Supplement 1

1. Study protocol as submitted for initial ethical approval

2. Changes to study protocol

3. Statistical Analyses Report

1. Study protocol as submitted for initial ethical approval:

A randomised controlled trial of fully automated digital Cognitive Behavioural Therapy for Insomnia versus sleep hygiene education: the impact of improved sleep on functional health, quality of life and psychological wellbeing

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Abstract

Background: Previous research has demonstrated that digital CBT (dCBT), delivered via the internet, is a scalable and effective intervention for treating insomnia in otherwise healthy adults and leads to significant improvements in primary outcomes relating to sleep. The majority of people with insomnia, however, seek help because of the functional impact and daytime consequences of poor sleep not because of sleep discontinuity per se. Although some secondary analyses suggest that dCBT may have wider health benefits, no adequately powered study has investigated these as a primary endpoint. This study specifically aims to investigate the impact of dCBT for insomnia upon health and wellbeing, and will investigate sleep-related changes as mediating factors.

Methods/design: We propose a pragmatic, parallel group, randomised controlled trial of 1000 community participants with insomnia disorder. In the DIALS trial (Digital Insomnia therapy to Assist your Life as well as your Sleep), participants will be randomised to dCBT delivered using web and/or mobile channels [in addition to treatment as usual (TAU)] or to sleep hygiene education (SHE) comprising a website plus a downloadable booklet (in addition to TAU). Online assessments will take place at 0 (baseline), 4 (mid-treatment), 8 (post-treatment), and 24 (follow up) weeks. At week 25 all participants allocated to SHE will be offered dCBT; at which point the controlled element of the trial will be complete. Naturalistic follow up will be invited at weeks 36 and 48. Primary outcomes are functional health and wellbeing at 8 weeks. Secondary outcomes are mood, fatigue, sleepiness, concentration, productivity and social functioning. All main analyses will be carried out at the end of the final controlled follow-up assessments and will be based on the intention-to-treat principle. Further analyses will determine whether observed changes in functional health and wellbeing are mediated by changes in sleep. The trial is funded by Big Health Ltd.

Discussion: This study will be the first large scale, specifically designed investigation of the health and wellbeing benefits of CBT for insomnia, and the first causal test of the relationship between CBT-mediated sleep improvement and health status.

Trial registration: ISRCTN 60530898

Key words: Insomnia; Sleep; CBT; digital; health; function; wellbeing

Background

The importance of insomnia

Insomnia disorder comprises a complaint of poor sleep, with associated significant daytime effects, occurring ≥3 nights per week for ≥3 months[1]. Worldwide, epidemiologic studies report the prevalence of a chronic clinical insomnia disorder at 10% to 12%[2 3 4]. Although prevalence is high, natural remission is low. In one study, 74% of those with insomnia continued to have insomnia a year later and 46% reported insomnia persisting over three years[5]. Traditionally considered as "secondary", subsumed as symptoms of other clinical diagnoses within mental health care, the recently revised DSM-5 outlines the 'need for independent clinical attention of a sleep disorder' (pg1)[1]. This is supported by research demonstrating not only that rates of mental and physical health co-morbidity are high, but that pre-existing chronic insomnia is an independent risk factor for development of depression[6], cardiovascular disease[7] and Type 2 diabetes[8 9]. From the standpoint of public health and wellbeing, sleep appears to be a more important matter than has been hitherto recognised[10 11].

The relationship between poor insomnia, daytime functioning and quality of life

Typically, insomnia is associated with increased fatigue, impaired work productivity, reduced quality of life and relationship satisfaction, as well as increased ill health[12 13 14]. Despite such evidence of poor functioning being attributed to poor sleep, and also being an essential diagnostic criterion for insomnia, there has been comparatively little research on quality of life. This is all the more surprising given that perceived impact on personal functioning serves as an important driver of complaint and of help-seeking behavior rather than simply perceived sleep loss[15 16]. In one large epidemiological study, four of the five most commonly cited reasons for seeking a sleep consultation with a health professional, were daytime consequences of fatigue, psychological distress, physical discomfort, and reduced work productivity[16]. Clinician reports of patient consultations, and cross-sectional and prospective questionnaire studies[17 18] further demonstrate that individuals with insomnia complain of deficits in mood and cognitive abilities (concentration, memory, attention), coupled with elevated levels of anxiety, fatigue and physical pain/discomfort. Thus, once a threshold of noticeable effect on one's life is reached, such individuals may feel motivated to seek medical advice.

Cognitive Behavioural Therapy (CBT) for insomnia

CBT, regarded as the treatment of first choice for persistent poor sleep[19 20 21]is a psychological treatment designed to break the patterns of maladaptive thinking and behaviour that serve to maintain insomnia. CBT comprises a range of techniques including a behavioural component (stimulus control, sleep restriction, relaxation) combined with a cognitive (managing sleep related worries, the racing mind and intrusive thoughts) and an educational (sleep hygiene) component. Meta-analyses indicate that CBT has moderate to large and durable effects on sleep quality, sleep efficiency, sleep onset latency and wake time after sleep onset[22 23 24]. Moreover, approximately 60% of those who receive CBT respond to treatment and 39% reach remission[25]. What is much less well established is the effect that CBT may have upon the daytime symptom and functional health profile of people with insomnia. Logically, effective treatment should alleviate such impairments; and furthermore, based on the evidence that impaired sleep may be causally related to reduced quality of life domains (well-being and impaired daytime functional status), improving sleep should improve functioning. There is some preliminary evidence from secondary analyses that CBT may yield generalized benefits[26 27 28 29 30], and even some primary data in small samples that CBT for insomnia may reduce depressive or anxiety symptoms[31 32], but an adequately powered, definitive trial looking at functional health status and wellbeing is long overdue.

The current study

This study seeks to ascertain the impact of improved sleep on three key areas of quality of life: functional health status, patient-generated (sleep-related) quality of life impairment and psychological wellbeing. Over the past 5 years, self-help CBT delivered via the internet has been introduced, not least because of the importance of widening access to effective psychological therapy. Several randomised controlled trials (RCTs) have evaluated digital CBT applications; each of which has found moderate to large improvements in insomnia symptoms relative to waitlist groups[33 34 35]. Only one programme, however, has been tested versus a placebo intervention[35]; and it is this dCBT intervention that will be used in the present study. Data from the programme show that 90% of participants complete the course within 10 weeks.

The primary hypotheses for the trial are that, compared to SHE:

1. The dCBT intervention will improve functional health status by the end of treatment (8 weeks)
2. The dCBT intervention will improve positive psychological wellbeing by the end of treatment (8 weeks)
3. The dCBT intervention will reduce patient-generated sleep-related quality of life impairment (8 weeks)
4. The effect of dCBT on outcomes (8 weeks) will be mediated by sleep status during the treatment phase (4 weeks)

The secondary hypotheses are that, compared to SHE:

1. The dCBT intervention will reduce symptoms of negative mood, fatigue and relationship/ social dysfunction by the end of treatment (8 weeks)
2. The dCBT intervention will reduce problems with sleepiness, concentration and productivity by the end of treatment (8 weeks)
3. Improvements will be maintained at follow up (24, 36, 48 weeks)
4. The effect of dCBT on longer-term outcomes (24, 36, 48 weeks) will be mediated by sleep status during and upon completion of the treatment phase (4, 8 weeks)

Methods

Research design

The study is a parallel group, superiority, randomised controlled trial (RCT) of dCBT (+TAU) versus SHE (+TAU). The trial design is summarised in Figure 1. The study will be carried out completely on-line. Participants will be administered screening, participant information (See Appendix 1), informed consent (See Appendix 2), assessments, allocation to condition, and intervention via web or mobile platforms. The study has received ethical approval from the University of Oxford Medical Sciences Inter-Divisional Ethics Committee (ref XXXXXXXX).

Figure 1 about here

Participants

We will recruit 1000 community participants. Our inclusion criteria comprise: a) a positive screen for probable DSM-5 insomnia disorder; b) a test score of ≤16 on the Sleep Condition Indicator[36] c) being aged 18 or older (no upper age limit); d) having reliable internet access at home or at work; and e) being able to read and understand English. We will screen for comorbid conditions and medication use at baseline but exclude only those people whose health may be considered to be unstable such as significant current symptoms of a) an additional sleep disorder (e.g. excessively sleepy and possible obstructive sleep apnoea); b) psychosis or mania; c) serious physical health concerns necessitating surgery or with prognosis <6 months; d) those undergoing a psychological treatment programme for insomnia with a health professional; and e) habitual night shift, evening, or rotating shift-workers. We will not omit participants who take medication for sleep problems, or for any other physical or mental health problems providing they report their health to be stable. The study will recruit through several channels. These may include online, print and broadcast media announcements or advertisements and the use of contact lists where adults who have volunteered to be involved in research will be re-contacted (See Appendix 3). For example, following completion of open access sleep surveys such as the Great British Sleep Survey (GBSS: www.greatbritishsleepsurvey.com or World Sleep Survey (WSS: www.worldsleepsurvey.com). Potential participants will also be alerted to the study by information placed on the Sleepio website (www.sleepio.com) and on the Sleepio App site.

Randomisation and allocation concealment

This study will use simple randomisation with an allocation ratio of 1:1, as recommended for large clinical trials[37]. It will be carried out by the automated online system. Hence the research team will be unable to influence randomisation, and will have no access to future allocations.

Blinding

This is a single blind trial. Self-report assessments will be completed online and hence the research team will be blind to outcomes during the trial. Participants will be informed of their randomisation outcome by an automatic email, and so they will not be blind to treatment allocation. The research team is unlikely to have any contact with research participants and therefore will be unable to bias the allocation or influence the assessments. If participants do contact the team and reveal the allocation, the assessments will remain blinded. Analyses will be conducted by an independent researcher (RE).

Assessment points

Assessments will take place at weeks 0 (baseline), 4 (mid-treatment), 8 (post-treatment), and 24 (follow up). In consideration of ethical matters, at week 25 all participants in the control group will be offered dCBT to help with their sleep problems, and so at that point the controlled element of the trial will be complete. Thereafter there will be a naturalistic follow up. All participants will be invited to complete further assessments at weeks 36 and 48.

Planned intervention

Digital Cognitive Behavioural Therapy (dCBT) will be delivered using the Sleepio® programme[35] (www.sleepio.com and associated Sleepio App). The programme is fully automated and its underlying algorithms feed the delivery of information, support, and advice in a personally tailored manner. Delivery is structured into six sessions, lasting an average of 20 minutes each. All participants have to at least start the programme online. Certain tools (such as sleep diaries and relaxation audios) can also be accessed using the web browser of any smartphone. All of the six core sessions, sleep diaries, relaxation audios, and the scheduling tool can also be accessed using an iOS app, but this is only an option for participants who have an iPhone®. The treatment content is based on CBT for insomnia manuals[26] [27] [28] and includes a behavioural component (sleep restriction, stimulus control, and relaxation), a cognitive component (paradoxical intention, cognitive restructuring, mindfulness, positive imagery, and putting the day to rest) and an educational component (psycho-education and sleep hygiene).

The programme is highly interactive, and content is presented by an animated virtual therapist. Participants make a time for the session and are prompted via email and/or SMS if they do not 'attend'. Participants complete daily sleep diary information throughout the intervention, which is used by the programme to provide tailored, personalised help. Participants receive an email and/or SMS reminder each morning to prompt them to fill in their sleep diary. In addition, participants complete a short questionnaire at the beginning of therapy to set treatment goals. Throughout the course of therapy, participants have access to a moderated online community and an online library of information about sleep. Participants can view their online case file, which includes four sections: a progress review, a reminder of strategies to try out between sessions, an agreed sleep schedule, and a list of further reading. The system provides online analytics, which can be used to monitor adherence by assessing how many sessions were completed and the number of weeks to complete the course. Participants will have access to the intervention for up to 12 weeks. Digital CBT will in effect be dCBT + TAU because there will be no requirement for participants to alter their usual care in any way. Physicians for example will be free to offer appointments, to prescribe, and to maintain/discontinue prescriptions as they see fit.

Sleep Hygiene Education (SHE) has been selected for the control arm because this is what people with insomnia are offered most typically in routine care. To ensure consistency of approach and content, SHE will be delivered on a dedicated website (under development) where materials can be viewed and downloaded. SHE will be based on recognised sleep hygiene advice[38 39 40] and will comprise behavioural advice concerning both lifestyle factors and environmental factors associated with sleep and sleeplessness. The latter in particular will focus on creating the optimal bedroom environment for good sleep. Content of SHE will cover the importance of limiting caffeine, nicotine, and alcohol and of carefully managing diet and exercise (lifestyle), as well as limiting noise and light, managing room temperature and body temperature, and improving air quality and bed comfort (environment). SHE will in effect be SHE + TAU because again here will be no requirement for the usual care of participants to be altered in any way.

Outcome measures

Participants will be prompted by email to complete the assessments online. The order of the assessments will be consistent across all participants and all time-points. If participants do not complete measures within two days they will receive further email reminders. The full battery of questionnaires amounts to around 100 items in total, and takes 20-25 minutes to complete. Demographic and descriptive clinical data will be gathered at baseline only. Measurements to permit health economic evaluation will form part of the descriptive demographic data, with some aspects audited at each assessment point (e.g. medication use, visits to health professionals, other healthcare utilisation).

The co-primary measures that relate to functional health and wellbeing will be the Patient Reported Outcome Measurement Information System: Global Health scale[41] (PROMIS-10), the Warwick-Edinburgh Mental Wellbeing Scale[42] (WEMWBS) and the Glasgow Sleep Impact Index[43](GSII). The PROMIS-10 is a reliable ($\alpha \geq .92$) but brief (10-item), generic measure that has proven to be very useful in measuring outcomes in clinical trials. It can also be used to estimate cost-utility using QALYs (quality-adjusted life-years)[44 45]. The WEMWBS is a short (14-item) and psychometrically robust measure ($\alpha \geq .91$) of mental wellbeing and is included because it focuses entirely on positive aspects of functional mental health. The GSII is a patient-reported outcome (PRO) measure that asks patients to individually generate, and then assess, three domains of sleep-related impairment unique to their own individual context. Its strength is ecological validity and the GSII has been shown to be sensitive to change following CBT. This combination of PRO, generic functional health status, and positive mental state (rather than symptom reduction) matches our intention to evaluate the impact of dCBT upon quality of life domains.

Secondary outcomes relate to specific measurement of the six areas of daytime consequence that are associated with the clinical diagnosis of insomnia disorder[1 14 46]. These are mood [Patient Health Questionnaire (PHQ9: 9 items[47]) and Generalised Anxiety Disorder (GAD7: 7 items[48])]; energy (Flinders Fatigue Scale (FFS: 7 items[49]); relationship satisfaction [Relationship Assessment Scale (RAS: 7 items[50])]; Medical Outcomes Study Cognitive Failures Scale Revised (MOS-COG-R, X items[51]); work performance and satisfaction [Work Productivity and Activity Impairment questionnaire (WPAI: 6 items[52]), one item on job satisfaction[53])]; and sleepiness

(Epworth Sleepiness Scale (ESS: 8 items[54]). As an exploratory measure, participants will also complete one item about their general life satisfaction[55].

In order to appraise the mediating effects of sleep improvement per se we will use the Sleep Condition Indicator[36] (SCI) and estimates of sleep diary parameters[56]. The SCI is an internally consistent (α = .86), 9-item measure with a clinical cut off that can correctly identify 89% of those with probable DSM-5 insomnia disorder. The SCI and sleep diary variables have proven to be sensitive to change following dCBT[35].

In addition to these formal assessments the web/mobile platform will provide online analytics for the dCBT group. These can be used for example to measure the process of change (Sleep Diary) and to monitor how many sessions were completed and the number of weeks to complete the course. These will be used in exploratory analyses. We will also gather information on the demographics of the sample, employment, work satisfaction and economic outcomes, their health characteristics, and their use of clinical services during the period of their trial participation.

Assessment of safety

The likelihood of serious adverse events occurring during this trial is low since dCBT for insomnia has not been reported to cause them. The intervention offered in the trial has previously been tested in a randomised controlled trial testing change in insomnia and no adverse outcomes were reported[29] [35]**.** However, studies have shown that daytime sleepiness and vigilance impairment may increase during SRT (one component of CBT-I), owing to restricted sleep opportunity[57]. We will record the occurrence of any serious adverse events in trial participants, defined as: 1. All deaths, 2. Suicide attempts, 3. Serious violent incidents, 4. Admissions to secure units, 5. Formal complaints about the online intervention. Owing to the online nature of the assessments and intervention, it is unlikely that the research team will become aware of all such events. At the end of treatment we will also ask participants to complete, in both arms, a specific adverse effects measure[58] to assess differential rates of self-reported adverse effects.

Sample size calculation

Our planned primary intention to treat analyses will compare dCBT +TAU versus SHE + TAU for each of the three primary outcomes separately. Assuming a significance level of 1.667% (adjusted from 5% because of having three primary outcomes) and a power of 90%, to detect a standardised effect size of 0.25 we require a minimum of 433 participants in each of the groups in the analysis. Accounting for a conservative dropout rate of 13%, we will recruit 500 participants in each treatment group, or 1000 participants in all. This sample size will have more than 80% power to detect a large sized indirect effect through the sleep mediator (proportion mediated ≈ 75%) for each between group comparison.

Statistical analysis

All analyses will be carried out using Stata[59]. In accordance with CONSORT guidelines, we will report all participant flow. Descriptive statistics of recruitment, drop-out and completeness of interventions will be provided.

The main efficacy analysis will be via intention-to-treat including all participants, with no planned interim analysis for efficacy or futility. Baseline characteristics will be presented by randomised group without formal statistical tests. We will test the primary hypothesis for between-group change in the primary outcomes at 8 weeks using analysis of covariance with baseline outcome measure and treatment assignment as fixed effects, and apply standard regression diagnostics. The analysis will use statistical techniques for handling missing outcome data under a missing at random assumption. The secondary outcomes will be analysed using an analogous method, as will subsequent measures of the primary outcomes at 24 weeks. Analysis of all treatment effects will be undertaken after all 24 week outcome measures are completed.

We will use modern causal inference methods to investigate the mediation hypothesis[60]. If the efficacy analysis shows significant between group differences in the SCI at 4 and 8 weeks, then we will use parametric regression models to test for the indirect effect of SCI on outcomes, and the residual direct effect of treatment on outcomes at 8 and 24 weeks respectively. Since all the measures are continuous, the indirect effects are calculated by multiplying relevant pathways and bootstrapping is used to produce valid standard errors for the indirect effects. All analyses

will adjust for baseline measures of the SCI, outcomes and putative measured confounders. Mediation analyses are potentially biased by measurement error in mediators and hidden confounding between mediators and outcomes and we will investigate the sensitivity of the estimates to these problems.

