. (2018). Different ways to estimate treatment effects in randomised controlled trials. *Contemporary Clinical Trials Communications, 10*, 80-85. https://doi.org/10.1016/j.conctc.2018.03.008

van Maanen, A., Meijer, A. M., van der Heijden, K. B., & Oort, F. J. (2016). The effects of light therapy on sleep problems: A systematic review and meta-analysis. *Sleep Medicine Reviews*, *29*, 52–62. https://doi.org/10.1016/j.smrv.2015.08.009

Wigal, T. L., Newcorn, J. H., Handal, N., Wigal, S. B., Mulligan, I., Schmith, V., & Konofal, E. (2018). A Double-Blind, Placebo-Controlled, Phase II Study to Determine the Efficacy, Safety, Tolerability and Pharmacokinetics of a Controlled Release (CR) Formulation of Mazindol in Adults with DSM-5 Attention-Deficit/Hyperactivity Disorder (ADHD). *CNS Drugs*, *32*(3), 289–301. https://doi.org/10.1007/s40263-018-0503-y

Wu, L. M., Amidi, A., Valdimarsdottir, H., Ancoli-Israel, S., Liu, L., Winkel, G., … Redd, W. H. (2018). The Effect of Systematic Light Exposure on Sleep in a Mixed Group of Fatigued Cancer Survivors. *Journal of Clinical Sleep Medicine*, *14*(01), 31–39. https://doi.org/10.5664/jcsm.6874

Yost, K. J., Eton, D. T., Garcia, S. F., & Cella, D. (2011). Minimally important differences were estimated for six PROMIS-Cancer scales in advanced-stage cancer patients. *Journal of Clinical Epidemiology, 64*(5), 507-516. doi:10.1016/j.jclinepi.2010.11.018.

Yu, L., Buysse, D. J., Germain, A., Moul, D. E., Stover, A., Dodds, N. E., … Pilkonis, P. A. (2012). Development of Short Forms From the PROMIS™ Sleep Disturbance and Sleep-Related Impairment Item Banks. *Behavioral Sleep Medicine, 10*(1), 6–24. https://doi.org/10.1080/15402002.2012.636266

Zachariae, R., Amidi, A., Damholdt, M. F., Clausen, C. D. R., Dahlgaard, J., Lord, H., … Ritterband, L. M. (2018). Internet-Delivered Cognitive-Behavioral Therapy for Insomnia in Breast Cancer Survivors: A Randomized Controlled Trial. *JNCI: Journal of the National Cancer Institute, 110*(8), 880–887. https://doi.org/10.1093/jnci/djx293

Appendix A - Inclusion and Exclusion Criteria

1. Inclusion Criteria

(a) **Breast cancer** diagnosis;

(b) Age ≥ 18 years;

(c) Receiving oral or intravenous cytotoxic chemotherapy, with at least 6 more weeks of treatment anticipated at the time of enrolment;

(d) Able to understand intervention materials in English and complete surveys in English;

(e) Able to provide informed consent;

(f) Having regular access to email and internet.

2. Exclusion Criteria

(a) History of suffering migraines;

(b) Report severe current psychopathology, including Manic and Hypomanic Episodes, Post-traumatic Stress Disorder other than cancer-related and Psychotic Disorders; OR psychopathology within the past 12 months including alcohol Dependence/Abuse and Substance Dependence/Abuse;

(c) Male;

(d) Daily use of sleep medications or herbal sleep aids for the previous two weeks and/or ongoing or planned daily use during the trial (occasional use is allowed), an example list is provided at the end of this appendix;

(e) Brain metastasis with daily steroid use;

(f) Participants who show the following symptoms of sleep disorders:

a. Sleep apnoea: loud snoring OR observed gasping or pauses in breathing OR previously diagnosed with apnoea hypopnea index >15 but not/inadequately treated, as assessed through the SCISD-R interview.

b. Previously diagnosed Periodic Limb Movement Disorder with arousal index > 15

c. Restless Legs Syndrome (RLS; based on the SCISD-R) occurring ≥3 times/week, with duration of at least one month.

d. Circadian rhythm disorders (based on the SCISD-R):

- Irregular Sleep Wake Disorder
- Non-24-Hour Sleep-Wake Syndrome
- Advance Sleep-Phase Syndrome (if habitual bedtime is earlier than 9 pm and habitual wake time is earlier than 5 am. Occasional deviation from this schedule is allowed.)

- Delayed Sleep-Phase Syndrome (if habitual bedtime is later than 2 am and habitual wake time is later than 10 am. Occasional deviation from this schedule is allowed.)
- Fixed night shift work between midnight and 5 a.m., or rotating work schedules that require night shifts during their participation.
- Narcolepsy.

e. Other previously diagnosed sleep disorders – if severe (discuss with CPI).

3. General Rationale and Justification

Inclusion and exclusion criteria were purposefully selected to be broad to promote the generalizability of findings and to be consistent with other large clinical trials of sleep in cancer (e.g., Garland et al, 2014 published in *JCO*, the top medical oncology journal; Zacharieae, et al., 2018, published in *JNCI*, one of the top medical oncology journals; https://clinicaltrials.gov/ct2/show/NCT02444026). These trials excluded other sleep disorders and severe psychiatric disorders, but did not exclude based on medications or other treatments (other than current sleep treatment). Consistent with this approach, we designed our exclusion criteria primarily to address contexts where the intended sleep treatments are unlikely to produce benefit or may cause harm (e.g., non-24-hour sleep-wake syndrome makes it impossible to accurately time delivery of light without collecting burdensome circadian biomarkers; migraines where bright light can trigger migraines). Sleep medications are commonly prescribed and used to manage poor sleep and are not an exclusion criteria for this trial when used acutely as it is common practice, safe, and still effective to deliver CBT alongside sleep medications and there is no evidence of contraindications for sleep medications and BLT. Instead, we have included exclusion criteria for regular use (see below 5.D) and will carefully assess and control for infrequent sleep medication use in analysis, with coding and classification of medications overseen by Dr. Alexander, an expert in pharmacological research. Similarly, insomnia is commonly comorbid with physical and psychiatric conditions and treated concurrently (e.g., Manber et al, 2016). A systematic review suggests that CBT remains effective in these populations, including those with dependence on hypnotics (Taylor & Pruiksma, 2014). Therefore, we do not anticipate safety risks associated with participants on medications and to allow findings to be more representative of typical oncology populations elected not to exclude people on non-regular medication use.

There are no exclusion criteria based on insomnia symptoms for three reasons. First, data suggest that up to 87% of people with cancer experience some symptoms of sleep

disturbance so we anticipate most participants will have room to benefit. Second, it is known that sleep and fatigue often worsen during chemotherapy. Even if someone does not currently have significant symptoms, they may develop. Third, unpublished data from a previous sleep trial in our group for women with breast cancer going through chemotherapy showed that of women with "no clinically significant insomnia", captured by a score of 0 - 7 on the Insomnia Severity Index, at screening and randomisation, 64.3% of them reach subthreshold symptoms at least once during the 12 weeks of the trial demonstrating that in the specific populations and sites from which we will recruit, excluding based on an initial screen risks not offering sleep treatment to women who may benefit later.

4. Rational and Justification for Inclusion Criteria

(a) We are focusing on breast cancer as our prior study provides a strong foundation to build on in this population.

(b) We require all participants to be adults as our intervention involves a large self-directed component (via emails and audio files) tailored towards adults.

(c) Research shows chemotherapy is the time of the highest sleep disturbance in cancer. No data currently indicates whether specific types of chemotherapy have more or less impact on sleep, so all types are allowed.

(d) We require all participants to be able to understand and respond to surveys in English. Although some questions and aspects of the intervention can readily be translated, some of the patient reported outcomes are not validated in other languages. Further cultural differences in somatic symptoms exist. These are interesting and important areas of research, but are outside the scope of this current trial.

(e) Due to the large self-directed components of this trial, people with significant cognitive impairments that would require a guardian providing informed consent on their behalf would make this trial inappropriate.

(f) In consultation with cancer consumers, we selected email as the format to deliver additional, remote components of the intervention. Receiving these components requires internet access.

5. Rational and Justification for Exclusion Criteria

(a) People with migraines often are sensitive to bright light and bright light is a risk factor for triggering migraines. As bright light is a key component of this trial, we exclude these individuals to minimize any risk from participating in the trial.

(b) Severe current psychopathology can interfere with the ability to fully engage in the self-directed aspects of this trial and the trial is not an appropriate sleep treatment for

these conditions. When identified, we will refer these participants to appropriate supportive services, which may include both psychosocial and specialist sleep support as needed.

(c) Nearly all people with breast cancer are women (over 99%). Thus, we are unable to recruit sufficient men with breast cancer to examine whether the intervention is safe and effective for them. In addition, preliminary meta-analysis of individual patient data in our group show that men and women differ in their response to cognitive behavioural therapy for insomnia, which could add heterogeneity. Therefore, men are excluded from the current study and we hope to run future trials in cancer types that include men.

(d) Regular use of sleep medications or select herbal sleep aids for which an evidence base exists would prevent examining the effect or our intervention effects and even if stopping would preclude a true baseline assessment. Ongoing or planned use of sleep medications or evidence-based herbal sleep aids also would impact trial results. A detailed list is included at the end of this appendix.

(e) Our trial is focused primarily on treating sleep disturbance and insomnia. Other sleep disorders can cause disturbed sleep but require pharmacological (e.g., periodic limb movement disorder) or mechanical (e.g., obstructive sleep apnoea) treatment that is not provided in the current trial. If these disorders are identified during interviews, appropriate referrals to specialist sleep clinics will be made. As part of the Monash Sleep Network (https://www.monash.edu/medicine/msn/home), we have close connections to the highest quality specialist sleep clinicians across Victoria and we will ensure any participants identified as likely having another sleep disorder are referred to a nearby, appropriate sleep service.

Excluded Sleep Medication and Herbal Sleep Aids

- Benzodiazepines and benzodiazepine-like medications
  - temazepam (Temaze, Restoril)
  - nitrazepam (Mogadon, Alodorm)
  - zolpidem (Stilnox, Ambien, Intermezzo)
  - flunitrazepam
  - zopiclone / eszopiclone (Imovane, Zimovane, Lunesta)
  - triazolam (Halcion)
  - midazolam (Versed, Dormicum, Hypnovel)

    - zaleplon (Sonata)
    - diazepam (Valium)
    - alprazolam (Xanax)
    - oxazepam (Serax)
    - lorazepam (Ativan)
    - bromazepam (Lexotan, Lexotanil)
    - clobazam (Onfi)
    - clonazepam (Klonopin)
    - clorazepate (Tranxene)
    - chlordiazepoxide (Librium)
- suvorexant (Belsomra)
- melatonin (Circadin)
- Herbal Sleep Aids
    - Valerian
    - Kava
    - Wuling
    - Hops

Appendix B – Cognitive Behaviour Therapy Protocol

A trained member of the research team will meet in person with participants for an initial orientation session covering the following aspects: (a) overview and rationale, this includes an introduction to program core principles (e.g., cognitive behavioural principles), an overview of topics covered, and highlight of core components; (b) structure of the program and logistics, and; (c) importance of practice and regular application of strategies.

The cognitive-behavioural intervention material will be delivered via email. These materials will contain evidence-based information and strategies for application. Content will be written in succinct plain language with appropriate layout and presentation to assist readability and utility.

Program materials will be delivered to participants in the CBT and CBT+BLT intervention groups. The program materials themselves are provided in an attached document. A description of weekly email content is outlined below.

Module	Content Overview
1a	This email module includes an overview of the factors that determine how well we sleep and some healthy habits toward sleep that we encourage participants to practice throughout their cancer treatment.
1b	This email module will cover how healthy beliefs and thoughts about sleep can help promote good sleep and help manage daytime impairment.
2a	This email module will cover the differences between sleep deprivation and insomnia and how to cope with these experiences. This email also includes information on ‘stimulus control’, a strategy that improves sleep.
2b	This email module will review healthy practices and attitudes that help support good sleep.
3a	This module will give you tools to better understand and manage fatigue and improve daytime functioning.
3b	This module will provide information on staying present, anchoring attention and calming the mind. Practising these techniques will help participants to quiet their mind before bed.
4a	This email module includes information on relaxation and strategies to reduce feelings of stress and tension that often interfere with good sleep. We will also cover some techniques for sleeping with pain and physical discomfort.
4b	This email module includes some techniques for coping with symptoms of pain and physical discomfort that often occur during cancer treatment.
5a	This email module includes information on dealing with anxiety and the worries that participants are likely to experience throughout their cancer diagnosis.
5b	This email module provides strategies for managing pre-sleep worries and ruminations.
6a	This email is aimed to prepare participants for sleeping well into the future, even after the conclusion of this six-week program.
6b	This final email covers the most important points covered in previous modules. Participants are encouraged to reflect on what has worked for them and make mental notes on strategies and concepts they want to remind themselves of in the future.

Appendix C - Bright Light Therapy 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+BLT or BLT session and will be instructed to wear them for a minimum of 20 minutes per day with glasses fixed at 1500 lux upon awakening each morning. Specific timing of light glasses use will be established individually with each participant during the initial consultation .

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 Structured Clinical Interview for Sleep Disorders Revised (SCISD-R).

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 bright light therapy initial consultation , 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 (BLT) – Daytime

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

- Review habitual sleep timing using information already obtained from SCISD 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 BLT 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 per day (with glasses fixed at 1500 lux) 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 BLT 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 them to the correct wearing angle. Check that they are comfortable with the 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 BLT 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 optimal.

- Acknowledge natural fluctuation of sleep/wake timing. If they get 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 SCISD-R) AND do not wish to further advance sleep timing AND do not have any morning grogginess/fatigue: ask them to use the glasses two hours 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 BLT use

- Explain that some benefits of BLT use may be noticeable soon after they commence BLT, 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 BLT 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 BLT 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 BLT 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. Forgetting to wear the glasses in the morning – set an alarm/reminder on your phone, have a reminder note next to your bed.

2. Not getting enough time in the morning to use the light glasses – explain that they can still undertake their daily activities as usual and the glasses will generally not interfere with their tasks.
3. Tendency to use electronic devices at night (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. Turning on many lights during the night (e.g., to care for 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
    - BLT has many benefits for improving sleep, mood and fatigue
    - 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 BLT 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

Appendix D - Risk Management Protocol

This document details how any sleep disorders, physical or mental health concerns that may be identified during this project will be managed, to ensure patient safety.