Discussion

It is already well established that CBT is the treatment of first choice for people with chronic insomnia, and that sleep-related outcomes, whether on index measures of insomnia or on derivations from sleep diaries, show sustained improvement[19 20 21]. A recent definitive placebo controlled RCT has also demonstrated that dCBT yields effect sizes that mirror conventionally delivered face to face therapy[35]. What is yet to be established is whether or not CBT for insomnia is directly associated with changes in functional health, quality of life and psychological wellbeing. This is crucial for two reasons. First, a diagnosis of insomnia disorder cannot be made unless there are clear attributed daytime consequences of night-time poor sleep; and second, it is the degradation of people's lived experience and quality of life that often leads to clinical complaint and help-seeking behaviour. An investigation of such as primary outcomes is long overdue. This study will be the first specifically designed investigation of the health and wellbeing benefits of CBT for insomnia, and the first large scale causal test of the relationship between CBT mediated sleep improvement and health status. The results can be expected to influence care provision for the 10-12% of the adult population who have persistent insomnia problems, and because we will be using a dCBT approach, a scalable solution to insomnia may be demonstrated as both viable and effective.

Trial status

Recruitment will begin in December 2015. It is anticipated that recruitment will be complete in Summer 2016. Therefore trial results will become available in late 2016.

List of abbreviations

CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CTS	Conflict Tactics Scales (5 item version)
dCBT	digital Cognitive Behavioural Therapy
DSM-5	Diagnostic and Statistical Manual of Mental Disorders (5th edition)
ESS	Epworth Sleepiness Scale
FFS	Flinders Fatigue Scale
GAD-7	Generalised Anxiety Disorder assessment (7 item version)
GBSS	Great British Sleep Survey
GSII	Glasgow Sleep Impairment Index
WPAI	Work and Performance Assessment Index
MOS-COG-R	Medical Outcomes Scale Cognitive Failures Scale Revised
PHQ-9	Patient Health Questionnaire – 9 item version
QALY	Quality-adjusted life-years
PROMIS-10	Patient Reported Outcomes Measurement Information System: Global Health scale (10 items)
RAS	Relationship Assessment Scale
RCT	Randomised Controlled Trial
SCI	Sleep Condition Indicator (SCI)

SCNi	Sleep and Circadian Neuroscience institute
SHE	Sleep Hygiene Education
TAU	Treatment as Usual
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale
WSS	World Sleep Survey

Competing interests

CAE is co-founder and Clinical & Scientific Director of the CBT for insomnia programme [Big Health (Sleepio) Ltd]. Peter Hames is co-founder/ CEO, and SB is Head of UK Operations for the programme. AIL holds a position at Oxford that is funded by the programme. JC provides clinical advice and support to the programme, BS provides monthly support for an online discussion forum run by the programme and SDK and JCO provide consultancy support. MN has worked as an intern for the programme. The programme is being provided to all participants at no cost. No other investigators have conflicts of interest. The study will be conducted by the University of Oxford, Sleep & Circadian Neuroscience Institute. The University of Oxford has a Memorandum of Understanding with Big Health (Sleepio) for the conduct of joint research.

Author contributions

CAE is the chief investigator, conceived of the study, contributed to the design, and drafted the manuscript. AIL is the trial co-ordinator, helped to draft the manuscript and is responsible for the computer programming that carries out the screening, assessments, and links to the digital intervention. JC contributed to the design, and helped to draft the manuscript. CLD contributed to the design, and helped to draft the manuscript. ANS contributed to the design, and helped to draft the manuscript. JCO contributed to the design, and helped to draft the manuscript. CG contributed to the design, and helped to draft the manuscript. SB contributed to the design and is responsible for the digital therapy programme. PH contributed to the design. MN helped to

draft the manuscript, and will assist with the computer programming that carries out the screening, assessments, and links to the digital intervention. BS contributed to the design, and helped to draft the manuscript. RF contributed to the design of the trial. DF contributed to the design of the trial. JC-F contributed to the design, and helped to draft the manuscript. RE contributed to the design, is responsible for the main statistical outcome analysis and is responsible for the statistical mediation analysis. SDK conceived of the study, contributed to the design, and helped to draft the manuscript. All authors approved the final manuscript.

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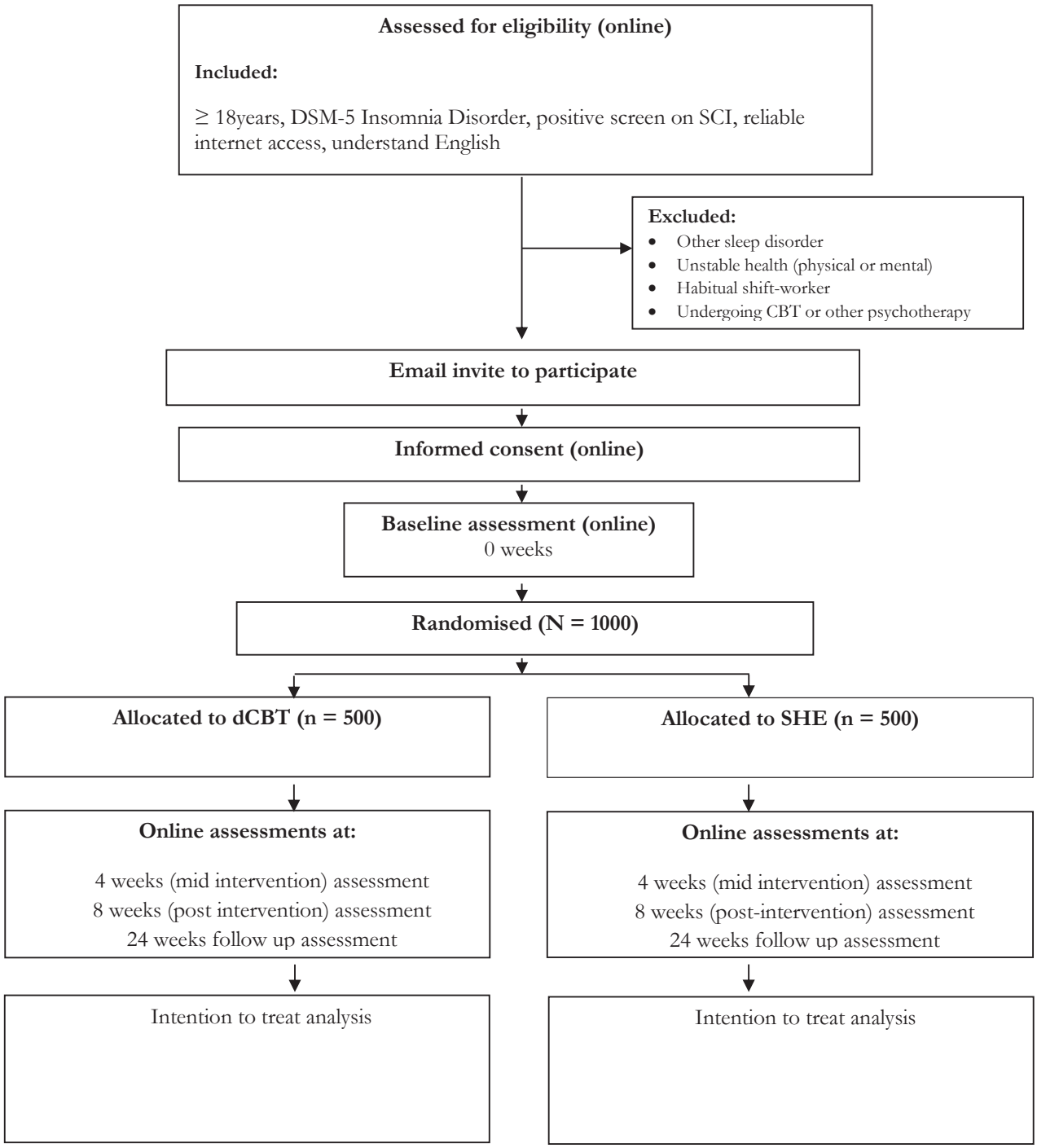

Figure 1. Summary of the trial design for the DIALS study

[SCI: Sleep Condition Indicator; dCBT: digital Cognitive Behavioural Therapy; SHE: Sleep Hygiene Education]

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Appendix 1

Participant Information Sheet

Digital Insomnia therapy to Assist your Life as well as your Sleep (DIALS) Study

We would like to invite you to take part in a research study. This webpage should provide you with all the information you need to decide whether or not you'd like to take part. If we've missed anything, do get in touch with the team [hyperlinked to contact information] and we'll be happy to answer your questions.

Key information:

- This study is for people with current sleep problems who are aged 18 and above and who have reliable internet access.

- The aim is to find out whether digital Cognitive Behavioural Therapy (dCBT) for Insomnia can improve health, quality of life and well-being and whether any changes are the result of changes in sleep.

- Everyone who takes part will be given access at no cost to a digital sleep improvement programme delivered via web and mobile (Sleepio www.sleepio.com). The programme consists of 6 weekly sessions which take about 20 minutes each to complete. Depending on which group you are assigned to, access will be given either directly or after 6 months.

- Participants will be assigned at random into one of two groups:

    - Group A will be offered *Sleep programme 1* (digital cognitive behavioural therapy).
    - Group B will be offered *Sleep programme 2* (sleep hygiene education). They can take *Sleep programme 1* after 6 months if they so wish.

- If you take part you will therefore have a 50% chance of getting access to *Sleep programme 1* now and 50% chance of getting access in 6 months.

- We'll ask everyone to fill in online questionnaires to investigate changes in sleep and well-being at the following time points: at the start of the study, after 4 weeks, 8 weeks, 24 weeks, 36 weeks and 48 weeks.

What is the purpose of this study?

We want to find out if digital Cognitive Behavioural Therapy can improve health and well-being and whether any changes are the result of changes in sleep. In particular we are interested in the impact that sleep has on quality of life, psychological well-being, mood, energy, relationships, concentration, productivity and sleepiness.

To find out whether better sleep improves people's health, quality of life and well-being, we are offering participants an online / mobile phone delivered course, proven (through previous research) to improve sleep. We want to see whether those people who receive this course immediately see any changes in their health, quality of life and well-being in comparison to those people who receive sleep hygiene education.

Why is the study important?

Adults experience problems with their sleep on a regular basis. Not only do people find it difficult to sleep, they also experience lack of energy, upset mood and poor concentration. It is often such daytime effects on health, wellbeing and quality of life that lead people to seek help.

Why have I been invited to take part?

You have been invited to take part because you may have a sleep problem, and may be interested in an insomnia research study. It could be that you have seen a notice, news story or advertisement about our research, or have expressed an interest in volunteering for future research projects, following completion of open access sleep surveys such as the Great British Sleep Survey (GBSS: www.greatbritishsleepsurvey.com or World Sleep Survey (WSS: www.worldsleepsurvey.com). You might also have expressed your interest in taking part via the Sleepio website (www.sleepio.com) or on the Sleepio App site. We are looking for around 1000 people to take part. Participants must be aged 18 or older, have access to the internet at work or at home and be able to read and understand English.

Do I have to take part?

No, it is up to you to decide whether to take part or not.

What will happen to me if I take part?

Everybody who takes part will complete an online assessment at the beginning and then after 4 weeks, 8 weeks, 24 weeks, 36 weeks and 48 weeks. The online assessment is made up of a series of questionnaires asking about your sleep, and various aspects of your health and wellbeing. These are all questionnaires that have been used in other studies. You can complete the assessment wherever is most convenient for you, as long as you have access to the internet.

After you complete the first assessment, it will be decided at random if you will receive *Sleep programme 1* or *Sleep programme 2*. Those who are assigned to *Sleep programme 2* will also have access to *Sleep programme 1* after 6 months in the study. The decision about who will receive which sleep programme immediately is made by an automated computer system (rather like throwing a dice). Everyone gets a 50% chance of being assigned being assigned to either sleep programme. The reason we need people to start with different sleep programmes is so that we can compare the effects of the two programmes. It is only by doing this that we can be sure that any changes are due to a specific programme we are offering.

You will be prompted to complete any questionnaires and to enter the website for the sleep programmes by a series of automated emails. This is the only way we will contact you, and there will be no face-to-face contact with the research team. If however you have any difficulties throughout your time in the study you are very welcome to make contact with the research team using the contact details provided below.

When you come to access *Sleep programme 1* you will be sent a code to enter a separate website that provides the programme. You will then need to answer some extra questions about yourself and your sleep. Some of these questions will be the same as the ones you complete as part of the initial assessment. We apologise for the repetition; the sleep programme website is separate from the study website and will need your information to provide help that is personal to you.

In total you will receive six online sessions in *Sleep programme 1,* all focused on relieving your sleep problems. This will include thinking about things that you can do differently both in the day and at night, adjusting unhelpful thinking patterns that get in the way of you sleeping and calming negative emotions. As well as the weekly sessions you will also have access to an online community of other people who have been through the course and many useful fact sheets about various aspects of sleep. Throughout the course you will need to complete a daily online sleep diary so that the website can monitor any

changes that happen and adjust the advice you receive accordingly. The website can also help you to set up prompts to remind you to fill these in.

When you come to access *Sleep programme 2*, you will receive an automatic email that will give you access to the dedicated webpages.

Will I be compensated for my time?

There shall be no financial or other rewards for participants.

What are the possible disadvantages, risks or side effects of any examination received when taking part?

We do not anticipate that there are any risks in taking part.

Will my taking part in the study be kept confidential?

The information you provide to the DIALS research team, during the course of the study, will be kept confidential, subject to normal legal requirements. All research data will be anonymised so no-one can be identified. We will not share any individual data with anyone outside of the immediate team. The only exception to this is that responsible members of University of Oxford staff may require access to the data for monitoring and/or audit of the study, to make sure we are complying with all regulations. Maintenance of confidentiality of information is subject to normal legal requirements. You should note that the sleep improvement programme is a separate company with its own terms and conditions regarding how they use the data you provide.

The company is committed to protecting the confidentiality of personal information in any form, complying with best practice in relation to obtaining, recording, holding, using and disclosing information and conforming to statute law (including the Data Protection Act 1998 and the Human Rights Act 1998). Once we send you the link to the sleep improvement programme, you are encouraged to read the 'terms and conditions' and 'privacy policy' pages before registering for the programme. Lastly, whilst the sleep improvement programme is separate to the DIALS research team, all data that you provide to the programme may be shared with the DIALS research team, but not the other way around.

What will happen if I don't want to carry on with the study?

Participants can withdraw from the study at any time. You do not have to give a reason and your medical care and legal rights will not be affected. Simply contact the researchers using the contact details provided below.

What if there is a problem?

The University has arrangements in place to provide for harm arising from participation in the study for which the University is the Research Sponsor. If you were to be upset about anything concerning the research then you would be welcome to speak to Professor Colin Espie (contact details below) who is an experienced clinician.

What if I have a complaint?

If you have a concern about any aspect of this project, please speak to Professor Colin Espie (contact details at the foot of this document) who will do his best to answer your query. A researcher will acknowledge your concern within 10 working days and give you an indication of how he intends to deal with it. If you remain unhappy or wish to make a formal complaint, please contact the chair of the Research Ethics Committee at the University of Oxford (Chair, Medical Sciences Inter-Divisional Research Ethics Committee; Email: ethics@medsci.ox.ac.uk; Address: Research Services, University of Oxford, Wellington Square, Oxford OX1 2JD). The chair will seek to resolve the matter in a reasonably expeditious manner.

What will happen to the results of the study?

A copy of the results will be made available on the Sleep and Circadian Neuroscience Institute of the Oxford University webpage. You will be emailed a link to this if you have indicated that you are interested in reading the results of the study. The results will also be published in academic journals and discussed at relevant conferences. No person will be identified in the results – we are interested in changes across the two study groups of people, not individuals.

Who is funding the study?

The study is funded by Big Health Ltd, the company who have developed the digital insomnia therapy.

Who has reviewed the study?

This study has been reviewed by, and received ethics clearance through, the University of Oxford Central University Research Ethics Committee.

Who is running the study?

The chief investigator for the study is Professor Colin Espie (Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford). The wider study team comprises both members of the University of Oxford and a commercial company which delivers the sleep improvement program.

CONTACT DETAILS FOR THE TEAM: You can contact the research team using the following details:

Dr Annemarie Luik

Email address: annemarie.luik@ndcn.ox.ac.uk, telephone number: +44 (0)1865 618665, postal address: Dr Annemarie Luik, Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Sir William Dunn School of Pathology, South Parks Road, OX1 3RE, UK.

Prof dr Colin Espie

Email address: colin.espie@ndcn.ox.ac.uk, postal address: Prof Dr Colin Espie, Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Sir William Dunn School of Pathology, South Parks Road, OX1 3RE, UK.

Appendix 2

Consent Page*

Digital Insomnia therapy to Assist your Life as well as your Sleep (DIALS) Study

This study is designed to investigate the impact of digital Cognitive Behavioural Therapy for insomnia upon health and wellbeing, and will examine whether any observed changes are the result of changes in sleep.

It is necessary to consent to each of the following statements in order to take part. If any of the following statements are unclear please refer to the Participant Information [instructions for access / hyperlink included here].

1. I confirm that I have read and understand the Information Page for the DIALS study. ☐
2. Only if you completed the Great British Sleep Survey: I am happy for any data that I previously provided for the Great British Sleep Survey to be used for the DIALS study. ☐
3. I understand that if I have questions I can contact the study team. If I have asked questions, I confirm that I have received satisfactory answers. ☐
4. I understand that I can withdraw from the study at any point, without penalty, by advising the researcher of my decision. ☐
5. I understand that the study has received ethical approval by the University of Oxford Central University Research Ethics Committee. ☐
6. I understand who will have access to my personal data, how it will be stored and what will happen to the data after the end of the study. ☐
7. I consent to information collected as part of the sleep improvement programme being shared with the DIALS research team. ☐

8. I understand how to raise a concern and make a complaint. ☐
9. I agree to participate in the above study. ☐

Click next ➡

For further information or questions please contact:

Dr Annemarie Luik

Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences

University of Oxford

Sir William Dunn School of Pathology

South Parks Road

Oxford, OX1 3RE, UK

Email: annemarie.luik@ndcn.ox.ac.uk

Tel: +44 (0)1865 618665

***The consent page will include all text as stated here but will be retrieved by an electronic system**

Appendix 3

Problems sleeping – need some help?

The University of Oxford, in collaboration with Big Health Ltd, is conducting an online study on insomnia.

Most people with insomnia have not only poor sleep, but also problematic daytime effects after a bad night. Therefore, the aim of the study is to find out whether digital Cognitive Behavioural Therapy (that is by web and mobile) can improve health, quality of life and wellbeing as well as poor sleep.

The study is suitable for adults aged 18 years and above who have persistent problems getting to sleep and/ or staying asleep.

For further information about the study and whether or not this might be suitable for you please go to:

[website URL]

or contact:

Dr Annemarie Luik

Email address: annemarie.luik@ndcn.ox.ac.uk, telephone number: +44 (0)1865 618665, postal address: Dr Annemarie Luik, Sleep & Circadian Neuroscience Institute, Nuffield Department of Clinical Neurosciences, University of Oxford, Sir William Dunn School of Pathology, South Parks Road, OX1 3RE, UK.