Initial screening questionnaires as well as follow-up questionnaires administered throughout the study include questions about sleep disorders, as well as current and past mental health. Light Therapy glasses will also be provided to the corresponding intervention arms. A variety of methods to ensure appropriate care and safety of participants will be undertaken.

Study Coordinator (responsible for recruitment)

Jordan Maccora (study coordinator) is a provisional psychologist undertaking his Doctor of Philosophy (Clinical Psychology) degree. He will be undertaking and overseeing recruitment on this project. Recruitment will take place on set days at each site, typically while participants are receiving chemotherapy. Follow-up phone calls will also be made to study participants on set days, from recruitment sites or Monash University.

Supervision of the Study coordinator

Throughout this study, Jordan will attend supervision on a regular basis (and upon request) with the PeterMac Site Principal investigator Ms Justine Diggens. Justine is a Senior Clinical Psychologist in the Psychosocial Oncology Service at the Peter MacCallum Cancer Centre with extensive experience in mental health triage, assessment and intervention.

Jordan will also attend weekly supervision with Coordinating Principal Investigator Dr Joshua Wiley. Dr Wiley is a Research Psychologist with extensive experience in the implementation of research in clinical settings and chief investigator on multiple clinical trials in oncology.

Identification of sleep disorders

- During screening for eligibility, participants will be screened for the following sleep disorders: narcolepsy, sleep apnoea, periodic limb movement disorder, restless legs syndrome, circadian rhythm sleep disorders.
- The Study coordinator will also monitor online survey responses over time to identify severe symptoms of sleep disturbance (ISI > 22).
- When sleep disorders or severe sleep disturbances are identified, the Study coordinator will initiate a discussion with the participant (during the screening itself, or via phone contact) to inform them of their responses to the survey's and explore their symptoms. *"You mentioned….. (describe sleep concerns to do with apnoea, restless leg or delayed*

or advanced sleep phase/irregular patterns, or severe scores on ISI). Have you ever seen a doctor or sleep specialist about these problems?" If not: *"Does your sleep pattern impact you negatively? Would you like to talk about some services that could help treat your sleep problems?"* If yes: The study coordinator will encourage participants to discuss screening results and referral options with their oncologist or GP. High ISI scores will not preclude participants from continuing in the study.

- The study coordinator will notify the participants' medical treating team of screening outcomes by email (and inform the participant they will do this), and the study coordinator will write a brief note in the participant's electronic medical file (e.g, *"Participant identified as at risk for sleep apnoea during survey screening as part of the following study; The SleepCare Study: a randomized controlled trial for sleep and fatigue during chemotherapy. Screening results were discussed with the patient, and the patient reported this was/was not a significant problem for her. Participants were advised to discuss screening results and referral options with their oncologist or GP").*
- The appropriate Site Principal Investigator will be cc'd into the email to the participants' treating team.

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 Study coordinator will notify the participants' medical treating team, and write a brief note in the participant's electronic medical file (*e.g, "During participation in the study; The SleepCare Study: a randomized controlled trial for sleep and fatigue during chemotherapy, the participant reported physical complaints of (insert specific problem). The participant's medical treating team were notified to provide follow-up care").*

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

There are a number of time points in this study where participants may disclose distress or mental health concerns.

- During participant consent and screening for eligibility with the Study coordinator or a trained member of the research team.

- During the initial face to face consultation (30-75 mins, depending on group allocation) with the Study coordinator or a trained member of the research team.
- During a 30-minute phone consultation with the Study coordinator or a trained member of the research team mid-way through the study to check on participants' experience of the study emails and light glasses (Researcher to call from recruitment site or Monash University)
- During participant call-back following messages left on the study phone number. These will be responded to within one week by the Study coordinator or a trained member of the research team and all response calls will be made from recruitment site or Monash University.
- Through monitoring of online survey responses by the Study coordinator, for undesirable experiences (high anxiety or depression scores – see below for more detail).
- During telephone administration of study surveys (if the participant declines to respond online). These include surveys about sleep, depression, anxiety, fatigue, pain, thoughts and beliefs.

<u>During Consent and Screening for Eligibility</u>

During the recruitment and consent process, and included in the PICF, participants will be advised of the following: There are no significant foreseen risks in participating in this study. It is possible that when completing some questionnaires about your feelings, you might think about things that upset you. If you do not wish to answer a question, you may skip it and go to the next question, or you may stop immediately. If you become upset or distressed as a result of your participation in this research, or if the research team is concerned about your physical or psychological well-being, we will inform your treating team (this may include your oncologist, nurse, allied health or psychosocial departments) who will be able to discuss your needs and assist in arranging appropriate support and follow-up. You can also contact Jordan Maccora or Dr Josh Wiley during business hours 9am – 4pm on weekdays (contact information is detailed at the end of this form). Any counselling or psychological support provided by staff at the Peter MacCallum Cancer Centre or Monash Health will be provided free of charge. If you prefer to speak to someone independent of this study about your distress, we strongly encourage you to speak to your GP, who will be able to link you to appropriate support. If you are in crisis and would like to speak to a trained professional urgently, please call Lifeline at 13 11 14. A list of mental health services (includes 24-hour help lines) will also be provided where appropriate.

Participants are also advised in the PICF that they are able to withdraw from the project at any time and project participation and/or withdrawal will not impact any aspect of their cancer treatment and healthcare.

Participants will also be verbally informed of the reasons for screening for eligibility : *"Before we start, I need to let you know that the sleep program is not necessarily going to be suitable or the right fit for everyone, so I am going to ask some questions to help determine this. These questions are about your sleep, as well as your emotional health and well-being. If any concerns come up about your sleep or emotional well-being while we work through these questions, we can talk more about them, and see if there any other services or supports that would be helpful for you.*

The M.I.N.I will also be administered by the Study coordinator, which screens for psychiatric disorder (modules A, C, H, I, J, K, N, including major depressive disorder, manic/hypomanic/bipolar disorder, substance or alcohol use disorder, PTSD, psychotic disorder, and generalised anxiety disorder). Recruitment will cease at 2pm at the latest (in person with the patient or by phone from the recruitment site), to ensure sufficient time within business hours that day to manage any urgent risk issues that may be identified.

When psychiatric disorder identified during screening

Any patient with psychiatric condition/s identified during screening will have their screening results discussed with them.

The Study coordinator will briefly explore the participant's concerns and existing supports. For example, *"You mentioned… (describe psychiatric disorder identified). Are these symptoms a concern for you? Do they cause you any trouble or distress in your life? Are you receiving any support or assistance from a health professional? If Yes, clarify the nature of treatment. Do you feel it would be helpful to speak to a health professional about these concerns/symptoms?*

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 psychological support services available to them through the site of their cancer treatment (Peter MacCallum Cancer Centre or Monash Health), and options of self-referral.
- Options of direct referral by the Study Coordinator to site specific psychological support services when deemed appropriate, for intake of their needs.
- That they discuss their concerns with their GP.

Outcomes will be discussed with the participant e.g., *"That's great, I'm glad that you are receiving support at the moment from your psychiatrist. I am going to let your treating team here know as well, just so they are aware of what's going on for you. Your wellbeing is our priority. Please let them know if you think you need additional supports. They can help you work out a plan."*

Informing the participants treating team of outcomes

The Study coordinator or a trained member of the research team will email the participant's treating team (medical oncologist and nurse coordinator) regarding symptoms disclosed and outcomes – e.g.,

- "The participant did not feel symptoms were of concern and declined options of being linked into support services"
- "The participant was happy to discuss their concerns/symptoms with their existing GP/psychologist/psychiatrist and reported that they will continue to receive support/assistance from these health professionals"
- "The participant would like to discuss referral/treatment options with their medical team, and I have encouraged them to raise these at their next appointment with you"
- "A direct referral to the psychological support services (at PMCC or Monash Health) was discussed, and the participant accepted/declined this offer"

Documentation in participant's electronic medical file

The Study coordinator will document outcomes in the participant's electronic medical file.

Clarification of urgency and risk

- If there is any indication of thoughts of suicidal ideation or harm to self or others, the Study coordinator will undertake some screening questions. For example: *Do you have thoughts of hurting or harming yourself/anyone else? Do you intend to act on these thoughts? How? When? Are you thinking or hurting or harming yourself today?*
- If there is any uncertainty about the person's immediate safety, the Study coordinator will follow site-specific processes to arrange an urgent assessment of the participant.

Disclosure of mental health issues during other time points in the study

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

- Regarding monitoring of survey responses, the Study coordinator will monitor online survey responses through the four time-points of the study (baseline, midpoint, endpoint and three-month follow-up). If any participant reports depression or anxiety (PROMIS Depression or Anxiety T-Scores ≥ 75), the Study coordinator or a trained member of the research team will call the participant from their recruitment site, to explore their needs.

In all these situations, the Study coordinator or a trained member of the research team will call/discuss with the participant their survey responses/reported distress, to explore these symptoms further, and follow steps as outlined above (informing the treating team, and documentation in medical file).

If urgent risk issues arise (a participant discloses suicidal ideation) during phone contact, the Study coordinator or a trained member of the research team 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 appropriate psychology services may be initiated as above.

Appendix E - List of Support Services

SUPPORT SERVICES
Peter MacCallum Cancer Centre If participant is a patient of the Peter MacCallum Cancer Centre, they may ask hospital staff or a member of the research team to make a referral to the Psychosocial Oncology Service or self-refer by calling 8559 5265.
Monash Health **If participant is a patient of Monash Health, they may ask for a referral to the available psychological support services.**
Beyond Blue Helpline (24 hours/7 days a week) 1300 224 636 https://www.beyondblue.org.au/
Cancer Council Free, confidential telephone information and support service 13 11 20
SANE helpline 1800 187 263 (weekdays 10am-10pm) https://www.sane.org/services/help-centre
MindSpot 1800 614 434 (weekdays 8am-8pm) **https://mindspot.org.au/**
Cancer Support Helpline 1-888-793-9355 (9am-9pm) https://www.cancersupportcommunity.org/cancer-support-helpline
Head to Health (H2H) 380 online resources for mental health. https://headtohealth.gov.au/?utm_source=mindhealthconnect&utm_medium=301
24-hour crisis lines Lifeline: 13 11 14 Emergency: 000

Appendix F – List of Measures

See attachment.

Appendix G – Power Analysis

This appendix contains further information on the Monte Carlo study used for power analysis. Code to reproduce this Monte Carlo study is available online: https://github.com/behavioralmedicinelab/SleepCarePlanning

Latent growth models were estimated with an intercept and a linear slope with loadings constrained to 0, 0.5, and 1.0 for times t_0, t_2, and t_3, respectively. The means and variances of the intercept and slope factors were freely estimated (corresponding to random effects in linear mixed models) and the intercept and slope covariance was estimated. The residual variance was constrained to equality across time and residuals were assumed uncorrelated, corresponding to an independent, homogenous residual structure. Intercepts of indicators were constrained to 0 to allow estimation of the latent random intercept mean.

There are three stratification factors: site (Peter MacCallum Cancer Centre vs Monash Health), cancer stage (≤ 3, 4) and insomnia severity index at screening (≤ 7, ≥ 8). These factors will be crossed creating eight groups. Estimated percentages of each group in the final trial were based on prevalence of Low vs High insomnia and stage in our previous SleepWell trial along with number of patients at each site. Dummy codes will be created and included as covariates to adjust for their effect on the random intercept (Kahan & Morris, 2011; Kahan & Morris, 2012). Dummy codes for BLT, CBT, and the BLT x CBT interaction were created and entered as predictors of the random slope. Intervention factors were constrained to 0 for the random intercept, to implement use so-called "constrained longitudinal data analysis" (Coffman, Edelman, Woolson, 2016; Twisk, Bosman, Hoekstra, et al, 2018). Based on the SleepWell trial, we conservatively estimated 25% missing at t_2 and 35% missing at t_3. These conservative estimates ensure that even with considerable dropout, sufficient power will be maintained.

Using currently available data from the SleepWell Trial, identical models (but with slightly different stratification and intervention variables) were estimated. These models were used to identify estimates of the residual variance, random intercept variance, random

intercept mean, random slope variance, covariance of the random intercept and slope, and the effect of stratification factors on the outcomes. For the control condition, change in insomnia severity index was estimated at -2 and change in fatigue symptoms at -0.2, based on control estimates from preliminary SleepWell data. Monte Carlo simulations were run by specifying the expected population parameter values in Mplus.

Insomnia severity index: We created all possible combinations of the following factors, resulting in a total of 24 different conditions:

- residual variance: SleepWell, SleepWell + 10%
  these two values were used as we anticipate results being similar to SleepWell, yet recognise that with the addition of another site, somewhat more heterogeneity may be added, captured by a 10% increase
- random intercept variance: SleepWell, SleepWell + 10%
  these two values were used as we anticipate results being similar to SleepWell, yet recognise that with the addition of another site, more heterogeneity may be added, particularly between individuals, captured by a 10% increase
- Simple effect of BLT: -3, beyond control, the minimally important difference selected for the insomnia severity index.
- Simple effect of CBT: -3 and -4, beyond control. -3 is the minimally important difference selected for the insomnia severity index, and -4 is a slightly larger, but plausible effect given previous trials. No larger effects were tested for BLT as we expect BLT to have relatively weaker effects than CBT on insomnia severity index.
- Interaction of BLT x CBT: -3, +0, and +3. These correspond to no interaction (what is expected given that CBT and BLT operate of very different mechanisms), the minimally important difference either as a diminishing returns of combining BLT and CBT (+3) and as augmenting returns from combining the interventions (-3).