2. Changes to study protocol

10 December 2015	- Exchanged Medical Outcomes Study – Cognitive Functioning Scale – Revised (MOS-COG-R) to Cognitive Failures Questionnaire (CFQ).
6 July 2016	- Extend project data until 1 December 2017.
	- Add wording to Participant Information Sheet for Australian participants to allow recruitment via Woolcock Institute, University of Sydney, Australia.
	- Change wording to explicitly mention worldwide recruitment
13 October 2016	- Amend intended recruitment number to a minimum of a 1000 participants to cover attrition.

DIALS

Statistical Analysis Report

A parallel group, randomised controlled trial of digital cognitive behavioural therapy for insomnia versus sleep hygiene education: the impact of improved sleep on functional health, quality of life and psychological well-being.

Short title: DIALS

Ethics Ref: MS-IDREC-C2-2015-024

Trial registration: ISRCTN60530898

Version: 1.5

Date: 07th December 2017

Authors: Dr Antonia Marsden, University of Manchester, Jake Emmerson, University of Manchester and Prof Richard Emsley, University of Manchester

Trial statistician: Prof Richard Emsley, University of Manchester

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1. INTRODUCTION

1.1 PREFACE

This document details the analysis set out in the statistical analysis plan for Big Health Ltd. funded randomised controlled trial to evaluate the use of digital cognitive behavioural therapy (dCBT) for insomnia versus sleep hygiene education (SHE). Subsequent analyses of a more exploratory nature will not be bound by the strategy set out in the statistical analysis plan, though they are expected to follow the broad principles laid down in the statistical analysis plan.

The analysis strategy will be available on request when the principal papers are submitted for publication in a journal. Suggestions for subsequent analyses by journal editors or referees, will be considered carefully, and carried out as far as possible in line with the principles of this analysis strategy; if reported, the source of the suggestion will be acknowledged.

This report is based on the statistical analysis plan **Statistical Analysis Plan - DIALS v1.0.pdf** dated **21 August 2017**. Any deviations from the statistical analysis plan will be described and justified in this report of the trial.

Chief Investigator: Prof Colin Espie, University of Oxford

Trial Manager: Dr Annemarie Luik, University of Oxford

Trial statistician: Prof Richard Emsley, The University of Manchester

1.2 VALIDATION

The primary and secondary analyses comparing the various outcome measures across the two treatment groups were performed independently by both Antonia Marsden and Jake Emmerson to avoid coding and transcription errors.

1.3 SOFTWARE EMPLOYED

Stata version 14.0.

2. METHODS

2.1 BACKGROUND INFORMATION

Insomnia is a common psychological disorder which can lead to other psychological disorders such as depression, anxiety and psychosis. It has been previously demonstrated that digital cognitive behavioural therapy is effective in improving primary outcomes relating to sleep. However, it is the functional impact and daytime consequences of poor sleep that people with insomnia typically wish to improve when seeking help, rather than improved sleep per se.

DIALS is a single blinded individual patient randomised controlled trial. 1711 community participants aged 18 or older presenting with symptoms of insomnia have been recruited and randomised to receive either digital cognitive behavioural therapy for insomnia plus treatment as usual, or to sleep hygiene education plus treatment as usual (1:1).

2.2 TRIAL DESIGN

DIALS is a single blinded individual patient randomised controlled trial. 1711 community participants aged 18 or older presenting with symptoms of insomnia have been recruited and randomised to receive either digital cognitive behavioural therapy for insomnia plus treatment as usual, or to sleep hygiene education plus treatment as usual (1:1).

Date of start of recruitment:	1 December 2015
Number recruited:	1711
Date of end of recruitment:	1 December 2017
Target number of subjects:	1000

2.3 OBJECTIVES

Primary objectives

1. To assess whether delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) improves function health status by the end of treatment (8 weeks)
2. To assess whether delivering dCBTi improves positive psychological well-being by the end of treatment (8 weeks)
3. To assess whether delivering dCBTi reduces patient-generated sleep-related quality of life-impairment by the end of treatment (8 weeks)
4. To assess whether the effect of dCBTi is mediated by sleep status during the treatment phase (4 weeks).

Secondary objectives

1. To assess whether delivering dCBTi reduces symptoms of negative mood, fatigue and relationship/social dysfunction by the end of treatment (8 weeks).
2. To assess whether delivering dCBTi reduces problems with sleepiness, cognitive impairment and productively by the end of treatment (8 weeks).
3. To assess whether improvements from delivering dCBTi are maintained at follow-up (24, 36, 48 weeks).
4. To assess whether the effect of dCBTi on longer-term outcomes (24, 36, 48 weeks) are mediated by sleep status during and upon completing the treatment phase (4, 8 weeks).

2.4 TARGET POPULATION

Inclusion criteria

- Symptoms of insomnia, indicated by the sleep condition indicator
- Age $\geq$ 18.
- Reliable internet access at home
- The ability to read and understand English

Exclusion criteria

- People whose health may be considered to be unstable such as significant current symptoms of (a) an additional sleep disorder (e.g. excessively sleepy and possible obstructive sleep apnoea), (b) psychosis or mania, (c) serious physical health concerns necessitating surgery or with a prognosis less than 6 months, (d) those undergoing a psychological treatment programme for insomnia with a health professional, and (e) habitual night shift, evening, or rotating shift-workers.

2.5 INTERVENTIONS

Control: Sleep Hygiene Education, delivered on a dedicated website where materials can be viewed and downloaded. Information is based on recognised sleep hygiene advice concerning both lifestyle and environmental factors associated with sleep and sleepiness.

Test treatment: The CBT for insomnia intervention is delivered using the Sleepio® programme.[1] The programme is fully automated and its underlying algorithms feed the delivery of information, support, and advice in a personally tailored manner. Delivery is structured into six sessions, lasting an average of 20 minutes each. Certain tools (such as sleep diaries and relaxation audios) can also be accessed using the web browser of any smartphone. All of the six core sessions, sleep diaries, relaxation audios, and the scheduling tool can also be accessed using an iOS App, but this is only an option for participants who have an iPhone®. The treatment content is based on CBT for insomnia manuals[2-4] and includes a behavioural component (sleep restriction, stimulus control, and relaxation), a cognitive component (paradoxical intention, cognitive restructuring, mindfulness, positive imagery, and putting the day to rest) and an educational component (psycho-education and sleep hygiene).

The programme is highly interactive, and content is presented by an animated virtual therapist. Participants make a time for the session and are prompted via email and/or short text message (SMS) if they do not 'attend'. Participants complete daily sleep diary information throughout the intervention, which is used by the programme to provide tailored, personalised help. Participants receive an email and/or SMS reminder each morning to prompt them to fill in their sleep diary. In addition, participants complete a short questionnaire at the beginning of therapy to set treatment goals. Throughout the course of therapy, participants have access to a moderated online community and an online library of information about sleep. Participants can view their online case file, which includes four sections: a progress review, a reminder of strategies to try out between sessions, an agreed sleep schedule, and a list of further reading. The system provides online analytics, which can be used to monitor adherence by assessing how many sessions were completed and the number of weeks to complete the course. All information gathered for the programme will be stored in encrypted form on secure servers. Passwords are stored in encrypted form and all sensitive traffic is transmitted securely via SSL by default. Participants will have access to the intervention for up to 12 weeks. Digital CBT will in effect be dCBT + TAU because there will be no requirement for participants to alter their usual care in any way. Physicians, for example, will be free to offer appointments, to prescribe, and to maintain/discontinue prescriptions as they see fit.

2.6 OUTCOME MEASURES

2.6.1 PRIMARY OUTCOMES

The primary outcome measure to assess functional health and well-being is the Patient Reported Outcome Measure Information System: Global Heath scale (PROMIS-10). [1] The PROMIS-10 total score is calculated by summing the scores from ten items, where each item has a score between 1 and 5. The total score can range between 10 and 50 and a higher score indicates better health and well-being. The PROMIS-10 physical health score is calculated by adding together the scores from four of the ten items and the PROMIS-10 mental health score is calculated by adding together the scores from a different four of the ten items, resulting in a score ranging between 4 and 20 for both.

The primary outcome measure to assess psychological well-being is the Warwick-Edinburgh Mental Well-being Scale (WEMWBS).[2] The WEMWBS total score is calculated by summing the score from 14 items, where each has a score between 1 and 5. The total score ranges between 14 and 70 and a higher score indicates better psychological well-being.

The primary outcome measure to assess patient-generated sleep-related quality of life-impairment is the Glasgow Sleep Impact Index.[3] This assessment asks users to generate and rank in terms of importance three domains of sleep-related impairment and rate how 'bothered' they had been by each impairment in the past two weeks on a visual analogue scale (VAS) ranging 1-100mm, with a higher score indicating a more negative assessment of the impairment.

In the assessment of mediation by sleep status of the relationship between dCBTi and each of the three primary outcomes, sleep status is measured using the Sleep Condition Indicator (SCI)[4] and estimates of sleep diary parameters.[5] The SCI is an eight-item assessment concerning sleep outcomes where each item is given a score between 0 and 4. The total score can range between 0 and 32 and a higher score indicates better sleep.

2.6.2 SECONDARY OUTCOMES

Listed below are the secondary outcomes, along with the objective to which they relate.

- To assess whether delivering dCBTi reduces symptoms of negative mood:
    - Patient Health Questionnaire (PHQ-9).[6] A 9-item questionnaire where each item is scored between 0 and 3. The overall score is calculated by summing each item and ranges between 0 and 27. A higher score indicates a more negative mood.
    - Generalised Anxiety Disorder (GAD-7). [7] A 7-item questionnaire where each item is scored between 0 and 3. The overall score is calculated by summing each item and ranges between 0 and 21. A higher score indicates a higher level of anxiety.
- To assess whether delivering dCBTi reduces fatigue
    - Flinders Fatigue Scale (FFS).[8] A 7-item questionnaire where 6 items are scored between 0 and 4, and one item is scored between 0 and 7. The overall score is calculated by summing each item and ranges between 0 and 31. A higher score indicates a higher level of fatigue.
- To assess whether delivering dCBTi reduces relationship/social dysfunction

    - Relationship Assessment Scale (RAS). [9] A 7-item questionnaire where each item is scored between 1 and 5. The overall score is calculated by summing each item and ranges between 7 and 35. A higher score indicates a higher satisfaction with the respondent's relationship.
- To assess whether delivering dCBTi reduces problems with sleepiness
    - Epworth Sleepiness Scale (ESS). [10] An 8-item scale where each item is scored between 0 and 3. The overall score is calculated by summing each item and ranges between 0 and 24. A higher score indicates a higher level of sleepiness.
- To assess whether delivering dCBTi reduces problems with cognitive impairment:
    - Cognitive Failures Questionnaire (CFS).[11] A 25-item scale where each item is scored between 0 and 4. The overall score is calculated by summing each item and ranges between 0 and 100. A higher score indicates a higher level of cognitive impairment.
- To assess whether delivering dCBTi reduces problems with work productivity and absenteeism.
    - Work Productivity and Activity Impairment questionnaire: Specific Health Problem (WPAI: SHP).[12] A 6-item questionnaire which assesses absenteeism and work productivity. To assess work productivity is participants give a score between 0 and 10 relating to productivity at work and productivity regarding other daily activities, apart from their job. A higher score indicates a higher level of productivity impairment. Absenteeism is assessed for sleep problems specific as the number of hours missed from work due to sleep problems over total hours worked and general absenteeism as the total number of hours missed from work over total hours worked. A higher score indicates a higher absenteeism.
    - One item on job satisfaction.[13] A score between 1 and 7 where a higher score indicates a higher level of overall job satisfaction.

Participants will also complete one item about their general life satisfaction, giving a score between 1 and 4.[14] A score of 1 indicates very dissatisfied and score of 4 indicates very satisfied.

2.7 SAMPLE SIZE

According to the original protocol, a sample size of 433 participants per treatment group was required to detect a standardised effect size of 0.25 with 90% power assuming a significance level of 1.667% (adjusted from 5% due to the three primary outcomes). This was increased to 500 per treatment arm to account for a 13% dropout. This sample size wuld have more than 80% power to detect a large-sized indirect effect through the sleep mediator for each between-group comparison.

2.8 RANDOMISATION AND BLINDING IN THE ANALYSIS STAGE

Once they have completed the baseline (week 0) assessment, participants are randomised to either digital cognitive behavioural therapy for insomnia plus treatment as usual or sleep hygiene education plus treatment as usual. Simple randomisation with an allocation ratio of 1:1 will be used and randomisation will be completed via an automated online system.

The study is single blinded, as the participants are aware of which arm of the trial they are allocated to, but the researcher assessors are blinded of the study arm of the participant.

2.9 DATA CLEANING

All questionnaire items were first checked to ensure that each score was valid. Composite scores were calculated as described for the different primary and secondary outcomes, once the individual items had been confirmed as valid inputs.

All complete case data was included in the analysis with treatment set as randomised. Missing data was considered in a sensitivity analysis.

2.10 DEFINITION OF POPULATION FOR ANALYSIS

The intention to treat (ITT) population consists participants who were randomised to a study arm. All the completed outcomes were analysed according to the study arm assigned, assuming missing data was missing at random (MAR). A pattern mixture model was applied to the data allowing informative missing parameters to express the magnitude of departure from Missing Completely at Random assumption.

2.11 DEVIATIONS FROM THE SAP

There were no deviations from the SAP.

3. RESULTS

3.1 RECRUITMENT

1711 participants were recruited into the study. 7 of these participants entered the trial twice but only one of the entries contributed to the data analysis.

3.2 BASELINE CHARACTERISTICS OF PATIENTS

Table 1 provides the baseline characteristics of the participants recruited into each of the treatment arms. Simple randomisation was used with an allocation ratio of 1:1, as recommended for large trials. The covariates describing age, gender, ethnicity, height, weight, BMI, partnership status, children at home, employment status, years in education, smoking status, drink habits, caffeine intake, exercise habits, comorbidities and use of sleeping medications are well balanced between the two study arms.

TABLE 1 TABLE OF BASELINE CHARACTERISTICS

Baseline Characteristics	***SLEEPIO (N= 853)***	***TAU (N= 858)***
Age (Years)	48.4 (13.9)	47.7 (13.6)
Gender		
Male	199 (23.3%)	183 (21.3%)
Female	654 (76.7%)	675 (78.7%)
Other	0 (0.0%)	0 (0.0%)
Ethnicity		
Do not wish to state	8 (0.9%)	9 (1.1%)
Asian	21 (2.5%)	24 (2.8%)
Black/African American	7 (0.8%)	12 (1.4%)
White	785 (92.0%)	773 (90.1%)
Mixed	20 (2.3%)	16 (1.9%)
Other	12 (1.4%)	23 (2.7%)

Baseline Characteristics	***SLEEPIO*** ***(N= 853)***	***TAU*** ***(N= 858)***
		(1 missing – 0.1%)
Height in cm	167.3 (9.4) (5 missing – 0.6%)	168.0 (9.4) (7 missing – 0.8%)
Weight in kg	70.4 (16.3) (18 missing – 2.1%)	71.4 (17.8) (17 missing – 2.0%)
BMI	25.1 (5.1) (18 missing – 2.1%)	25.3 (6.0) (20 missing – 2.3%)
Partnership status		
No	213 (25.0%)	240 (28.0%)
Yes, living apart	77 (9.0%)	64 (7.5%)
Yes, living together	560 (65.7%) (3 missing – 0.4%)	553 (64.5%) (1 missing – 0.1%)
Children at home?		
No	577 (67.6%)	574 (66.9%)
Yes	274 (32.1%) (2 missing – 0.2%)	282 (32.9%) (missing 2 observations – 0.2%)
Age of youngest child at home	12.3 (7.7) (15 missing of those who had children at home – 5.5%)	12.4 (7.6) (24 missing of those who had children at home – 8.5%)
Employment status		
Full-time employed	393 (46.1%)	411 (47.9%)
Part-time employed	161 (18.9%)	187 (21.8%)
Unemployed	40 (4.7%)	34 (4.0%)
Retired	152 (17.8%)	149 (16.2%)
Full-time student	46 (5.5%)	32 (3.7%)
Full-time homemaker or carer	56 (6.6%) (4 missing – 0.5%)	52 (6.1%) (3 missing – 0.4%)
Years continuous full education	16.5 (3.9) (30 missing – 3.5%)	16.6 (3.5) (18 missing – 2.1%)
Smoking how often		
Never, and never have	481 (56.6%)	483 (54.9%)
Never, but have previously	297 (34.8%)	309 (36.0%)
Rarely	31 (3.6%)	29 (3.4%)
1-10 a day	28 (3.3%)	19 (2.2%)
11-20 a day	13 (1.5%)	19 (2.2%)
21+ a day	0 (0.0%) (1 missing – 0.1%)	8 (0.9%) (3 missing – 0.4%)
Alcohol how often		
Never	205 (24.0%)	200 (23.3%)
Less than once a week	154 (18.1%)	183 (21.3%)
Once a week	127 (14.9%)	116 (13.5%)
2-3 times a week	221 (25.9%)	223 (26.0%)
4+ times a week	145 (17.0%) (1 missing – 0.1%)	135 (15.7%) (1 missing – 0.1%)
Caffeine how often		
Never	81 (9.5%)	106 (12.1%)
Less than once a day	111 (13.0%)	114 (13.3%)
Once a day	204 (23.9%)	197 (23.0%)
2-3 times a day	330 (38.7%)	305 (35.6%)
4+ times a day	124 (14.5%) (3 missing - 0.4%)	134 (15.6%) (4 missing – 0.5%)
Exercise how often		
Never	77 (9.0%)	85 (9.9%)
Less than once a week	85 (10.0%)	111 (12.9%)
Once a week	136 (15.9%)	134 (15.6%)
2-3 times a week	317 (37.2%)	279 (32.5%)
4+ times a week	237 (27.8%) (1 missing – 0.1%)	247 (28.8%) (2 missing – 0.2%)
Diagnosed with heart disease or high blood pressure	106 (12.4%)	106 (12.4%)
Diagnosed with Diabetes	18 (2.1%)	18 (2.1%)
Diagnosed with stroke or other neurological problems	16 (1.9%)	8 (0.9%)
Diagnosed with cancer	39 (4.6%)	41 (4.8%)
Diagnosed with arthritis or other joint problems	87 (10.2%)	90 (10.5%)
Diagnosed with digestive disorders	123 (14.4%)	121 (13.9%)
Diagnosed with depression or anxiety	317 (37.2%)	333 (38.8%)