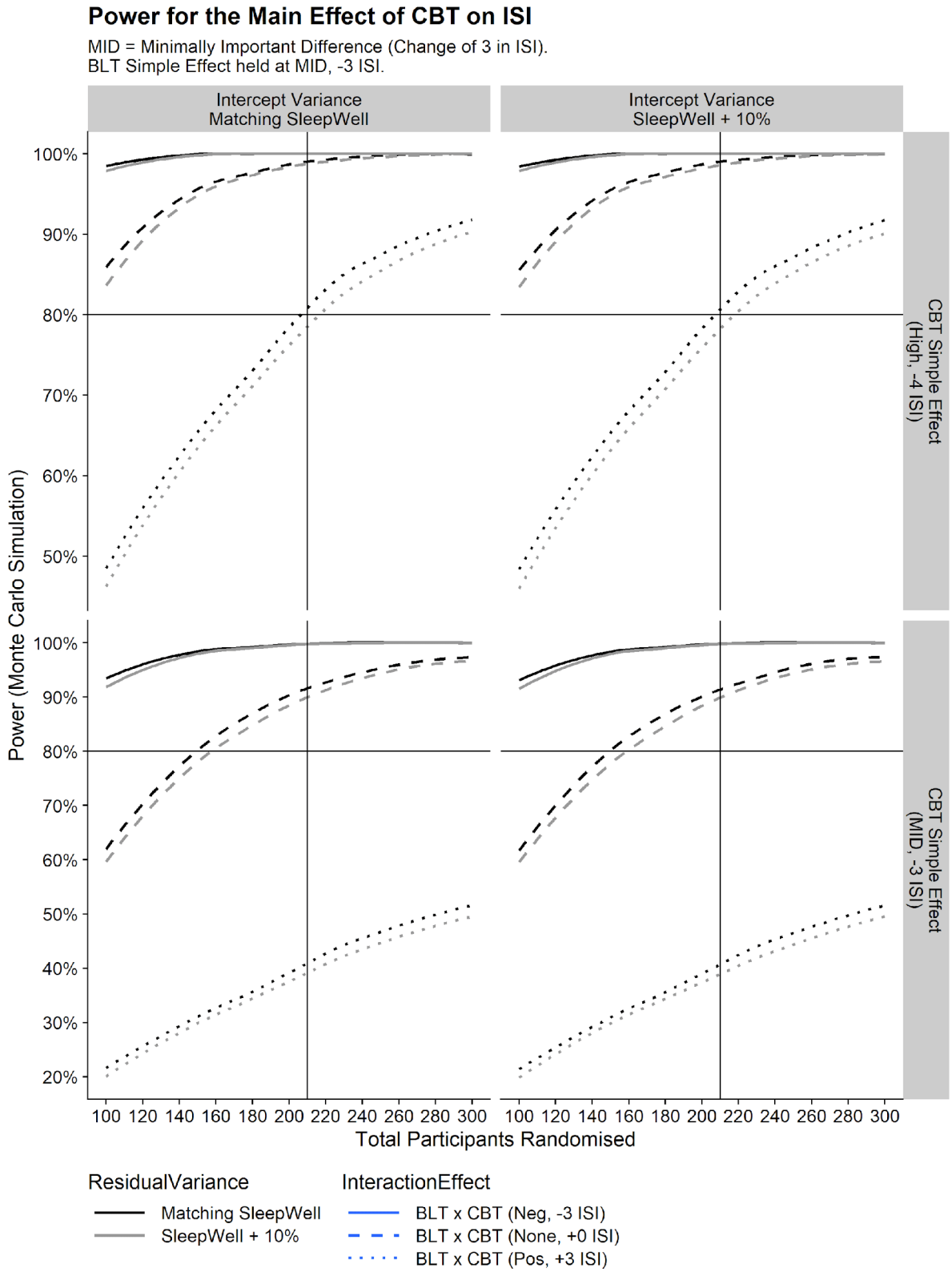
Fatigue symptoms: We created all possible combinations of the following factors, resulting in a total of 24 different conditions:

- residual variance: SleepWell, SleepWell + 10%
  these two values were used as we anticipate results being similar to SleepWell, yet recognise that with the addition of another site, more heterogeneity may be added, captured by a 10% increase

- random intercept variance: SleepWell, SleepWell + 10%
  these two values were used as we anticipate results being similar to SleepWell, yet recognise that with the addition of another site, more heterogeneity may be added, particularly between individuals, captured by a 10% increase
- Simple effect of BLT: -4 and -5. -4 is the minimally important difference selected for fatigue symptoms and -4 is a slightly larger, but plausible effect given previous trials
- Simple effect of CBT: -4, beyond control. -4 is the minimally important difference selected for fatigue symptoms. No larger effects were tested as we expect BLT to have relatively stronger effects than CBT on fatigue.
- Interaction of BLT x CBT: -4, 0, and +4. These correspond to no interaction (what is expected given that CBT and BLT operate of very different mechanisms), the minimally important difference in fatigue symptoms as a diminishing returns of combining BLT and CBT (+4) and as an augmenting returns of the combined intervention (-4).

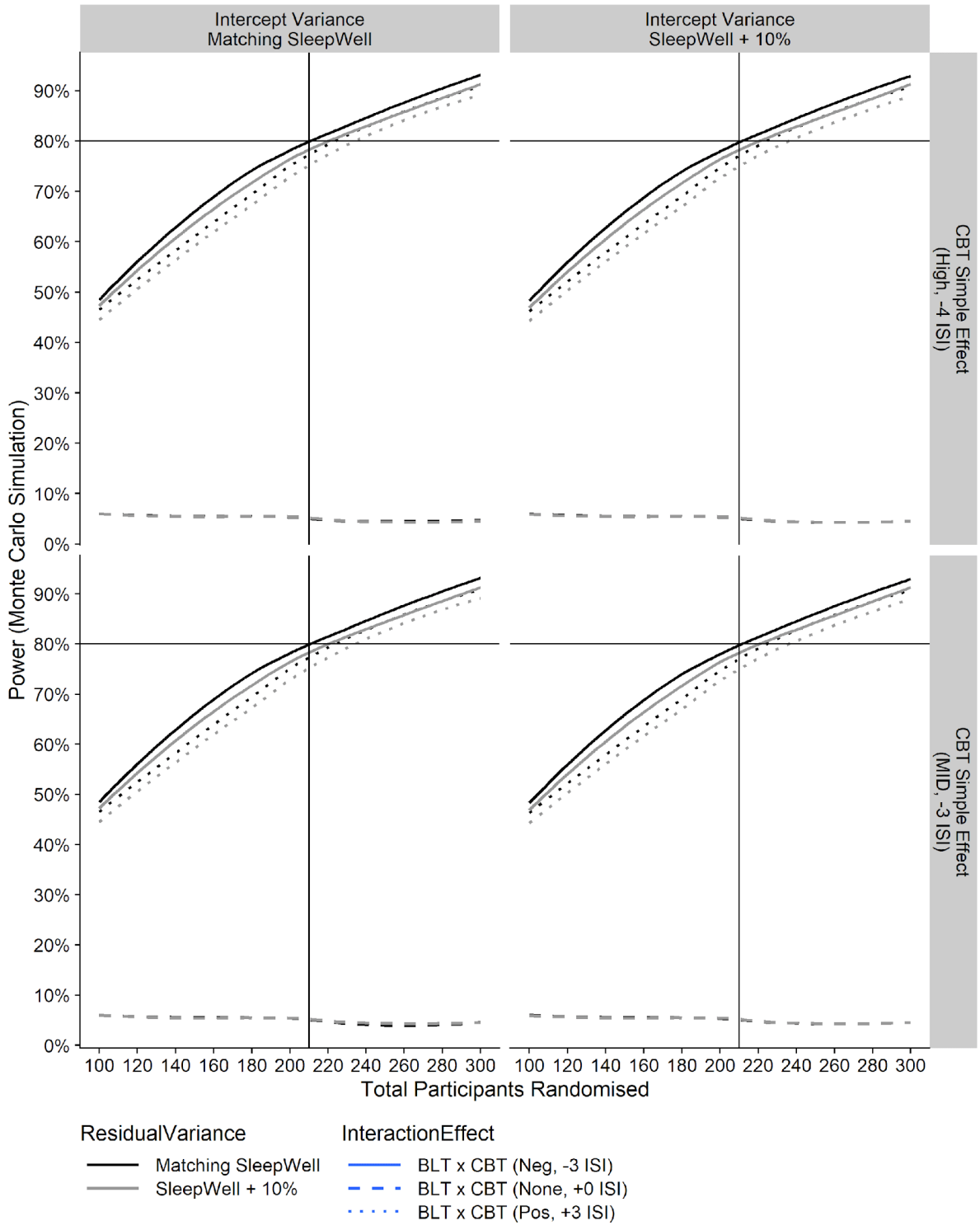
For both insomnia severity symptoms and fatigue symptoms, sample sizes were varied from 100 to 300 in increments of 10 for each of the 24 different conditions. Each time, 500 simulations were conducted and analysed. The proportion of times a parameter was significant at the alpha = .05 level was calculated and used as an empirical power estimate. We focused on three estimates of interest for the power analysis. First, the main effect of BLT, calculated incorporating both the simple effect and the interaction effect. Second, the main effect of CBT, calculated incorporating both the simple effect and the interaction effect. Third, the interaction of BLT x CBT. Only the main effects are primary aims of the SleepCare Trial. The interaction effect is an exploratory aim as we do not expect to have a sufficient sample size to detect a significant interaction, as the effect is likely small. Empirical results were graphed using locally weighted regression smoothers to smooth out variation due to sampling variability and discrete sample sizes (increments of 10 rather than continuous sample size increments). Results are shown in graphs on the following pages.

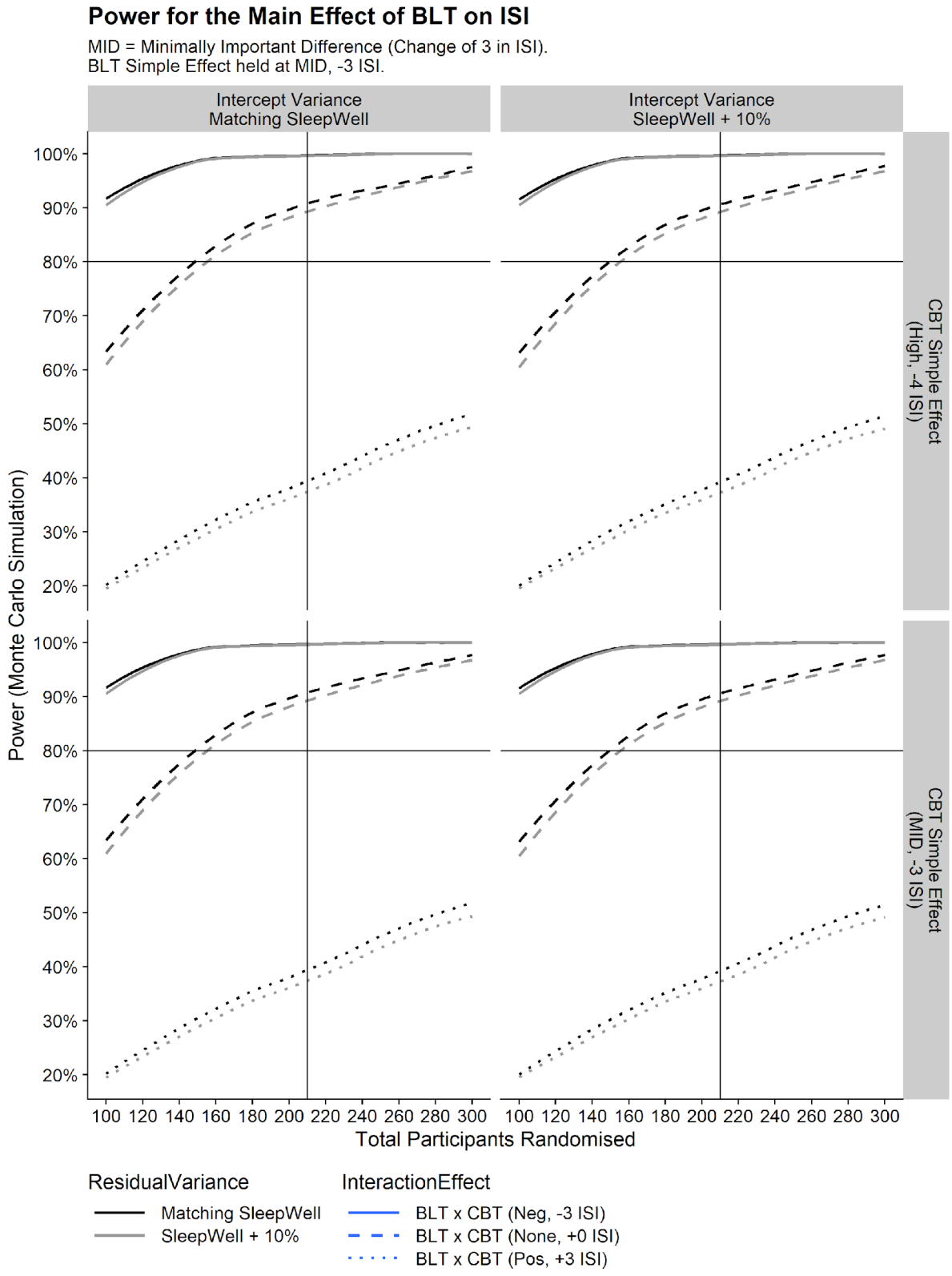
Results of the power analyses revealed that randomising 210 women will provide >80% power to detect main effects of CBT and BLT on ISI and Fatigue under most assumptions with $\alpha = 0.05$.