Baseline Characteristics	*SLEEPIO (N= 853)*	*TAU (N= 858)*
Diagnosed with hormonal problems	70 (8.2%)	57 (6.6%)
Other diagnosed comorbidity	127 (14.9%)	115 (13.4%)
Any diagnosed comorbidity		
No	262 (30.7%)	253 (29.5%)
Yes	561 (65.8%)	570 (66.4%)
	(30 missing – 3.5%)	(35 missing – 4.1%)
How many nights in last two weeks have taken prescribed sleeping medication	1.6 (3.7)	1.6 (3.4)
How many nights in last two weeks have taken non-prescribed sleeping medication	2.2 (3.9)	2.3 (3.9)
Outcomes at Baseline		
SCI-8	6.5 (3.2)	6.6 (3.3)
SCI-9	7.5 (3.7)	7.6 (3.7)
GSII		
Bothered by most important concern	87.8 (12.8)	87.3 (12.7)
Bothered by 2nd most important concern	76.3 (17.3)	75.4 (16.4)
Bothered by 3rd most important concern	60.9 (21.4)	60.2 (21.3)
Combined score	224.9 (45.9)	222.9 (44.5)
ESS	6.1 (4.4)	6.2 (4.5)
	(2 missing – 0.2%)	(2 missing - 0.2%)
FFS	19.0 (5.5)	19.1 (5.4)
	(3 missing – 0.4%)	(1 missing - 0.1%)
PROMIS-10		
Physical	14.4 (2.3)	14.3 (2.2)
Mental	11.2 (3.0)	11.4 (3.0)
Total	31.8 (5.8)	31.8 (5.6)
WEMWBS	43.1 (7.7)	43.2 (7.9)
PHQ-9	9.7 (4.1)	9.8 (4.2)
GAD-7	7.4 (4.7)	7.4 (4.7)
	(1 missing - 0.1%)	(1 missing – 0.1%)
RAS	27.8 (5.8)	27.6 (5.8)
	(293 missing – 34.4%)	(304 missing – 35.4%)
CFQ	43.1 (15.4)	42.5 (16.8)
	(8 missing – 0.9%)	(5 missing – 0.6%)
WPAI		
Absenteeism due to Sleep score	7.38 (16.3)	8.03 (16.9)
	(348 missing – 40.8%)	(302 missing – 35.2%)
Absenteeism due to other factors score	4.57 (13.6)	4.21 (13.4)
	(349 missing – 40.9%)	(312 missing – 36.4%)
Impact on productivity at work score	42.2 (24.0)	41.0 (23.2)
	(310 missing – 36.3%)	(275 missing – 32.1%)
Impact on productivity in general score	45.3 (25.0)	45.3 (24.4%)
	(17 missing – 2.0%)	(5 missing – 0.58%)
Job satisfaction	3.4 (2.1)	3.6 (2.0)
	(60 missing – 7.0%)	(50 missing – 5.8%)
Life satisfaction	2.8 (0.7)	2.8 (0.7)
How many times visiting a GP in the past month	0.6 (0.9)	0.6 (0.9)
	(3 missing - 0.4%)	(1 missing – 0.1%)
How many times visiting a specialist in the past month	0.3 (0.7)	0.3 (0.7)
	(2 missing - 0.2%)	(2 missing – 0.2%)
How many times in an emergency room in the past month	0.04 (0.2)	0.04 (0.2)
	(3 missing – 0.4%)	(1 missing – 0.1%)
How many times staying in a hospital overnight or longer in the past month	0.01 (0.1)	0.01 (0.1)
	(2 missing - 0.2%)	(1 missing – 0.1%)
How many total nights spent in the hospital in the past month	0.02 (0.2)	0.02 (0.3)
	(2 missing - 0.2%)	(1 missing - 0.2%)
***Data are either frequency (%) or mean (standard deviation) as indicated**		

3.3 OUTCOME MISSINGNESS AT 8 WEEKS

Table 2 provides a breakdown of the patients who were lost to follow up at the time of the primary outcome measure, week 8, in terms of their treatment and baseline covariates, as well as the p-value for the association of treatment and the baseline characteristics for predicting missingness from a logistic regression model.

There is an association between missingness and the treatment to which the participant was allocated. There is also an association between missingness and many of the baseline covariates including age, gender, height, partnership status, employment status, smoking status, amount of exercise, heart disease, cancer and a non-specified other comorbidity.

Several of the baseline outcome measure values were associated with missingness including SCI-8, SCI-9, PROMIS physical and mental health scores, WEMWBS, PHQ-9 and GAD-7.

TABLE 2 TABLE OF SUMMARY STATISTICS OF BASELINE COVARIATES OF THOSE PARTICIPANTS WHO COMPLETED AND THOSE WHO WERE LOST TO FOLLOW UP FOR THE PRIMARY OUTCOME AT 8 WEEKS, TOGETHER WITH THE PROBABILITY OF THE STUDY ARM AND EACH OF THE COVARIATES PREDICTING MISSINGNESS FROM THE LOGISTIC REGRESSION MODEL

Baseline Characteristics	***Predicting missingness (p-value)***	***SLEEPIO (N= 853)***		***TAU (N= 858)***	
	Study arm *p < 0.063*	*Missing* *(N=389)*	*Not Missing* *(N=464)*	*Missing* *(N=353)*	*Not Missing* *(N=505)*
Age (Years)	p < 0.001	45.2 (13.6)	51.2 (13.5)	44.7 (13.7)	49.7 (13.1)
Gender					
Male		100 (25.7 %)	99 (21.3%)	88 (24.9%)	95 (18.8%)
Female	0.009	289 (74.3%)	365 (78.7%)	265 (74.1%)	410 (81.2%)
Ethnicity					
Do not wish to state		5 (1.3%)	3 (0.7%)	4 (1.1%)	5 (1.0%)
Asian		13 (3.3%)	8 (1.7%)	13 (3.7%)	11 (2.2%)
Black/African American		5 (1.3%)	2 (0.4%)	5 (1.4%)	7 (1.4%)
White		347 (89.2%)	438 (94.4%)	318 (90.3%)	455 (90.1%)
Mixed		11 (2.8%)	9 (1.9%)	4 (1.1%)	12 (2.4%)
Other	0.356	8 (2.1%)	4 (0.9%)	8 (2.7%)	15 (3.0%)
Height in cm	0.017	168.1 (9.5)	166.7 (9.2)	168.4 (9.6)	167.6 (9.3)
Weight in kg	0.101	72.2 (17.2)	68.9 (15.2)	71.1 (15.1)	71.5 (19.4)
BMI	0.478	25.5 (5.5)	24.7 (4.7)	25.0 (4.9)	25.4 (6.6)
Partnership status					
No		109 (28.1%)	104 (22.5%)	105 (29.8%)	135 (26.8%)
Yes, living apart		41 (10.6%)	36 (7.8%)	31 (8.8%)	33 (6.6%)
Yes, living together	0.011	238 (61.3%)	322 (69.7%)	217 (61.5%)	336 (66.7%)
Children at home?					
No		251 (64.5%)	326 (70.6%)	235 (66.8%)	339 (67.3%)
Yes	0.155	138 (35.5%)	136 (29.4%)	117 (33.2%)	165 (32.7%)
Age of youngest child at home	0.560	11.9 (8.0)	12.7 (7.3)	12.4 (8.0)	12.3 (7.3)
Employment status					
Full-time employed		190 (49.1%)	203 (43.9%)	199 (56.7%)	212 (42.1%)
Part-time employed		68 (17.6%)	93 (20.1%)	57 (16.2%)	130 (25.8%)
Unemployed		20 (5.2%)	20 (4.3%)	18 (5.1%)	16 (3.2%)
Retired		47 (12.1%)	105 (22.7%)	43 (12.3%)	96 (19.1%)
Full-time student		28 (7.2%)	19 (4.1%)	17 (4.8%)	15 (3.0%)
Full-time homemaker or carer	<0.001	34 (8.8%)	22 (4.8%)	17 (4.8%)	35 (6.9%)
Years continuous full education	0.856	16.5 (4.0)	16.4 (3.8)	16.6 (3.6)	16.6 (3.5)
Smoking how often					
Never, and never have		204 (52.4%)	279 (60.3%)	187 (53.1%)	284 (56.5%)
Never, but have previously		141 (36.3%)	156 (33.7%)	120 (34.1%)	189 (37.6%)
Rarely		20 (5.1%)	11 (2.3%)	17 (4.8%)	12 (2.4%)
1-10 a day		17 (4.4%)	11 (2.4%)	12 (3.4%)	7 (1.4%)
11-20 a day		7 (1.8%)	6 (1.3%)	12 (3.4%)	7 (1.4%)
21+ a day	0.001	0 (0.0%)	0 (0.0%)	4 (1.1%)	4 (0.8%)
Alcohol how often					
Never		96 (24.7%)	109 (23.5%)	95 (26.9%)	105 (20.8%)
Less than once a week		70 (18.0%)	84 (18.1%)	79 (22.4%)	104 (20.6%)
Once a week		53 (13.6%)	74 (16.0%)	44 (12.5%)	72 (14.3%)
2-3 times a week		106 (27.3%)	115 (24.8%)	84 (23.8%)	139 (27.6%)
4+ times a week	0.366	64 (16.5%)	81 (17.5%)	51 (14.5%)	84 (16.7%)
Caffeine how often					

Baseline Characteristics	***Predicting missingness (p-value)***	***SLEEPIO (N= 853)***		***TAU (N= 858)***	
	Study arm p < 0.063	*Missing (N=389)*	*Not Missing (N=464)*	*Missing (N=353)*	*Not Missing (N=505)*
Never		33 (8.5%)	48 (10.4%)	43 (12.3%)	61 (12.1%)
Less than once a day		43 (11.1%)	68 (14.7%)	50 (14.3%)	64 (12.7%)
Once a day	0.239	105 (27.1%)	99 (21.4%)	87 (24.8%)	110 (21.9%)
2-3 times a day		142 (36.6%)	188 (40.7%)	120 (34.2%)	185 (36.8%)
4+ times a day		65 (16.8%)	59 (12.8%)	51 (14.5%)	83 (16.5%)
Exercise how often					
Never		45 (11.6%)	32 (6.9%)	41 (11.6%)	44 (8.8%)
Less than once a week		43 (11.1%)	42 (9.1%)	53 (15.0%)	58 (11.5%)
Once a week		74 (19.0%)	62 (13.4%)	53 (15.0%)	81 (16.1%)
2-3 times a week		134 (34.5%)	183 (39.5%)	113 (32.0%)	166 (33.0%)
4+ times a week	0.003	93 (23.9%)	144 (31.1%)	93 (26.4%)	154 (30.6%)
Diagnosed with heart disease or high blood pressure	0.001	35 (9.0%)	71 (15.3%)	34 (9.6%)	72 (14.3%)
Diagnosed with Diabetes	0.418	9 (2.3%)	9 (1.9%)	9 (2.6%)	9 (1.8%)
Diagnosed with stroke or other neurological problems	0.321	6 (1.5%)	10 (2.2%)	2 (0.6%)	6 (1.2%)
Diagnosed with cancer	0.027	13 (3.4%)	26 (5.6%)	12 (3.4%)	29 (5.7%)
Diagnosed with arthritis or other joint problems	0.215	38 (9.8%)	49 (10.6%)	31 (8.8%)	59 (11.7%)
Diagnosed with digestive disorders	0.266	55 (14.2%)	68 (14.7%)	42 (11.9%)	77 (15.2%)
Diagnosed with depression or anxiety	0.359	142 (36.5%)	175 (37.7%)	149 (42.2%)	184 (36.4%)
Diagnosed with hormonal problems	0.465	31 (8.0%)	39 (8.4%)	29 (8.2%)	28 (5.5%)
Other diagnosed comorbidity	0.002	48 (12.3%)	79 (17.0%)	35 (9.9%)	80 (15.8%)
No diagnosed comorbidity	0.021	129 (33.2%)	132 (28.4%)	115 (32.6%)	139 (27.5%)
Any diagnosed comorbidity	0.028	242 (65.1%)	319 (70.7%)	226 (66.7%)	344 (71.1%)
How many nights in last two weeks have taken prescribed sleeping medication	0.020	1.8 (3.9)	1.5 (3.5)	1.9 (3.9)	1.3 (3.0)
How many nights in last two weeks have taken non-prescribed sleeping medication	0.43	2.3 (4.1)	2.3 (4.0)	2.2 (3.8)	2.2 (3.8)
Outcomes at Baseline					
SCI-8	<0.001	6.1 (3.3)	6.9 (3.2)	6.3 (3.2)	6.8 (3.3)
SCI-9	0.004	7.1 (3.7)	7.7 (3.6)	7.3 (3.8)	7.8 (3.6)
GSII					
Bothered by most important concern	0.022	88.9 (13.0)	86.8 (12.6)	87.7 (13.2)	87.0 (12.4)
Bothered by 2nd most important concern	0.005	78.2 (17.4)	74.7 (17.1)	76.0 (16.7)	75.0 (16.2)
Bothered by 3rd most important concern	0.152	62.9 (21.5)	59.1 (21.2)	59.6 (21.5)	60.5 (21.0)
Combined score	0.018	230.0 (45.7)	220.6 (45.8)	223.3 (45.5)	222.5 (43.9)
ESS	0.087	6.1 (4.4)	6.1 (4.4)	5.7 (4.4)	6.5 (4.5)
FFS	0.046	19.3 (5.8)	18.7 (5.2)	19.3 (5.3)	18.9 (5.4)
PROMIS-10					
Physical	0.083	14.1 (2.3)	14.6 (2.2)	14.4 (2.3)	14.3 (2.1)
Mental	0.001	10.9 (2.9)	11.5 (3.1)	11.1 (3.1)	11.5 (3.0)
Total	0.003	31.1 (5.7)	32.5 (5.9)	31.7 (5.8)	31.9 (5.5)
WEMWBS	<0.001	42.1 (7.4)	44.0 (7.9)	42.5 (7.9)	43.7 (7.8)
PHQ-9	<0.001	10.4 (4.1)	9.2 (4.0)	10.0 (4.0)	9.6 (4.2)
GAD-7	<0.001	7.9 (4.8)	6.9 (4.5)	7.8 (4.9)	7.2 (4.5)
RAS	0.084	27.6 (5.9)	28.0 (5.7)	27.1 (5.8)	27.9 (5.8)
CFQ	0.26	43.9 (14.9)	42.4 (15.8)	42.7 (18.1)	42.4 (15.8)
WPAI					
Absenteeism due to Sleep score	0.022	7.9 (16.9)	6.9 (15.8)	8.1 (15.1)	8.0 (18.2)
Absenteeism due to other factors score	0.005	4.3 (13.5)	4.8 (13.5)	4.4 (13.4)	4.1 (13.4)
Impact on productivity at work score	0.152	43.6 (24.5)	40.9 (23.4)	44.3 (22.5)	38.5 (23.4)
Impact on productivity in general score	0.018	47.4 (25.4)	43.5 (24.6)	47.3 (24.8)	43.9 (24.0)
Job satisfaction	0.010	3.6 (2.0)	3.3 (2.1)	3.8 (1.9)	3.5 (2.1)
Life satisfaction	0.005	2.8 (0.7)	2.8 (0.7)	2.7 (0.7)	2.9 (0.7)
How many times visiting a GP in the past month	0.029	0.6 (1.0)	0.6 (0.7)	0.6 (0.9)	0.5 (0.8)
How many times visiting a specialist in the past month	0.395	0.3 (0.7)	0.3 (0.7)	0.3 (0.8)	0.3 (0.7)
How many times in an emergency room in the past month	0.146	0.05 (0.3)	0.03 (0.2)	0.05 (0.2)	0.03 (0.2)
How many times staying in a hospital		0.01 (0.1)	0 (0)	0.01 (0.1)	0.01 (0.1)

Baseline Characteristics	***Predicting missingness (p-value)***	***SLEEPIO (N= 853)***		***TAU (N= 858)***	
	Study arm p < 0.063	*Missing (N=389)*	*Not Missing (N=464)*	*Missing (N=353)*	*Not Missing (N=505)*
overnight or longer in the past month	0.153				
How many total nights spent in the hospital in the past month	0.351	0.03 (0.3)	0.004 (0.07)	0.02 (0.2)	0.2 (0.3)
***Data are either frequency (%) or mean (standard deviation (sd)) as stated**					

3.4 PRIMARY ANALYSES

3.4.1 PRIMARY OUTCOMES

3.4.1.1 PROMIS-10 AT 8 WEEKS

Total score

The PROMIS-10 primary outcome is a composite score which can range from 10 to 50, with higher values indicating better health and well-being, and is assumed to be normally distributed. Table 3 provides the summary statistics of PROMIS-10 at 8 weeks. For the control group, the unadjusted mean score was 32.92 (sd=6.18). The Sleepio group had an unadjusted mean score of 35.08 (6.65).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 1. The outcome was found to have peaks at certain points but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

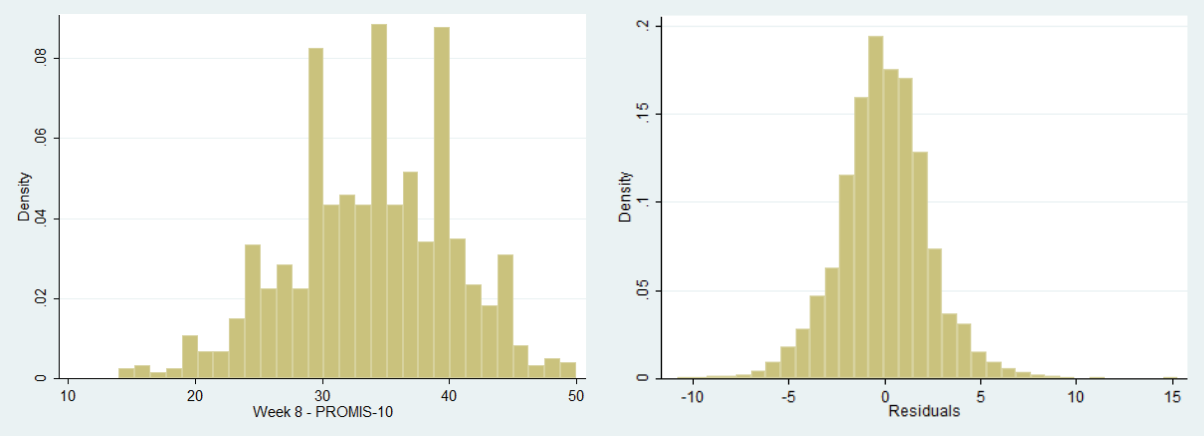

FIGURE 1 HISTOGRAMS OF THE PROMIS-10 TOTAL OUTCOME AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 3 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) TOTAL SCORE AT 8 WEEKS

	Treatment	
	Sleepio N=464	**TAU** N=505
Unadjusted Mean (Standard Deviation)	35.08 (6.65)	32.92 (6.18)
Adjusted Difference in Treatment Effect (C.I.)*	1.76 (1.24, 2.28)	
Cohen's d	0.31 (0.22, 0.40)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) improves general health and well-being by the end of treatment was tested by means of a linear mixed effects model (Table 3). At 8 weeks post randomisation, the estimated adjusted treatment effect was 1.76 (95% CI: 1.24, 2.28), indicating that participants in the Sleepio group had a higher PROMIS-10 total score than those in the control group. This treatment effect was highly significant (p<0.0001).

Physical health score

The PROMIS-10 physical health score is a calculated from four of the ten items of the PROMIS-10 questionnaire and can range from 4 to 20 with higher values indicating better physical health. Table 3 provides the summary statistics of PROMIS-10 physical health score at 8 weeks. For the control group, the unadjusted mean score was 14.55 (2.42). The Sleepio group had an unadjusted mean score of 15.47 (2.43).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 2. The outcome was found to be left skewed but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

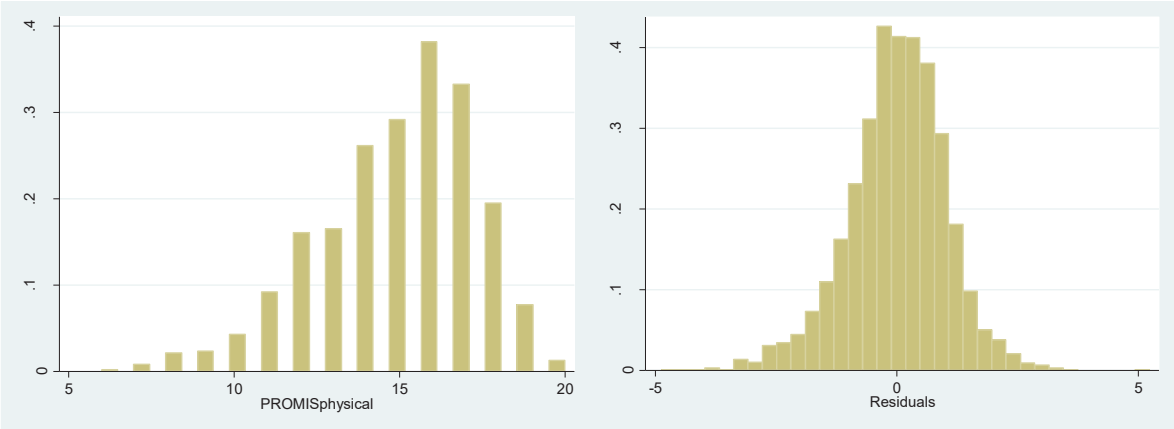

FIGURE 2 HISTOGRAMS OF THE PROMIS-10 PHYSICAL HEALTH OUTCOME AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 4 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) PHYSICAL HEALTH SCORE AT 8 WEEKS

	Treatment	
	Sleepio N=464	**TAU** N=505
Unadjusted Mean (Standard Deviation)	15.47 (2.43)	14.55 (2.42)
Adjusted Difference in Treatment Effect (C.I.)*	0.68 (0.46, 0.89)	
Cohen's d	0.31 (0.21, 0.40)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) improves physical health by the end of treatment was tested by means of a linear mixed effects model (Table 4). At 8 weeks post randomisation, the estimated adjusted treatment effect was 0.68 (0.46; 0.89), indicating that participants in the Sleepio group had a higher PROMIS-10 physical health score than those in the control group. This treatment effect was highly significant (p<0.0001).

Mental health score

The PROMIS-10 mental health score is a calculated from four of the ten items of the PROMIS-10 questionnaire and can range from 4 to 20 with higher values indicating better mental health. Table 5 provides the summary statistics of PROMIS-10 mental health score at 8 weeks. For the control group, the unadjusted mean score was 12.12 (3.16). The Sleepio group had an unadjusted mean score of 12.95 (3.46).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 3. The outcome looked normally distributed and residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

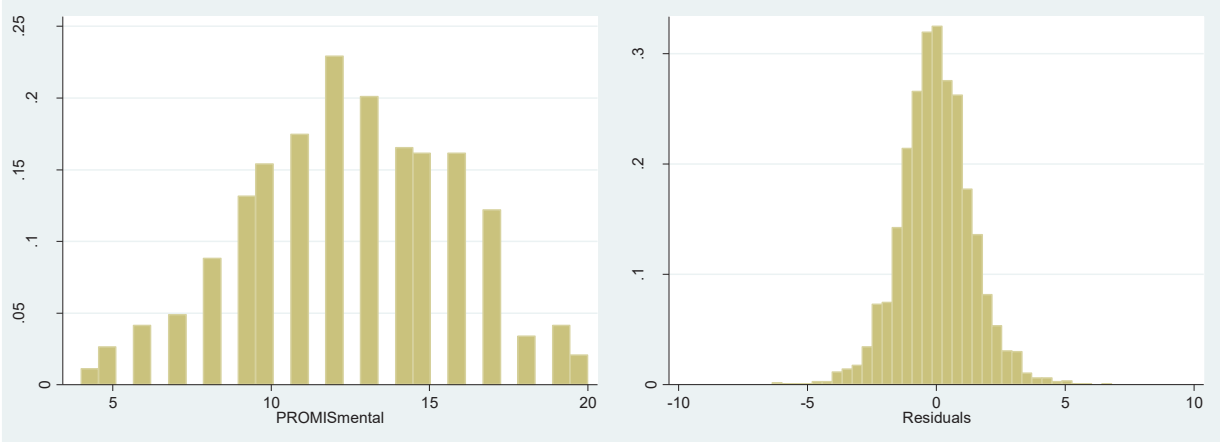

FIGURE 3 HISTOGRAMS OF THE PROMIS-10 MENTAL HEALTH OUTCOME AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 5 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) MENTAL HEALTH SCORE AT 8 WEEKS

	Treatment	
	Sleepio N=464	**TAU** N=505
Unadjusted Mean (Standard Deviation)	12.95 (3.46)	12.12 (3.16)
Adjusted Difference in Treatment Effect (C.I.)*	0.82 (0.54, 1.11)	
Cohen's d	0.27 (0.18, 0.37)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) improves mental health by the end of treatment was tested by means of a linear mixed effects model (Table 5). At 8 weeks post randomisation, the estimated adjusted treatment effect was 0.82 (0.54, 1.11), indicating that participants in the Sleepio group had a higher PROMIS-10 mental health score than those in the control group. This treatment effect was highly significant ($p<0.0001$).

3.4.1.2 WEMWBS AT 8 WEEKS

The WEMWBS total score is calculated by summing the score from 14 items, where each has a score between 1 and 5. The total score ranges between 14 and 70 and a higher score indicates better psychological well-being. Table 6 provides the summary statistics of WEMWBS score at 8 weeks. For the control group, the unadjusted mean score was 45.16 (8.77). The Sleepio group had an unadjusted mean score of 48.12 (8.82).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 4. The outcome was found to be slightly skewed to the left, but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

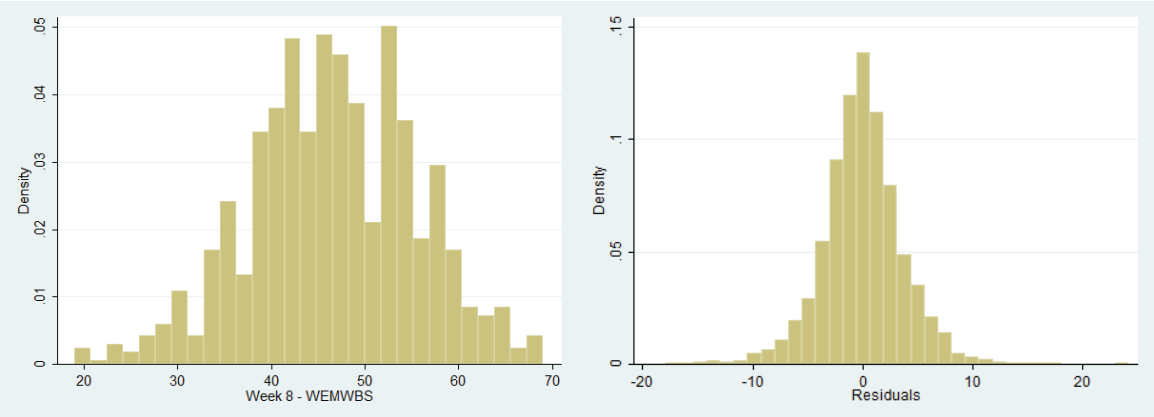

FIGURE 4 HISTOGRAMS OF THE WEMWBS (WARWICK-EDINBURGH MENTAL WELL-BEING SCALE) OUTCOME AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 6 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME WEMWBS (WARWICK-EDINBURGH MENTAL WELL-BEING SCALE) SCORE AT 8 WEEKS

	Treatment	
	Sleepio N=462	**TAU** N=502
Unadjusted Mean (Standard Deviation)	48.12 (8.82)	45.16 (8.77)
Adjusted Difference in Treatment Effect (C.I.)*	2.68 (1.89, 3.47)	
Cohen's d	0.35 (0.24, 0.45)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) improves psychological well-being by the end of treatment was tested by means of a linear mixed effects model (Table 6). At 8 weeks post randomisation, the estimated adjusted treatment effect was 2.68 (1.89, 3.47), indicating that participants in the Sleepio group had a higher WEMWBS score than those in the control group. This treatment effect was highly significant (p<0.0001).

3.4.1.3 GSII AT 8 WEEKS

The Glasgow Sleep Impact Index (GSII) assesses the patient-generated sleep-related quality of life impairment. The assessment asks users to generate and rank in terms of importance three domains of sleep-related impairment and rate how 'bothered' they had been by each impairment in the past two weeks on a visual analogue scale (VAS) ranging 1-100mm, with a higher score indicating a more negative assessment of the impairment.

Rank 1

Table 7 provides the summary statistics of GSII VAS score for rank 1 at 8 weeks. For the control group, the unadjusted mean score was 65.68 (25.86). The Sleepio group had an unadjusted mean score of 46.87 (29.90).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 5. The outcome did not look to be normally distributed but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

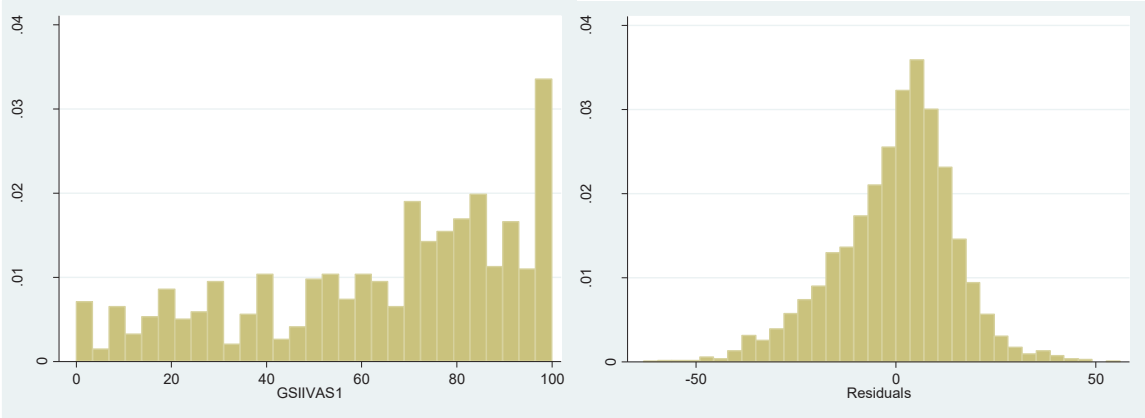

FIGURE 5 HISTOGRAMS OF THE GSII (GLASGOW SLEEP IMPACT INDEX) RANK 1 AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 7 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 1 AT 8 WEEKS

	Treatment	
	Sleepio N=467	**TAU** N=509
Unadjusted Mean (Standard Deviation)	46.87 (29.90)	65.68 (25.86)
Adjusted Difference in Treatment Effect (C.I.)*	-17.60 (-20.81, -14.39)	
Cohen's d	-1.38 (-1.63, -1.13)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) reduces patient-generated sleep-related quality of life-impairment was tested by means of a linear mixed effects model (Table 7). At 8 weeks post randomisation, the estimated adjusted treatment effect was -17.60 (-20.81, -14.39), indicating that participants in the Sleepio group had a lower GSII VAS score for the highest ranked impairment than those in the control group. This treatment effect was highly significant (p<0.0001).

Rank 2

Table 8 provides the summary statistics of GSII VAS score for rank 2 at 8 weeks. For the control group, the unadjusted mean score was 62.19 (26.14). The Sleepio group had an unadjusted mean score of 43.48 (29.67).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 6. The outcome did not look to be normally distributed but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

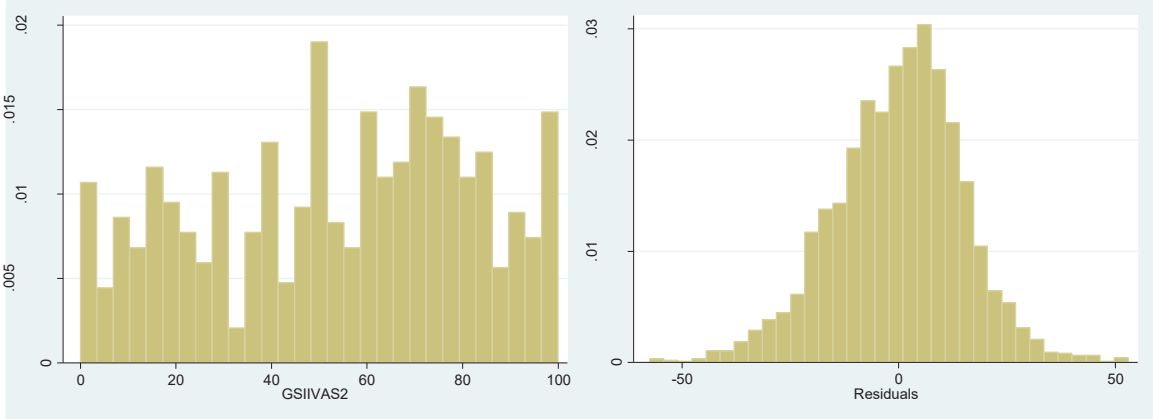

FIGURE 6 HISTOGRAMS OF THE GSII (GLASGOW SLEEP IMPACT INDEX) RANK 2 AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) reduces patient-generated sleep-related quality of life-impairment was tested by means of a linear mixed effects model (Table 8). At 8 weeks post randomisation, the estimated adjusted treatment effect was -17.37 (-20.53, -14.20), indicating that participants in the Sleepio group had a lower GSII VAS score for the second highest ranked important impairment than those in the control group. This treatment effect was highly significant (p<0.0001).

TABLE 8 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 2 AT 8 WEEKS

	Treatment	
	Sleepio N=467	**TAU** N=509
Unadjusted Mean (Standard Deviation)	43.48 (29.67)	62.19 (26.14)
Adjusted Difference in Treatment Effect (C.I.)*	-17.37 (-20.53, -14.20)	
Cohen's d	-1.03 (-1.22, -0.84)	
p-value	<0.0001	
* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.		

Rank 3

Table 9 provides the summary statistics of GSII VAS score for rank 3 at 8 weeks. For the control group, the unadjusted mean score was 58.57 (27.35). The Sleepio group had an unadjusted mean score of 41.35 (28.04).

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 7. The outcome did not look to be normally distributed but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

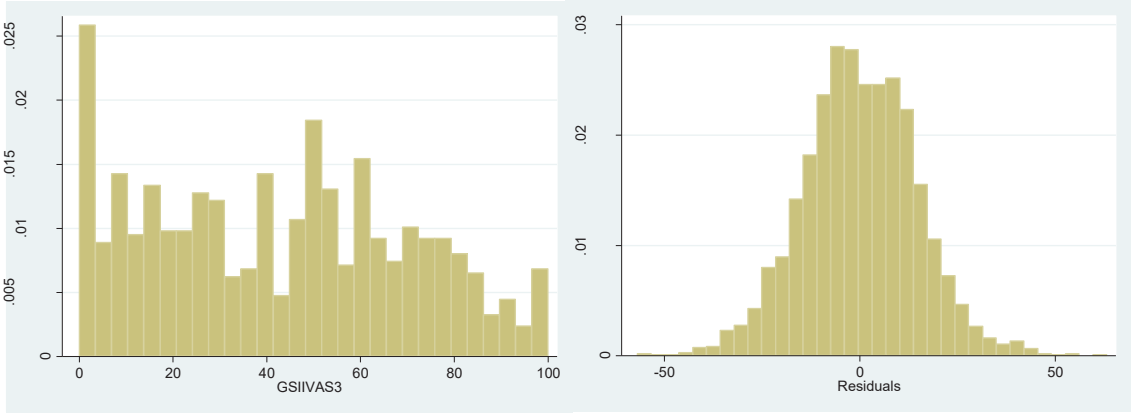

FIGURE 7 HISTOGRAMS OF THE GSII (GLASGOW SLEEP IMPACT INDEX) RANK 3 AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 9 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 3 AT 8 WEEKS

	Treatment	
	Sleepio N=467	**TAU N=509**
Unadjusted Mean (Standard Deviation)	41.35 (28.04)	58.57 (27.35)
Adjusted Difference in Treatment Effect (C.I.)*	-15.45 (-18.60, -12.29)	
Cohen's d	-0.72 (-0.87, -0.58)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) reduces patient-generated sleep-related quality of life-impairment was tested by means of a linear mixed effects model (Table 8). At 8 weeks post randomisation, the estimated adjusted treatment effect was -15.45 (-18.60, -12.29), indicating that participants in the Sleepio group had a lower GSII VAS score for the third highest ranked impairment than those in the control group. This treatment effect was highly significant (p<0.0001).

Combined ranks

The combined score is the sum of the three VAS scores for ranks 1-3, and thus ranges from 0 to 300, with a higher score indicating a more negative assessment of the three impairments in total.
Table 10 provides the summary statistics of GSII combined VAS scores for ranks 1-3 at 8 weeks. For the control group, the unadjusted mean score was 186.45 (70.88). The Sleepio group had an unadjusted mean score of 131.69 (79.89)

The skewness of the outcome and assumption of normality of the residuals were checked using graphical methods shown in Figure 8. The outcome did not look to be normally distributed but the residuals were sufficiently normally distributed in order to use the linear mixed effects model for parameter estimates and confidence intervals.