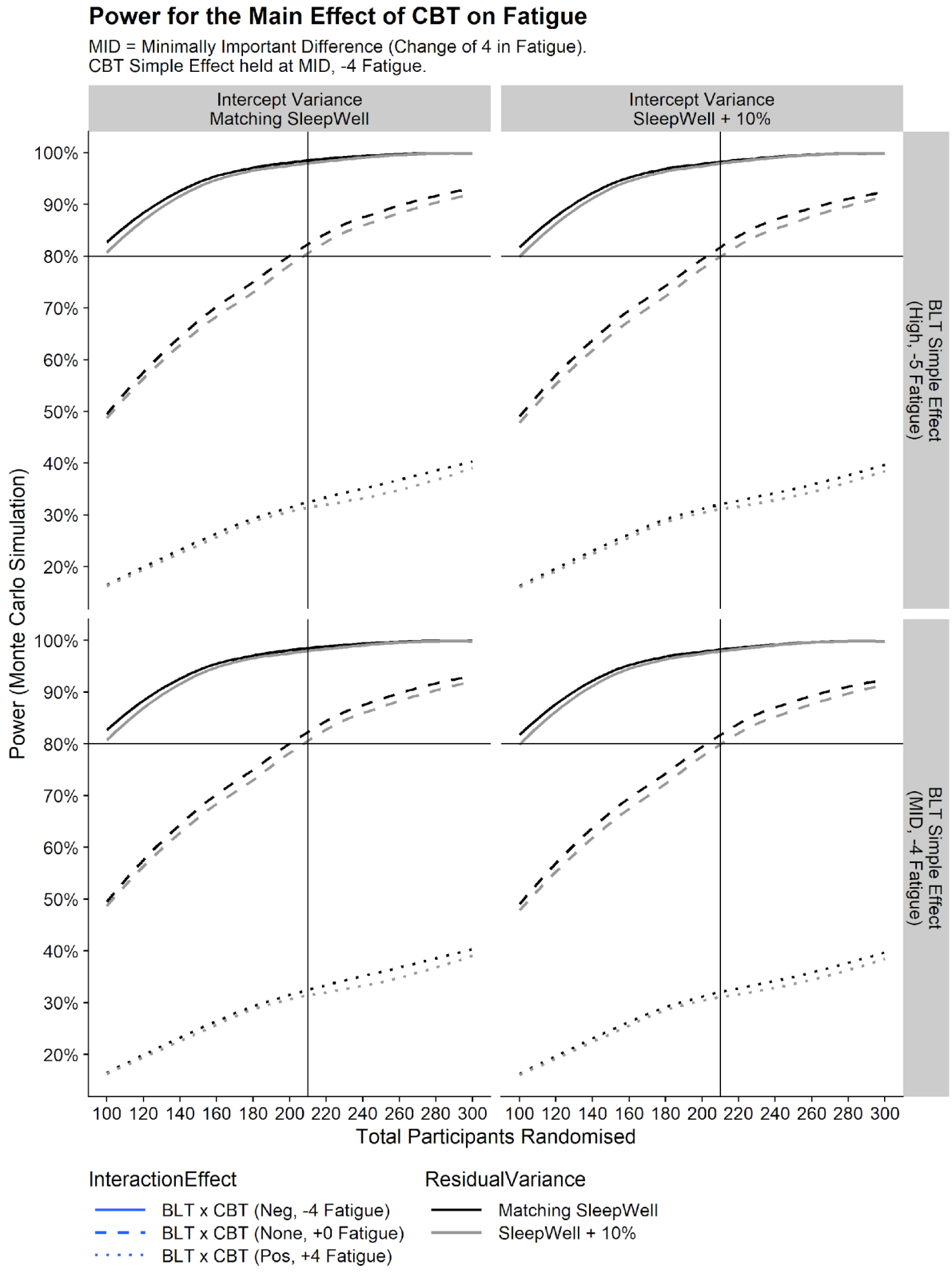

Power for the Main Effect of CBT on ISI
MID = Minimally Important Difference (Change of 3 in ISI).
BLT Simple Effect held at MID, -3 ISI.
Intercept Variance
Matching SleepWell
Intercept Variance
SleepWell + 10%
CBT Simple Effect
(High, -4 ISI)
CBT Simple Effect
(MID, -3 ISI)
Power (Monte Carlo Simulation)
100%
90%
80%
70%
60%
50%
40%
30%
20%
100 120 140 160 180 200 220 240 260 280 300
Total Participants Randomised
ResidualVariance
Matching SleepWell
SleepWell + 10%
InteractionEffect
BLT x CBT (Neg, -3 ISI)
BLT x CBT (None, +0 ISI)
BLT x CBT (Pos, +3 ISI)

Power for the BLT x CBT Interaction on ISI

MID = Minimally Important Difference (Change of 3 in ISI).
BLT Simple Effect held at MID, -3 ISI.