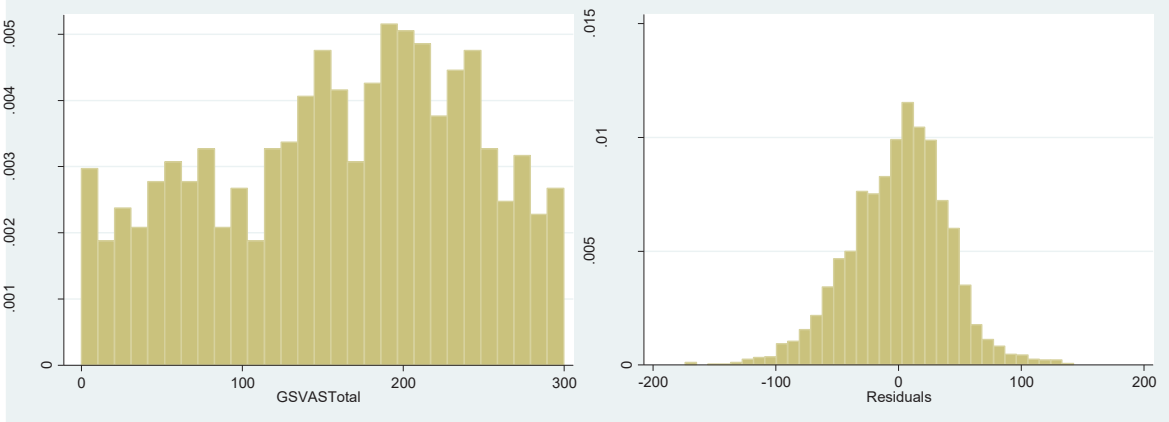

FIGURE 8 HISTOGRAMS OF THE GSII (GLASGOW SLEEP IMPACT INDEX) COMBINED OUTCOME AT 8 WEEKS AND RESIDUALS FROM MODEL FIT

TABLE 10 ADJUSTED AND UNADJUSTED RESULTS FOR THE PRIMARY OUTCOME GSII (GLASGOW SLEEP IMPACT INDEX) COMBINED OUTCOME AT 8 WEEKS

	Treatment	
	Sleepio N=467	**TAU N=509**
Unadjusted Mean (Standard Deviation)	131.69 (79.89)	186.45 (70.88)
Adjusted Difference in Treatment Effect (C.I.)*	-50.20 (-58.62, -41.78)	
Cohen's d	-1.11 (-1.30, -0.92)	
p-value	<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

The hypothesis that delivering a digital cognitive behavioural therapy for the treatment of insomnia (dCBTi) reduces patient-generated sleep-related quality of life-impairment was tested by means of a linear mixed effects model (Table 10). At 8 weeks post randomisation, the estimated adjusted treatment effect was -50.20 (-58.62, -41.78), indicating that participants in the Sleepio group had lower combined VAS score for all three ranked impairments than those in the control group. This treatment effect was highly significant (p<0.0001).

3.4.2 MEDIATION ANALYSIS

The fourth primary objective was to assess whether changes in insomnia symptoms mediates the changes in the three primary outcomes.

To test this hypothesis, we determined the extent to which the effect of the Sleepio intervention on the outcomes PROMIS-10, WEMWBS and GSII at 8 weeks was mediated by sleep status at 4 weeks. Sleep was measured using the SCI-8 score; the sleep condition indicator measure which assesses sleep status. The SCI outcome is a composite score which can range from 0 to 32, with higher values indicating better sleep. Mediation of the outcomes at 24 weeks by sleep at 8 weeks was also assessed.

The approach used was similar to the approach of Baron and Kenny (1986), making use of linear mixed effects models at each step, similar to the linear mixed effects models used in the primary analyses. In all models baseline levels of the outcome and mediator were included as covariates.

Table 11 provides the results of the mediation analysis.

TABLE 11 MEDIATION ANALYSIS RESULTS

		Total Effect			**Direct Effect**			**Indirect Effect**			**Percent mediated***
Outcome (week)	**Mediator (week)**	**Effect size**	**SE**	**p**	**Effect size**	**SE**	**p**	**Effect size**	**SE**	**p**	
PROMIS-10 (8)	**Insomnia SCI-8 (4)**	1.76	0.26	<0.001	0.65	0.27	0.0172	0.89	0.12	<0.001	50.5%
PROMIS-10 (24)	**Insomnia SCI-8 (8)**	1.75	0.27	<0.001	0.13	0.29	0.6614	1.47	0.14	<0.001	83.8%
PROMIS-physical (8)	**Insomnia SCI-8 (4)**	0.68	0.11	<0.001	0.28	0.11	0.0139	0.32	0.05	<0.001	47.0%
PROMIS-physical (24)	**Insomnia SCI-8 (8)**	0.59	0.11	<0.001	0.04	0.12	0.7147	0.51	0.05	<0.001	86.4%
PROMIS-mental (8)	**Insomnia SCI-8 (4)**	0.81	0.15	<0.001	0.31	0.15	0.0422	0.41	0.06	<0.001	50.9%
PROMIS-mental (24)	**Insomnia SCI-8 (8)**	0.85	0.15	<0.001	0.07	0.16	0.6583	0.71	0.07	<0.001	83.3%
WEM WBS (8)	**Insomnia SCI-8 (4)**	2.67	0.40	<0.001	1.21	0.42	0.0038	1.26	0.17	<0.001	47.0%
WEM WBS (24)	**Insomnia SCI-8 (8)**	2.93	0.41	<0.001	0.76	0.45	0.0876	2.17	0.20	<0.001	74.9%
GSII Rank 1 (8)	**Insomnia SCI-8 (4)**	-17.54	1.63	<0.001	-8.69	1.60	<0.001	-7.98	0.93	<0.001	45.5%
GSII Rank 1 (24)	**Insomnia SCI-8 (8)**	-18.63	1.68	<0.001	-7.84	1.68	<0.001	-12.27	0.84	<0.001	65.9%
GSII Rank 2 (8)	**Insomnia SCI-8 (4)**	-17.30	1.60	<0.001	-8.57	1.58	<0.001	-7.50	0.88	<0.001	43.3%
GSII Rank 2 (24)	**Insomnia SCI-8 (8)**	-19.79	1.65	<0.001	-9.41	1.65	<0.001	-11.79	0.91	<0.001	59.6%
GSII Rank 3 (8)	**Insomnia SCI-8 (4)**	-15.43	1.60	<0.001	-7.91	1.60	<0.001	-6.68	0.81	<0.001	43.3%
GSII Rank 3 (24)	**Insomnia SCI-8 (8)**	-18.82	1.64	<0.001	-9.63	1.70	<0.001	-10.71	0.87	<0.001	56.9%
GSII combined score	**Insomnia SCI-8 (4)**	-50.09	4.26	<0.001	-25.25	4.11	<0.001	-22.08	2.53	<0.001	44.1%
GSII combined score	**Insomnia SCI-8 (8)**	-57.19	4.40	<0.001	-26.92	4.27	<0.001	-34.69	2.59	<0.001	60.7%

*Indirect effect/total effect

When considering PROMIS-10 as the outcome, the Sleepio intervention improved sleep at 4 weeks by a mean of 2.83 (95% CI: 2.24, 3.43) and sleep at 8 weeks by a mean of 4.86 (95% CI: 4.24, 5.48). The estimated direct effect of the Sleepio intervention on PROMIS-10 at 8 weeks was an increase of 0.65 (95% CI: 0.12, 1.19). The estimated indirect (mediated) effect of the intervention on the PROMIS-10 at 8 weeks was an increase of 0.89 (95% CI: 0.66, 1.12). The proportion of the effect of the intervention on PROMIS-10 score at 8 weeks that was mediated by changes in sleep was 50.6%.

The estimated direct effect of the Sleepio intervention on PROMIS-10 at 24 weeks was an increase of 0.13 (95% CI: -0.45, 0.71). The estimated indirect (mediated) effect of the intervention on the PROMIS-10 at 24 weeks was an increase of 1.47 (95% CI: 1.20, 1.74). The proportion of the effect of the intervention on PROMIS-10 score at 24 weeks that was mediated by changes in sleep was 84.0%.

When considering WEMWBS as the outcome, the Sleepio intervention improved sleep at 4 weeks by a mean of 2.87 (95% CI: 2.27, 3.47) and sleep at 8 weeks by a mean of 4.89 (95% CI: 4.27, 5.52).The estimated direct treatment effect of the Sleepio intervention on the WEMWBS at 8 weeks was an increase in WEMWBS score of 1.21 (95% CI: 0.39, 2.02). The estimated indirect (mediated) effect of the intervention on the WEMWBS at 8 weeks was an increase of 1.26 (95% CI: 0.92, 1.59). The proportion of the effect of the intervention on WEMWBS score at 8 weeks that was mediated by changes in sleep was 47.0%.

The estimated direct treatment effect of the Sleepio intervention on WEMWBS at 24 weeks was an increase in WEMWBS score of 0.76 (95% CI: -0.11, 1.64). The estimated indirect (mediated) effect of the intervention on the WEMWBS at 24 weeks was an increase of 2.17 (95% CI: 1.77, 2.56). The proportion of the effect of the intervention on WEMWBS score at 24 weeks that was mediated by changes in sleep was 73.8%.

When considering GSII VAS score for rank 1 (the most important impairment) as the outcome, the Sleepio intervention improved sleep at 4 weeks by a mean of 2.88 (95% CI: 2.28, 3.48) and sleep at 8 weeks by a mean of 4.90 (95% CI: 4.28, 5.53).The estimated direct effect of the Sleepio intervention on the GSII VAS score for rank 1 at 8 weeks was an reduction of 8.69 (95% CI: 5.56, 11.82). The estimated indirect (mediated) effect of the intervention on the GSII VAS score for rank 1 at 8 weeks was a reduction of 7.98 (95% CI: 6.16, 9.79). The proportion of the effect of the intervention on GSII VAS score for rank 1 at 8 weeks that was mediated by changes in sleep was 45.5%.

The estimated direct treatment effect of the Sleepio intervention on GSII VAS score for rank 1 at 24 weeks was a reduction of 7.84 (95% CI: 4.55, 11.13). The estimated indirect (mediated) effect of the intervention on the GSII VAS score for rank 1 at 24 weeks was a reduction of 12.27 (95% CI: 10.42, 14.11). The proportion of the effect of the intervention on GSII VAS score for rank 1 at 24 weeks that was mediated by changes in sleep was 65.9%.

When considering GSII VAS score the combined ranks 1-3 as the outcome, the Sleepio intervention improved sleep at 4 weeks by a mean of 2.88 (95% CI: 2.29, 3.48) and sleep at 8 weeks by a mean of 4.90 (95% CI: 4.28, 5.52). The estimated direct effect of the Sleepio intervention on the GSII combined score at 8 weeks was a reduction of 25.25 (95% CI: 17.20, 33.30). The estimated indirect (mediated) effect of the intervention on the GSII combined score at 8 weeks was a reduction of 22.08 (95% CI: 17.11, 27.04). The proportion of the effect of the intervention on GSII combined score at 8 weeks that was mediated by changes in sleep was 44.0%.

The estimated direct treatment effect of the Sleepio intervention on GSII combined score for ranks 1-3 at 24 weeks was a reduction of 26.92 (95% CI: 18.55, 35.29). The estimated indirect (mediated) effect of the intervention on the GSII combined score for rank 1 at 24 weeks was a reduction of 34.69 (95% CI: 29.62, 39.76). The proportion of the effect of the intervention on GSII combined score at 24 weeks that was mediated by changes in sleep was 60.7%.

3.5 SECONDARY ANALYSES

3.5.1 PRIMARY OUTCOMES

3.5.1.1 FUNCTION HEALTH AND WELL-BEING, PROMIS-10

Total score

Table 12 provides the results at 4 weeks, 8 weeks and 24 weeks for the PROMIS-10 total score.

TABLE 12 ADJUSTED AND UNADJUSTED RESULTS FOR PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) TOTAL SCORE AT 4, 8 AND 24 WEEKS

	PROMIS-10 4 Weeks		PROMIS-10 8 Weeks		PROMIS-10 24 Weeks	
	Sleepio N=542	**TAU N=540**	**Sleepio** N=464	**TAU** N=505	**Sleepio N=402**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	33.84 (6.49)	32.52 (6.05)	35.08 (6.65)	32.92 (6.18)	35.24 (6.88)	33.10 (6.10)
Adjusted Difference (C.I.)*	0.90 (0.40; 1.40)		1.76 (1.24, 2.28)		1.76 (1.22, 2.30)	
Cohen's d	0.16 (0.07, 0.24)		0.31 (0.22, 0.40)		0.31 (0.21, 0.40)	
p-value	0.0004		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.1.1.1 COMPLIANCE

Partial compliance to the intervention was assessed by the number of Sleepio sessions completed. The means and standard deviations for the PROMIS-10 score at 4, 8 and 24 weeks are presented by the number of sessions completed (Table 13).

The complier-average causal effect was larger than the ITT, per protocol and as treated treatment effects at weeks 8 and 24 (Table 14). Partial compliance was defined as attending at least one session.

TABLE 13 SUMMARY STATISTICS BY SESSIONS ATTENDED (MEAN (STANDARD DEVIATION) N)

	PROMIS-10 4 Weeks	**PROMIS-10 8 Weeks**	**PROMIS-10 24 Weeks**
TAU (No sessions)	32.53 (6.05), 540	32.92 (6.18), 505	33.10 (6.10), 492
Sleepio Sessions			
0	31.55 (7.22), 29	32.40 (7.88), 25	32.11 (7.42), 28
1	32.43 (8.12), 14	37.20 (7.76), 10	37.83 (9.06), 6
2	34.74 (6.26), 35	35.37 (5.97), 19	31.89 (7.30), 9
3	33.94 (7.75), 34	34.00 (5.18), 13	34.69 (6.90), 16
4	33.11 (6.48), 18	34.14 (7.04), 14	36.29 (3.40), 7
5	33.31 (5.52), 35	33.41 (4.68), 29	34.65 (6.22), 26
6	34.05 (6.35), 377	35.41 (6.70), 354	35.63 (6.83), 310

TABLE 14 BETWEEN-GROUP DIFFERENCE IN MEAN CHANGE IN PROMIS-10 FROM BASELINE

	PROMISI-10 4 Weeks	PROMIS-10 8 Weeks	PROMIS-10 24 Weeks
ITT (C.I.)	0.90 (0.40; 1.40)	1.76 (1.24, 2.28)	1.76 (1.22, 2.30)
Per protocol	1.09 (0.58; 1.60)	1.93 (1.40; 2.46)	1.87 (1.33; 2.42)
As Treated	1.20 (0.70; 1.70)	1.98 (1.46; 2.49)	1.89 (1.35; 2.43)
CACE	1.13 (0.50; 1.75)	2.19 (1.54; 2.83)	2.18 (1.51; 2.85)
Linear regression model adjusted for gender, and student status.			

Physical health score

Table 15 provides the results at 4 weeks, 8 weeks and 24 weeks for the PROMIS-10 physical health score.

TABLE 15 ADJUSTED AND UNADJUSTED RESULTS FOR PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) PHYSICAL HEALTH SCORE AT 4, 8 AND 24 WEEKS

	PROMIS Physical Health 4 Weeks		PROMIS Physical Health 8 Weeks		PROMIS Physical Health 24 Weeks	
	Sleepio N=542	**TAU N=540**	**Sleepio** N=464	**TAU** N=505	**Sleepio N=402**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	15.00 (2.46)	14.47 (2.35)	15.47 (2.43)	14.55 (2.42)	15.43 (2.63)	14.63 (2.37)
Adjusted Difference (C.I.)*	0.32 (0.12, 0.53)		0.68 (0.46, 0.89)		0.59 (0.37, 0.82)	
Cohen's d	0.15 (0.05, 0.24)		0.31 (0.21, 0.40)		0.27 (0.17, 0.37)	
p-value	0.0022		<0.0001		<0.0001	
* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.						

Table 16 provides the results at 4 weeks, 8 weeks and 24 weeks for the PROMIS-10 mental health score.

TABLE 16 ADJUSTED AND UNADJUSTED RESULTS FOR PROMIS-10 (PATIENT REPORTED OUTCOME MEASURE INFORMATION SYSTEM: GLOBAL HEATH SCALE) MENTAL HEALTH SCORE AT 4, 8 AND 24 WEEKS

	PROMIS Mental Health 4 Weeks		PROMIS Mental Health 8 Weeks		PROMIS Mental Health 24 Weeks	
	Sleepio N=542	**TAU N=540**	**Sleepio** N=464	**TAU** N=505	**Sleepio N=402**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	12.36 (3.32)	11.82 (3.07)	12.95 (3.46)	12.12 (3.16)	13.04 (3.44)	12.18 (3.13)
Adjusted Difference (C.I.)*	0.50 (0.23, 0.77)		0.82 (0.54, 1.11)		0.86 (0.56, 1.16)	
Cohen's d	0.17 (0.07, 0.26)		0.27 (0.18, 0.37)		0.29 (0.19, 0.38)	
p-value	0.0003		<0.0001		<0.0001	
* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.						

3.5.1.2 MENTAL WELL-BEING, WEMWBS

Table 17 provides the results at 4 weeks, 8 weeks and 24 weeks for the WEMWBS score.

TABLE 17 ADJUSTED AND UNADJUSTED RESULTS FOR WEMWBS (WARWICK-EDINBURGH MENTAL WELL-BEING SCALE) SCORE AT 4, 8 AND 24 WEEKS

	WEMWBS 4 Weeks		WEMWBS 8 Weeks		WEMWBS 24 Weeks	
	Sleepio N=539	**TAU N=538**	**Sleepio** N=462	**TAU** N=502	**Sleepio N=401**	**TAU N=490**
Unadjusted Mean (Standard Deviation)	46.03 (8.55)	44.72 (8.21)	48.12 (8.82)	45.16 (8.77)	48.62 (9.02)	45.31 (8.88)
Adjusted Difference (C.I.)*	1.04 (0.28, 1.80)		2.68 (1.89, 3.47)		2.95 (2.13, 3.76)	
Cohen's d	0.13 (0.04, 0.23)		0.35 (0.24, 0.45)		0.38 (0.27, 0.48)	
p-value	0.0072		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.1.2.1 COMPLIANCE

Partial compliance to the intervention was assessed by the number of Sleepio sessions completed. The means and standard deviations for the WEMWBS score at each assessment are presented by the number of sessions completed (Table 18).

The complier-average causal effect was larger than the ITT, per protocol and as treated treatment effects at weeks 8 and 24 (Table 14). Partial compliance was defined as attending at least one session.

TABLE 18 SUMMARY STATISTICS BY SESSIONS ATTENDED (MEAN (STANDARD DEVIATION) N)

	WEMWBS 4 Weeks	**WEMWBS 8 Weeks**	**WEMWBS 24 Weeks**
TAU (No sessions)	44.72 (8.21), 538	45.16 (8.77), 502	45.31 (8.88), 490
Sleepio Sessions			
0	43.52 (10.88), 27	47.04 (9.66), 25	45.96 (9.02), 28
1	43.36 (9.96), 14	47.00 (8.80), 9	47.17 (9.22), 6
2	47.29 (9.63), 35	48.42 (10.96), 19	42.67 (13.75), 9
3	45.24 (9.19), 34	46.00 (7.67), 13	45.38 (10.11), 16
4	42.56 (5.55), 18	45.50 (9.65), 14	46.71 (7.43), 7
5	46.86 (6.75), 35	46.34 (7.36), 29	48.35 (8.34), 26
6	46.36 (8.37), 376	48.54 (8.76), 353	49.29 (8.82), 309

TABLE 19 BETWEEN-GROUP DIFFERENCE IN MEAN CHANGE IN WEMWBS FROM BASELINE

	WEMWBS 4 Weeks	**WEMWBS 8 Weeks**	**WEMWBS 24 Weeks**
ITT (C.I.)	1.04 (0.28, 1.80)	2.68 (1.89, 3.47)	2.95 (2.13, 3.76)
Per protocol	1.24 (0.47; 2.02)	2.87 (2.06; 3.68)	3.12 (2.29; 3.96)
As Treated	1.32 (0.56; 2.07)	2.86 (2.07; 3.65)	3.08 (2.26; 3.90)
CACE	1.30 (0.35; 2.25)	3.33 (2.35; 4.30)	3.65 (2.64; 4.66)

Linear regression model adjusted for gender, and student status.

3.5.1.3 GLASGOW SLEEP INDEX, GSII

Table 20 provides the results at 4 weeks, 8 weeks and 24 weeks for the GSII VAS score for rank 1.

TABLE 20 ADJUSTED AND UNADJUSTED RESULTS FOR GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 1 AT 4, 8 AND 24 WEEKS

	GSII Item A 4 Weeks		GSII Item A 8 Weeks		GSII Item A 24 Weeks	
	Sleepio N=546	**TAU N=546**	**Sleepio** N=467	**TAU** N=509	**Sleepio N=409**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	60.69 (26.20)	69.80 (23.64)	46.87 (29.90)	65.68 (25.86)	43.78 (31.25)	63.33 (27.26)
Adjusted Difference (C.I.)*	-8.76 (-11.83, -5.69)		-17.60 (-20.81, -14.39)		-18.72 (-22.04, -15.41)	
Cohen's d	-0.69 (-0.93, -0.44)		-1.38 (-1.63, -1.13)		-1.46 (-1.72, -1.21)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.1.3.1 COMPLIANCE

Partial compliance to the intervention was assessed by the number of Sleepio sessions completed. The means and standard deviations for the GSII rank 1 VAS score at each assessment are presented by the number of sessions completed (Table 21). Partial compliance was defined as attending at least one session.

TABLE 21 SUMMARY STATISTICS BY SESSIONS ATTENDED (MEAN (STANDARD DEVIATION) N)

	GSII Rank 1 4 Weeks	GSII Rank 1 8 Weeks	GSII Rank 1 24 Weeks
TAU (No sessions)	69.80 (23.64), 546	65.68 (25.86), 509	63.33 (27.26), 492
Sleepio Sessions			
0	72.86 (19.30), 29	58.60 (29.27), 25	62.17 (27.74), 28
1	74.67 (20.60), 15	64.30 (31.87), 10	56.56 (41.03), 9
2	68.31 (25.09), 35	48.30 (27.00), 20	50.44 (33.03), 9
3	64.72 (29.14), 36	61.57 (26.34), 14	58.56 (31.95), 16
4	73.50 (22.53), 18	55.40 (26.41), 15	62.14 (17.67), 7
5	55.31 (21.54), 36	67.28 (21.09), 29	43.41 (28.88), 27
6	58.00 (26.40), 377	42.85 (29.79), 354	40.44 (30.79), 313

TABLE 22 BETWEEN-GROUP DIFFERENCE IN MEAN CHANGE IN PROMIS-10 FROM BASELINE

	GSII Rank 1 4 Weeks	GSII Rank 1 8 Weeks	GSII Rank 1 24 Weeks
ITT (C.I.)	-8.76 (-11.83, -5.69)	-17.60 (-20.81, -14.39)	-18.72 (-22.04, -15.41)
Per protocol	-9.86 (-12.99, -6.73)	-18.68 (-21.94, -15.41)	-20.04 (-23.42, -16.66)
As Treated	-10.04 (-13.10, -6.99)	-18.46 (-21.67, -15.26)	-19.86 (-23.17, -16.55)
CACE	-10.97 (-14.82, -7.13)	-21.85 (-25.84, -17.87)	-23.18 (-27.29, -19.08)

Linear regression model adjusted for gender, and student status.

Table 23 provides the results at 4 weeks, 8 weeks and 24 weeks for the GSII VAS score for rank 2.

Table 24 provides the results at 4 weeks, 8 weeks and 24 weeks for the GSII VAS score for rank 3.

Table 25 provides the results at 4 weeks, 8 weeks and 24 weeks for the combined GSII VAS score for ranks 1-3.

TABLE 23 ADJUSTED AND UNADJUSTED RESULTS FOR GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 2 AT 4, 8 AND 24 WEEKS

	GSII Item B 4 Weeks		GSII Item B 8 Weeks		GSII Item B 24 Weeks	
	Sleepio N=546	**TAU N=546**	**Sleepio** N=467	**TAU** N=509	**Sleepio N=409**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	56.66 (26.67)	65.16 (24.05)	43.48 (29.67)	62.19 (26.14)	41.02 (30.48)	61.60 (26.29)
Adjusted Difference (C.I.)*	-8.48 (-11.51, -5.46)		-17.37 (-20.53, -14.20)		-19.92 (-23.19, -16.66)	
Cohen's d	-0.50 (-0.68, -0.32)		-1.03 (-1.22, -0.84)		-1.18 (-1.37, -0.99)	
p-value	0.0067		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

TABLE 24 ADJUSTED AND UNADJUSTED RESULTS FOR GSII (GLASGOW SLEEP IMPACT INDEX) VAS SCORE FOR RANK 3 AT 4, 8 AND 24 WEEKS

	GSII Item C 4 Weeks		GSII Item C 8 Weeks		GSII Item C 24 Weeks	
	Sleepio N=546	**TAU N=546**	**Sleepio N=467**	**TAU N=509**	**Sleepio N=409**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	52.31 (26.88)	62.59 (24.99)	41.35 (28.04)	58.57 (27.35)	38.00 (29.39)	58.12 (27.80)
Adjusted Difference (C.I.)*	-10.00 (-13.02, -6.98)		-15.45 (-18.60, -12.29)		-18.89 (-22.16, -15.64)	
Cohen's d	-0.47 (-0.61, -0.33)		-0.73 (-0.87, -0.58)		-0.89 (-1.04, -0.73)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

TABLE 25 ADJUSTED AND UNADJUSTED RESULTS FOR GSII (GLASGOW SLEEP IMPACT INDEX) COMBINED VAS SCORE AT 4, 8 AND 24 WEEKS

	GSII Total 4 Weeks		GSII Total 8 Weeks		GSII Total 24 Weeks	
	Sleepio N=546	**TAU N=546**	**Sleepio N=467**	**TAU N=509**	**Sleepio N=408**	**TAU N=491**
Unadjusted Mean (Standard Deviation)	169.66 (70.24)	197.65 (63.63)	131.69 (79.89)	186.45 (70.88)	122.81 (83.46)	183.04 (73.04)
Adjusted Difference (C.I.)*	-27.31 (-35.38, -19.24)		-50.20 (-58.62, -41.78)		-57.47 (-66.15, -48.79)	
Cohen's d	-0.60 (-0.78, -0.43)		-1.11 (-1.30, -0.92)		-1.27 (-1.46, -1.08)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2 SECONDARY OUTCOMES

3.5.2.1 INSOMNIA, SCI-8

The Sleep Conditional Indicator (SCI) evaluates the severity of insomnia. The SCI-8 total score is calculated by adding together the scores for the eight items. Each item ranges between 0 and 4, and the total score can range between 0 and 32. Higher scores indicate better sleep (Espie et al. 2014). Table 26 provides the results at 4 weeks, 8 weeks and 24 weeks for the SCI-8 total score.

TABLE 26 ADJUSTED AND UNADJUSTED RESULTS FOR SCI-8 (SLEEP CONDITION INDICATOR) TOTAL SCORE AT 4, 8 AND 24 WEEKS

	SCI-8 4 Weeks		SCI-8 8 Weeks		SCI-8 24 Weeks	
	Sleepio N=550	TAU N=551	Sleepio N=468	TAU N=516	Sleepio N=411	TAU N=495
Unadjusted Mean (Standard Deviation)	13.00 (5.01)	9.96 (4.70)	16.29 (6.17)	11.05 (5.32)	16.89 (6.91)	11.66 (5.84)
Adjusted Difference (C.I.)*	2.88 (2.28; 3.48)		4.90 (4.28; 5.53)		4.91 (4.27, 5.56)	
Cohen's d	0.89 (0.70, 1.07)		1.51 (1.32, 1.70)		1.51 (1.31, 1.71)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

These results suggest that the Sleepio intervention significant improves insomnia symptoms at 4, 8 and 24 weeks ; the estimated adjusted treatment effects were 2.85 (2.24, 3.45), 4.86 (4.23, 5.48) and 4.91 (4.26, 5.55) respectively at 4, 8 and 24 weeks. The improvement in SCI-8 was similar at 8 and 24 weeks, and these were higher than the improvements at 4 weeks.

3.5.2.2 DEPRESSION, PHQ-9

The Patient Health Questionnaire (PHQ-9) questionnaire includes 9 questions, scored from 0 to 3. Scores are summed to obtain an overall score which can range from 0 to 27, with higher values indicating increasing levels of depression. Table 27 provides the summary statistics and results from the linear mixed effects model.

TABLE 27 ADJUSTED AND UNADJUSTED RESULTS FOR PHQ-9 (PATIENT HEALTH QUESTIONNAIRE) SCORE AT 4, 8 AND 24 WEEKS

	PHQ-9 4 Weeks		PHQ-9 8 Weeks		PHQ-9 24 Weeks	
	Sleepio N=537	TAU N=538	Sleepio N=461	TAU N=500	Sleepio N=400	TAU N=488
Unadjusted Mean (Standard Deviation)	7.47 (4.26)	8.36 (4.38)	6.22 (4.40)	8.16 (4.90)	6.13 (4.59)	7.94 (4.58)
Adjusted Difference (C.I.)*	-0.72 (-1.15, -0.29)		-1.59 (-2.04, -1.14)		-1.58 (-2.05, -1.12)	
Cohen's d	-0.17 (-0.28, -0.07)		-0.38 (-0.49, -0.28)		-0.38 (-0.50, -0.27)	
p-value	0.0011		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.3 ANXIETY, GAD-7

The Generalised Anxiety Disorder (GAD-7) questionnaire is made up of 7 questions, scored from 0 to 3. Scores are summed to obtain overall score which can range from 0 to 21, with higher values indicating increasing levels of anxiety. Table 28 provides the summary statistics and results from the linear mixed effects model.

TABLE 28 ADJUSTED AND UNADJUSTED RESULTS FOR GAD-7 (GENERALISED ANXIETY DISORDER) SCORE AT 4, 8 AND 24 WEEKS

	GAD-7 4 Weeks		GAD-7 8 Weeks		GAD-7 24 Weeks	
	Sleepio N=536	**TAU N=536**	**Sleepio N=459**	**TAU N=499**	**Sleepio N=399**	**TAU N=487**
Unadjusted Mean (Standard Deviation)	5.51 (4.18)	6.23 (4.52)	4.68 (4.21)	6.10 (4.69)	4.70 (4.21)	6.05 (4.50)
Adjusted Difference (C.I.)*	-0.49 (-0.91, -0.06)		-1.19 (-1.63, -0.74)		-1.10 (-1.56, -0.64)	
Cohen's d	-0.10 (-0.19, -0.01)		-0.25 (-0.35, -0.16)		-0.24 (-0.33, -0.14)	
p-value	0.0256		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.4 FATIGUE, FFS

The Flinders Fatigue Scale (FFS) is a 7-item questionnaire where 6 items are scored between 0 and 4, and one item is scored between 0 and 7. The overall score is calculated by summing each item and ranges between 0 and 31. A higher score indicates a higher level of fatigue. The summary statistics and results from the linear mixed effects model for change in FFS score at 4, 8 and 24 weeks appears in Table 29.

TABLE 29 ADJUSTED AND UNADJUSTED RESULTS FOR FFS (FLINDERS FATIGUE SCALE) SCORE AT 4, 8 AND 24 WEEKS

	FSS 4 Weeks		FSS 8 Weeks		FSS 24 Weeks	
	Sleepio N=542	**TAU N=542**	**Sleepio N=465**	**TAU N=503**	**Sleepio N=401**	**TAU N=492**
Unadjusted Mean (Standard Deviation)	14.82 (5.96)	16.93 (5.87)	11.84 (6.54)	15.91 (6.08)	11.41 (6.64)	15.67 (6.46)
Adjusted Difference (C.I.)*	-2.01 (-2.63, -1.39)		-3.83 (-4.48, -3.19)		-4.06 (-4.72, -3.39)	
Cohen's d	-0.37 (-0.48, -0.25)		-0.71 (-0.83, -0.59)		-0.75 (-0.87, -0.62)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.5 RELATIONSHIP, RAS

The Relationship Assessment Scale (RAS) is a 7-item questionnaire where each item is scored between 1 and 5. The overall score is calculated by summing each item and ranges between 0 and 35. A higher score indicates a higher satisfaction with the respondent's relationship. Table 30 provides the summary statistics and results from the linear mixed effects model.

TABLE 30 ADJUSTED AND UNADJUSTED RESULTS FOR RAS (RELATIONSHIP ASSESSMENT SCALE) SCORE AT 4, 8 AND 24 WEEKS.

	RAS 4 Weeks		RAS 8 Weeks		RAS 24 Weeks	
	Sleepio N=499	**TAU N=477**	**Sleepio N=426**	**TAU N=461**	**Sleepio N=376**	**TAU N=445**
Unadjusted Mean (Standard Deviation)	24.98 (7.78)	24.45 (7.44)	25.23 (7.64)	24.36 (7.50)	25.45 (7.83)	24.72 (7.42)
Adjusted Difference (C.I.)*	0.12 (-0.38; 0.62)		0.07 (-0.44; 0.59)		0.01 (-0.53, 0.54)	
Cohen's d	0.02 (-0.07, 0.11)		0.01 (-0.08, 0.10)		0.00 (-0.09, 0.09)	
p-value	0.6438		0.7861		0.9836	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.6 SLEEPINESS, ESS

Epworth Sleepiness Scale (ESS) is an 8-item scale where each item is scored between 0 and 3. Scores are summed to obtain overall score which can range from 0 to 24, with higher values indicating increasing levels of sleepiness. Table 31 provides the summary statistics of the ESS score at 4, 8 and 24 weeks.

TABLE 31 ADJUSTED AND UNADJUSTED RESULTS FOR ESS (EPWORTH SLEEPINESS SCALE) SCORE AT 4, 8 AND 24 WEEKS

	ESS 4 Weeks		ESS 8 Weeks		ESS 24 Weeks	
	Sleepio N=544	TAU N=544	Sleepio N=465	TAU N=507	Sleepio N=406	TAU N=489
Unadjusted Mean (Standard Deviation)	5.55 (4.34)	6.41 (4.64)	4.81 (3.94)	6.14 (4.62)	4.67 (3.97)	6.24 (4.61)
Adjusted Difference (C.I.)*	-0.52 (-0.88, -0.17)		-1.01 (-1.38, -0.64)		-1.41 (-1.79, -1.03)	
Cohen's d	-0.12 (-0.20, -0.04)		-0.23 (-0.31, -0.14)		-0.32 (-0.40, -0.23)	
p-value	0.0040		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.7 COGNITIVE IMPAIRMENT, CFQ

The Cognitive Failures Questionnaire (CFQ) is a 25-item scale where each item is scored between 0 and 4. The overall score is calculated by summing each item and ranges between 0 and 100. A higher score indicates a higher level of cognitive impairment. Table 32 provides the summary statistics and results from the linear mixed effects model.

TABLE 32 ADJUSTED AND UNADJUSTED RESULTS FOR CFQ (COGNITIVE FAILURES QUESTIONNAIRE) SCORE AT 4, 8 AND 24 WEEKS

	CFQ 4 Weeks		CFQ 8 Weeks		CFQ 24 Weeks	
	Sleepio N=529	TAU N=526	Sleepio N=458	TAU N=493	Sleepio N=392	TAU N=485
Unadjusted Mean (Standard Deviation)	39.53 (15.54)	41.79 (16.79)	36.93 (16.44)	41.19 (16.97)	37.47 (15.47)	41.25 (16.49)
Adjusted Difference (C.I.)*	-2.08 (-3.23, -0.92)		-4.18 (-5.38, -2.99)		-3.38 (-4.60, -2.16)	
Cohen's d	-0.13 (-0.20, -0.06)		-0.26 (-0.31, -0.14)		-0.21 (-0.29, -0.13)	
p-value	0.0004		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.8 WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT, WPAI:SHP

The Work Productivity and Activity Impairment questionnaire: Specific Health Problem (WPAI: SHP) is a 6-item questionnaire from which participants are given a score between 0 and 100 relating to 1) absenteeism at work due to sleep problems, 2) absenteeism at work due to other reasons, 3) impairment in productivity at work, and 4) impairment in productivity in non-work activities. A higher score for each indicates a higher level of productivity impairment.

Tables 33-36 provide the summary statistics and results from the linear mixed effects model for each of the four outcomes from the WPAI: SHP.

TABLE 33 ADJUSTED AND UNADJUSTED RESULTS FOR WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM (WPAI: SHP) SCORE FOR ABSENTEEISM AT WORK DUE TO SLEEP PROBLEMS AT 4, 8 AND 24 WEEKS

	WPAI:SHP 1 4 Weeks		WPAI:SHP 1 8 Weeks		WPAI:SHP 1 24 Weeks	
	Sleepio N=292	TAU N=308	Sleepio N=258	TAU N=289	Sleepio N=233	TAU N=295
Unadjusted Mean (Standard Deviation)	3.22 (9.87)	2.56 (8.59)	2.34 (8.26)	3.54 (11.59)	3.41 (12.16)	4.61 (14.01)
Adjusted Difference (C.I.)*	0.39 (-1.31, 2.10)		-1.23 (-3.02, 0.56)		-2.09 (-3.95, -0.23)	
Cohen's d	0.02 (-0.08, 0.13)		-0.07 (-0.18, 0.03)		-0.13 (-0.24, -0.01)	
p-value	0.6514		0.1767		0.0276	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

TABLE 34 ADJUSTED AND UNADJUSTED RESULTS FOR WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM (WPAI: SHP) SCORE FOR ABSENTEEISM AT WORK DUE TO OTHER REASONS AT 4, 8 AND 24 WEEKS

	WPAI:SHP 2 4 Weeks		WPAI:SHP 2 8 Weeks		WPAI:SHP 2 24 Weeks	
	Sleepio N=286	TAU N=298	Sleepio N=242	TAU N=284	Sleepio N=222	TAU N=286
Unadjusted Mean (Standard Deviation)	7.22 (18.87)	4.96 (14.08)	5.43 (15.55)	6.66 (18.34)	3.57 (8.26)	4.68 (14.22)
Adjusted Difference (C.I.)*	2.42 (-0.22, 5.04)		-1.51 (-4.30, 1.27)		-1.08 (-3.96, 1.80)	
Cohen's d	0.18 (-0.02, 0.37)		-0.11 (-0.31, 0.09)		-0.08 (-0.29, 0.13)	
p-value	0.0719		0.2890		0.4607	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

TABLE 35 ADJUSTED AND UNADJUSTED RESULTS FOR WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM (WPAI: SHP) SCORE FOR IMPAIRMENT IN PRODUCTIVITY AT WORK AT 4, 8 AND 24 WEEKS

	WPAI:SHP 3 4 Weeks		WPAI:SHP 3 8 Weeks		WPAI:SHP 3 24 Weeks	
	Sleepio N=317	TAU N=335	Sleepio N=278	TAU N=312	Sleepio N=244	TAU N=315
Unadjusted Mean (Standard Deviation)	31.26 (23.52)	33.61 (23.82)	23.56 (21.21)	32.71 (23.32)	20.56 (20.69)	32.08 (23.37)
Adjusted Difference (C.I.)*	-2.27 (-5.47, 0.92)		-9.55 (-12.89, -6.21)		-9.94 (-13.42, -6.46)	
Cohen's d	-0.10 (-0.23, 0.04)		-0.41 (-0.55, -0.26)		-0.42 (-0.57, -0.27)	
p-value	0.1632		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

TABLE 36 ADJUSTED AND UNADJUSTED RESULTS FOR WORK PRODUCTIVITY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE: SPECIFIC HEALTH PROBLEM (WPAI: SHP) SCORE FOR IMPAIRMENT IN PRODUCTIVITY IN NON-WORK ACTIVITIES AT 4, 8 AND 24 WEEKS

	WPAI:SHP 4 4 Weeks		WPAI:SHP 4 8 Weeks		WPAI:SHP 4 24 Weeks	
	Sleepio N=526	TAU N=522	Sleepio N=448	TAU N=484	Sleepio N=384	TAU N=481
Unadjusted Mean (Standard Deviation)	33.55 (24.58)	38.99 (24.35)	24.54 (22.33)	35.79 (24.21)	23.91 (23.09)	35.59 (24.32)
Adjusted Difference (C.I.)*	-4.45 (-7.03, -1.86)		-10.63 (-13.35, -7.91)		-10.56 (-13.38, -7.74)	
Cohen's d	-0.18 (-0.28, -0.08)		-0.43 (-0.54, -0.32)		-0.43 (-0.54, -0.31)	
p-value	0.0008		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.9 JOB SATISFACTION

Participants were asked one item on job satisfaction, giving a score between 1 and 7 where a higher score indicates a higher level of overall job satisfaction. Table 37 provides the summary statistics and results from the linear mixed effects model.