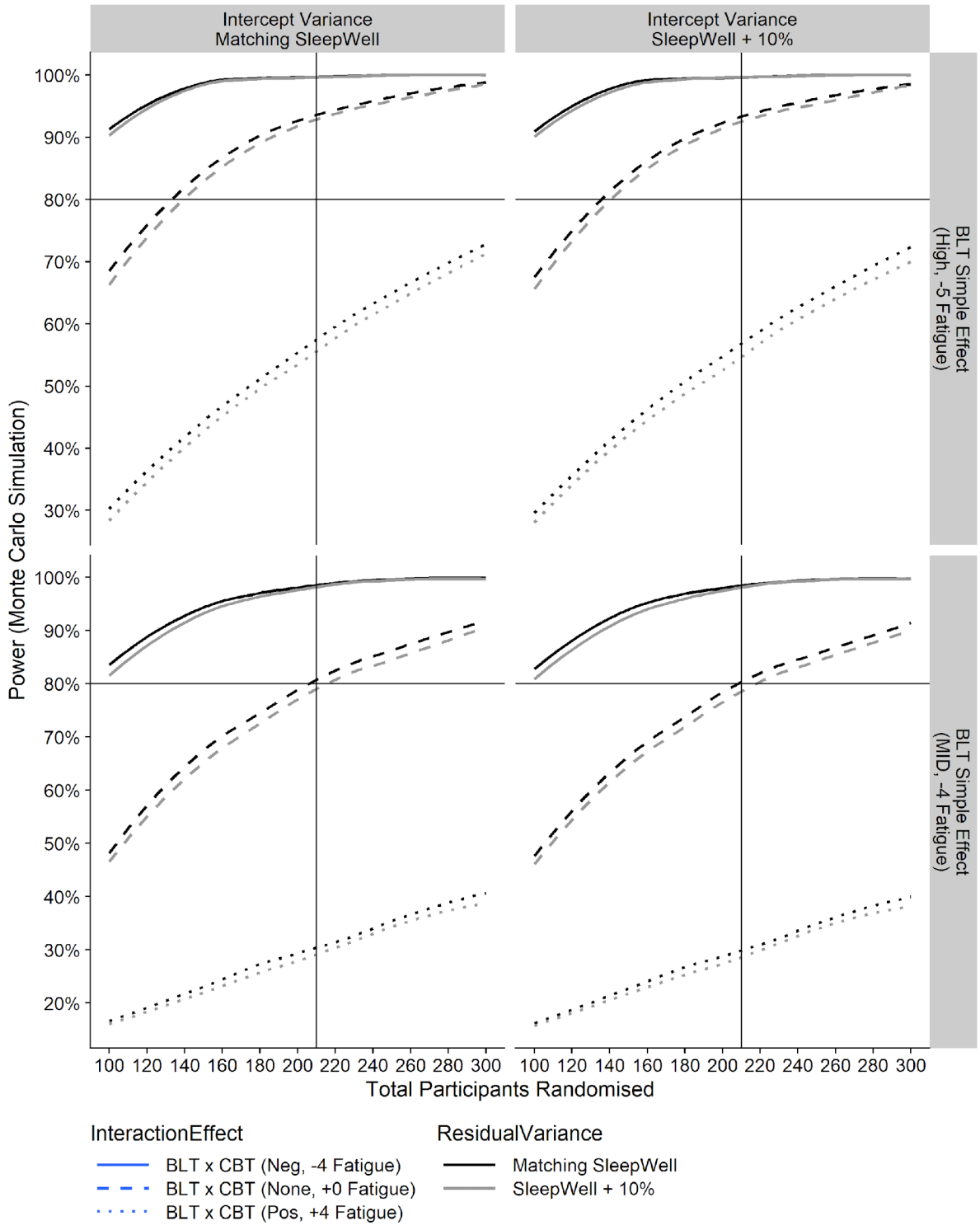


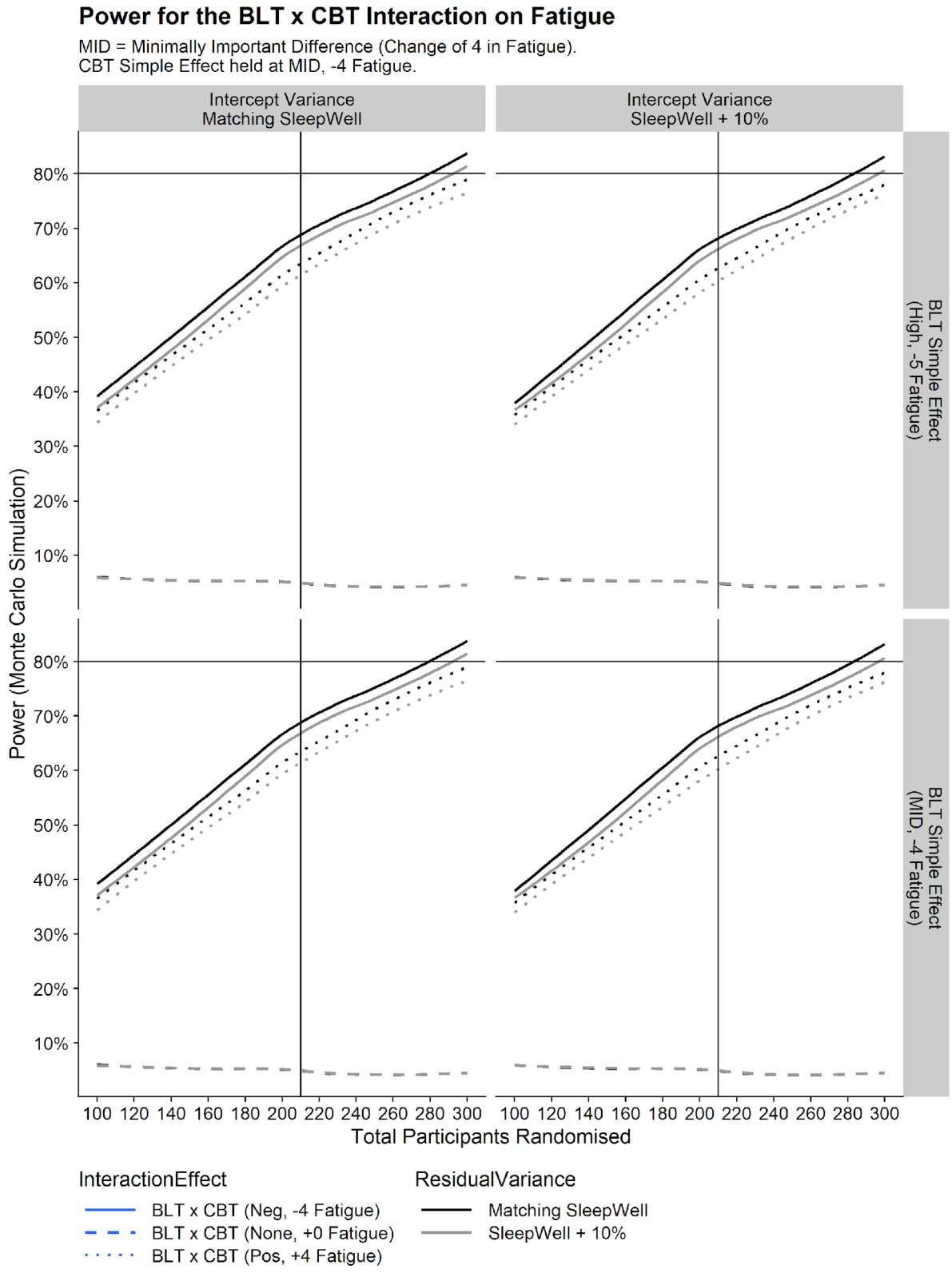

Power for the Main Effect of BLT on ISI
MID = Minimally Important Difference (Change of 3 in ISI).
BLT Simple Effect held at MID, -3 ISI.
Intercept Variance
Matching SleepWell
Intercept Variance
SleepWell + 10%
CBT Simple Effect
(High, -4 ISI)
CBT Simple Effect
(MID, -3 ISI)
Power (Monte Carlo Simulation)
100%
90%
80%
70%
60%
50%
40%
30%
20%
100 120 140 160 180 200 220 240 260 280 300
Total Participants Randomised
ResidualVariance
Matching SleepWell
SleepWell + 10%
InteractionEffect
BLT x CBT (Neg, -3 ISI)
BLT x CBT (None, +0 ISI)
BLT x CBT (Pos, +3 ISI)


Power for the Main Effect of CBT on Fatigue
MID = Minimally Important Difference (Change of 4 in Fatigue).
CBT Simple Effect held at MID, -4 Fatigue.
Intercept Variance
Matching SleepWell
Intercept Variance
SleepWell + 10%
BLT Simple Effect
(High, -5 Fatigue)
BLT Simple Effect
(MID, -4 Fatigue)
Power (Monte Carlo Simulation)
100%
90%
80%
70%
60%
50%
40%
30%
20%
100 120 140 160 180 200 220 240 260 280 300
Total Participants Randomised
InteractionEffect
BLT x CBT (Neg, -4 Fatigue)
BLT x CBT (None, +0 Fatigue)
BLT x CBT (Pos, +4 Fatigue)
ResidualVariance
Matching SleepWell
SleepWell + 10%

Power for the Main Effect of BLT on Fatigue

MID = Minimally Important Difference (Change of 4 in Fatigue).
CBT Simple Effect held at MID, -4 Fatigue.




Power for the BLT x CBT Interaction on Fatigue
MID = Minimally Important Difference (Change of 4 in Fatigue).
CBT Simple Effect held at MID, -4 Fatigue.
Intercept Variance
Matching SleepWell
Intercept Variance
SleepWell + 10%
BLT Simple Effect
(High, -5 Fatigue)
BLT Simple Effect
(MID, -4 Fatigue)
Power (Monte Carlo Simulation)
80%
70%
60%
50%
40%
30%
20%
10%
100 120 140 160 180 200 220 240 260 280 300
Total Participants Randomised
InteractionEffect
BLT x CBT (Neg, -4 Fatigue)
BLT x CBT (None, +0 Fatigue)
BLT x CBT (Pos, +4 Fatigue)
ResidualVariance
Matching SleepWell
SleepWell + 10%

Appendix H – Medical Record Extraction

All participants are asked for consent for medical record access to capture information about their cancer history and medical treatment factors. Based on consultations with clinicians and common metrics used in psycho-oncology research, the following measures are planned for extraction from medical records:

1. Date of breast cancer diagnosis
2. Chemotherapy: start date, finish date and regimen. Date of each cycle of chemotherapy during the study dates for an individual. Additional entries for multiple chemotherapy regimens. Whether this is women's first intravenous chemotherapy regimen or not
3. Radiation therapy: start date, finish date, type
4. Hormonal treatment / hormone replacement therapy: start date, finish date, type. Additional entries for multiple types of hormonal treatment. Will include if HRT was recently ceased after breast cancer diagnosis
5. Total number of surgeries for cancer treatment: Types of surgery, dates of surgery.
6. Reconstruction since diagnosis? If yes: Type of reconstruction, dates of reconstruction
7. Stage of breast cancer [if recorded] or pathology reports needed to stage
8. Is current cancer primary or recurrence?
9. If current cancer metastatic: site(s)
10. Height
11. Weight at each CDU visit during study, including closest visit to randomisation
12. List of all medications, such as concurrent GnRH agonists
13. Any hospitalisations during study dates for an individual