TABLE 37 ADJUSTED AND UNADJUSTED RESULTS FOR JOB SATISFACTION SCORE AT 4, 8 AND 24 WEEKS

	Job Satisfaction 4 Weeks		Job Satisfaction 8 Weeks		Job Satisfaction 24 Weeks	
	Sleepio N=497	TAU N=494	Sleepio N=422	TAU N=458	Sleepio N=363	TAU N=451
Unadjusted Mean (Standard Deviation)	3.30 (2.10)	3.48 (2.14)	3.43 (2.14)	3.45 (2.07)	3.58 (2.16)	3.49 (2.05)
Adjusted Difference (C.I.)*	-0.05 (-0.22; 0.12)		0.08 (-0.09; 0.26)		0.27 (0.09; 0.45)	
Cohen's d	-0.02 (-0.11, 0.06)		0.04 (-0.05, 0.13)		0.13 (0.04, 0.22)	
p-value	0.5797		0.3627		0.0038	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.10 LIFE SATISFACTION

Participants were asked one item on life satisfaction, giving a score between 1 and 4 where a higher score indicates a higher level of overall life satisfaction. Table 38 provides the summary statistics and results from the linear mixed effects model.

TABLE 38 ADJUSTED AND UNADJUSTED RESULTS FOR LIFE SATISFACTION SCORE AT 4, 8 AND 24 WEEKS

	Life Satisfaction 4 Weeks		Life Satisfaction 8 Weeks		Life Satisfaction 24 Weeks	
	Sleepio N=534	TAU N=354	Sleepio N=459	TAU N=495	Sleepio N=399	TAU N=486
Unadjusted Mean (Standard Deviation)	2.90 (0.72)	2.84 (0.72)	2.96 (0.73)	2.86 (0.70)	3.01 (0.74)	2.86 (0.70)
Adjusted Difference (C.I.)*	0.07 (-0.02; 0.13)		0.12 (0.05; 0.19)		0.16 (0.09; 0.24)	
Cohen's d	0.10 (-0.00, 0.19)		0.18 (0.07, 0.28)		0.24 (0.13, 0.34)	
p-value	0.0578		0.0007		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.5.2.11 DICHOTOMISED OUTCOMES

Outcomes SCI-8 PHQ-9 and GAD-7 were dichotomised and a mixed effects logistic regression model was fit for each to determine the effect of the Sleepio intervention on the existence of insomnia disorder (SCI-8≤16), depressive disorder (PHQ-9 ≥10) and anxiety disorder (GAD-7 ≥10) (Table 39).

The odds ratios indicate that participants in the treatment arm were significantly less likely to report insomnia disorder and anxiety disorder at 4, 8 and 24 weeks. Although the odds ratios were all less than 1 when comparing depressive disorder between the two groups at 4, 8 and 24 weeks, this was only statistically significant at 24 weeks.

TABLE 39 ODDS RATIO AND ADJUSTED ODDS RATIO FOR SLEEPIO VERSUS TAU OF EXCEEDING CLINICAL THRESHOLD AT 4 WEEKS, 8 WEEKS AND 24 WEEKS

	SCI-8 4 Weeks		**SCI-8 8 Weeks**		**SCI-8 24 Weeks**	
	TAU N=551	Sleepio N=550	TAU N=516	Sleepio N=468	TAU N=495	Sleepio N=411
Unadjusted odds ratio	0.41 (0.29; 0.58)		0.05 (0.03; 0.09)		0.07 (0.04; 0.12)	
Adjusted odds ratio (C.I)*	0.25 (0.15; 0.44)		0.08 (0.06; 0.12)		0.13 (0.09; 0.19)	
p-value	<0.0001		<0.0001		<0.0001	
	PHQ-9 4 Weeks		**PHQ-9 8 Weeks**		**PHQ-9 24 Weeks**	
	TAU N=538	Sleepio N=537	TAU N=500	Sleepio N=461	TAU N=488	Sleepio N=400
Unadjusted odds ratio	0.69 (0.53; 0.90)		0.49 (0.36; 0.67)		0.50 (0.36; 0.69)	
Adjusted odds ratio (C.I)*	0.81 (0.35; 1.87)		0.39 (0.14; 1.08)		0.36 (0.14; 0.94)	
p-value	0.6230		0.0692		0.0359	
	GAD-7 4 Weeks		**GAD-7 8 Weeks**		**GAD-7 24 Weeks**	
	TAU N=536	Sleepio N=536	TAU N=499	Sleepio N=459	TAU N=487	Sleepio N=399
Unadjusted odds ratio	0.71 (0.51; 0.98)		0.49 (0.36; 0.67)		0.50 (0.36; 0.69)	
Adjusted odds ratio (C.I)*	0.54 (0.31; 0.94)		0.33 (0.18; 0.60)		0.45 (0.24; 0.83)	
p-value	0.0301		<0.0001		0.0110	

* Logistic mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level. NB Baseline scores not included for SCI-8 and PHQ-9 analyses due to

3.6 ADVSERE OUTCOMES

Participants were asked if they had experienced 14 specific adverse events at 8 weeks follow-up. The frequency of each was compared between the Sleepio group and the control group via a chi-squared test (Table 40). The total number of symptoms (ranging from 0 – 14) and the average interference of symptoms were compared across the two groups via a Mann-Whitney test.

TABLE 40 FREQUENCY OF ADVERSE EVENTS BY TREATMENT GROUP

	Sleepio (N=458)	TAU (N=493)	*p*-value
	N (%)		*Chi-square test*
Low mood	99 (21.6)	102 (20.7)	0.7276
Fatigue and/or exhaustion	212 (46.3)	133 (27.0)	<0.0001
Extreme sleepiness	141 (30.8)	70 (14.2)	<0.0001
Feeling agitated	83 (18.1)	83 (16.8)	0.6015
Difficulty remembering things	88 (19.2)	72 (14.6)	0.0576
Bodily pain	54 (11.8)	58 (11.8)	0.9902
Headache and/or migraine	86 (18.8)	62 (12.6)	0.0084
Euphoria and/or intense increase in mood	17 (3.71)	12 (2.43)	0.2522
Difficulty concentrating and focussing on things	152 (33.2)	94 (19.1)	<0.0001
Reduced motivation and/or energy	150 (32.8)	119 (24.1)	0.0032
Changes in hunger and/or appetite	48 (10.5)	39 (7.93)	0.1727
Blurred vision	21 (4.59)	21 (4.26)	0.8071
Dizziness	30 (6.55)	19 (3.85)	0.0602
Feeling irritable	129 (28.2)	88 (17.9)	0.0002
	Mean (sd); median		*Mann-Whitney test*
Total number of symptoms (0-14)	2.86 (3.06); 2	1.97 (3.09); 0	<0.0001
Average interference	10.7 (13.3); 5.71	7.64 (13.6); 0	<0.0001

Participants in the Sleepio treatment group and the control group experienced a similar frequency of low mood, feeling agitated, bodily pain, euphoria and/or intense increase in mood, changes in hunger and/or appetite and blurred vision. Participants in the Sleepio group had a higher occurrence of difficulty remembering things (p=0.043), headache and/or migraine (p=0.013), dizziness (p=0.058), fatigue and/or exhaustion (p<0.0001), extreme sleepiness (p<0.0001), difficulty concentrating and focussing on things (p<0.0001), reduced motivation and/or energy (p=0.0004), and feeling irritable (p=0.0002). Patients in the Sleepio group also had a higher number of total symptoms and a higher average interference.

3.7 SENSITIVITY ANALYSES

3.7.1 MISSING DATA MECHANISM

3.7.1.1 PROMIS-10

The missing data mechanism was explored by means of a pattern mixture model. The results are displayed in Figure 9. If participants with a missing PROMIS-10 outcome at 8 weeks had an average PROMIS-10 total score of 4 less than those who were not missing, the treatment effect would still have been statistically significant between the two groups. If the same patients from the Sleepio group had an average PROMIS-10 total score of 5 less than those who were not missing, the treatment effect would not be statistically significant.

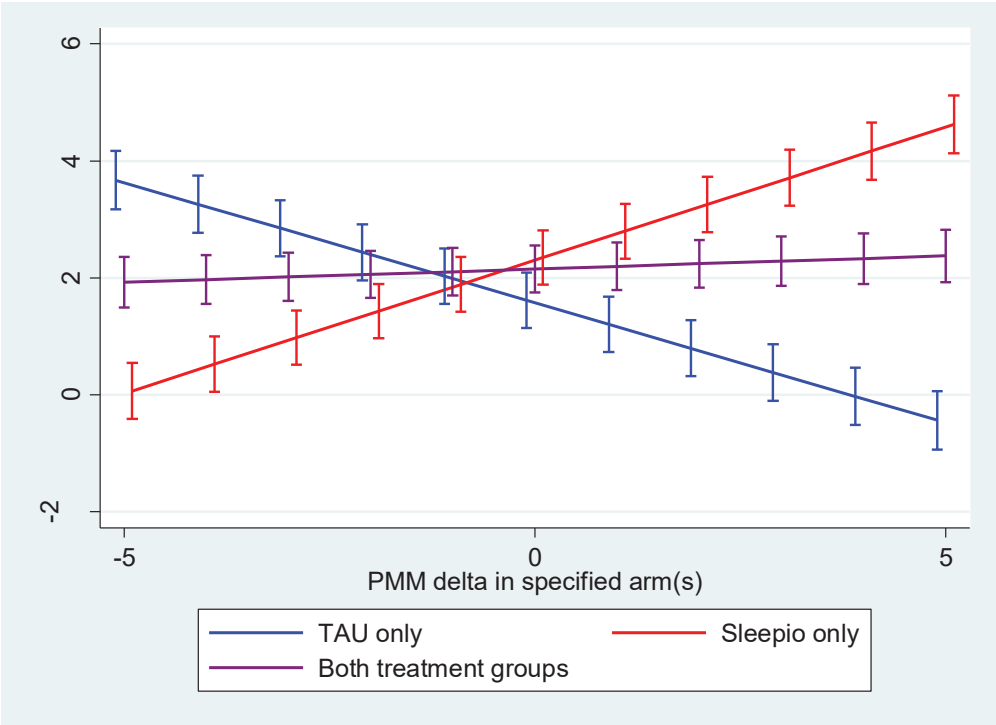

FIGURE 9 PATTERN MIXTURE MODEL RESULTS FOR THE PROMIS-10 OUTCOME AT 8 WEEKS

A sensitivity analysis was performed including baseline covariates which were found to be predictive of missingness at 8 weeks. The results are shown in Table 41. The treatment effect at 4 weeks was slightly closer than that in the main analysis. The treatment effect at 8 weeks was slightly larger than that in the main analysis (Table 12).

TABLE 41 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN PROMIS-10 SCORE BETWEEN THE TWO TREATMENT GROUPS WHEN AGE, SEX, PARTNER STATUS, HEIGHT, EMPLOYMENT STATUS, SMOKING STATUS, EXERCISE STATUS, HISTORY OF HEART DISEASE, CANCER AND OTHER COMORBIDITIES ARE INCLUDED AS COVARIATES

	PROMIS-10 4 Weeks		PROMIS-10 8 Weeks		PROMIS-10 24 Weeks	
	Sleepio N=542	TAU N=540	Sleepio N=464	TAU N=505	Sleepio N=402	TAU N=492
Unadjusted Mean (Standard Deviation)	33.84 (6.49)	32.52 (6.05)	35.08 (6.65)	32.92 (6.18)	35.24 (6.88)	33.10 (6.10)
Adjusted Difference (C.I.)*	0.88 (0.38, 1.39)		1.73 (1.21, 2.26)		1.75 (1.21, 2.29)	
p-value	0.0006		<0.0001		<0.0001	

* Linear mixed effects model adjusted for age, sex, Partner status, height, employment status, smoking status, exercise status, history of heart disease, cancer and other comorbidities, week and interaction of week with randomisation, and including a random effect at the individual-level.

A further sensitivity analysis was performed whereby missingness was assumed to be related to the outcome. The last observation carried forward method of imputation was used, where the last available measurement for a participant was imputed for all further missing measurements of that participant. The results are shown in Table 42. The treatment effects are still statistically significant at all time points, but the effect sizes are smaller.

TABLE 42 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN PROMIS-10 SCORE BETWEEN THE TWO GROUPS WHEN THE MISSING DATA ARE IMPUTED USING LAST OBSERVATION CARRIED FORWARD

	PROMIS-10 4 Weeks		PROMIS-10 8 Weeks		PROMIS-10 24 Weeks	
	Sleepio N=853	TAU N=858	Sleepio N=853	TAU N=858	Sleepio N=853	TAU N=858
Unadjusted Mean (Standard Deviation)	32.68 (6.39)	32.17 (5.95)	33.39 (6.66)	32.40 (6.13)	33.50 (6.68)	32.41 (6.14)
Adjusted Difference (C.I.)*	0.49 (0.15, 0.84)		0.97 (0.63, 1.32)		1.07 (0.73, 1.42)	
p-value	0.0054		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.7.1.2 WEMWBS

The missing data mechanism was explored by means of a pattern mixture model. The results are displayed in Figure 10. If participants with a missing WEMWBS outcome at 8 weeks in the Sleepio group had an average WEMWBS score of 5 less than those who were not missing, the treatment effect would still have been statistically significant between the two groups. If participants with a missing WEMWBS at 8 weeks in the control group had an average WEMWBS total score of 3 or less greater than those who were not missing, the estimated treatment effect would still be statistically significant. However, if participants with a missing WEMWBS score in the control group had an average WEMWBS score of 4 or more greater than those who were not missing, the estimated treatment effect would not be statistically significant.

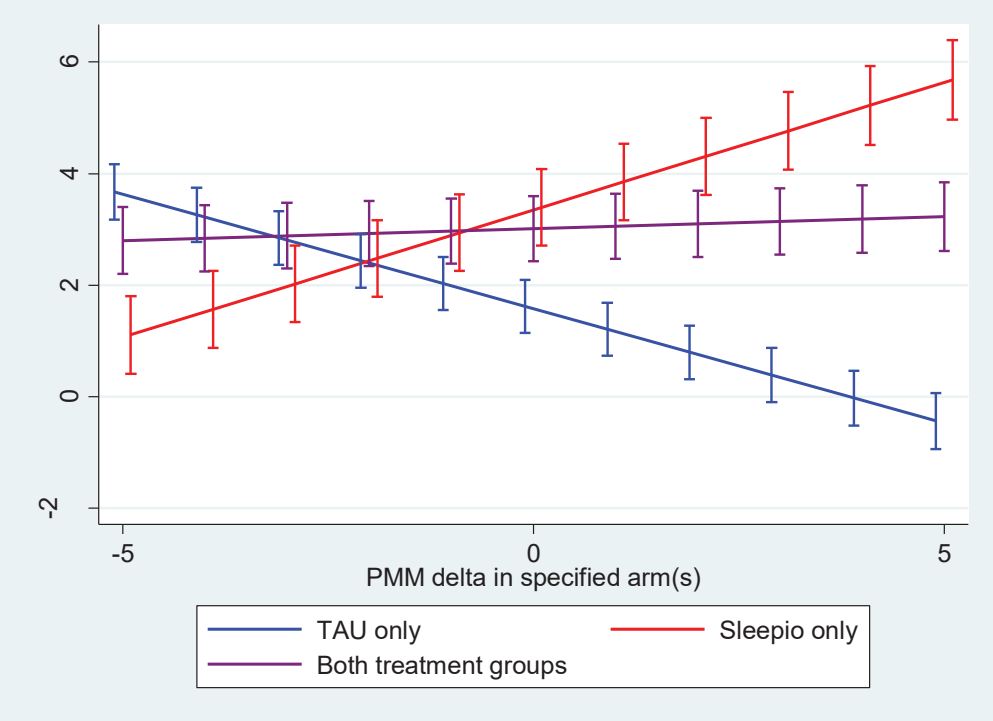

FIGURE 10 PATTERN MIXTURE MODEL RESULTS FOR THE WEMWBS OUTCOME AT 8 WEEKS

A sensitivity analysis was performed including baseline covariates which were found to be predictive of missingness at 8 weeks. The results are shown in Table 43. The estimated treatment effects are very close to those from the main analysis (Table 17).

TABLE 43 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN WEMWBS SCORE BETWEEN THE TWO TREATMENT GROUPS WHEN AGE, SEX, PARTNER STATUS, HEIGHT, EMPLOYMENT STATUS, SMOKING STATUS, EXERCISE STATUS, HISTORY OF HEART DISEASE, CANCER AND OTHER COMORBIDITIES ARE INCLUDED AS COVARIATES

	WEMWBS 4 Weeks		WEMWBS 8 Weeks		WEMWBS 24 Weeks	
	Sleepio N=539	TAU N=538	Sleepio N=462	TAU N=502	Sleepio N=401	TAU N=490
Unadjusted Mean (Standard Deviation)	46.03 (8.55)	44.72 (8.21)	48.12 (8.82)	45.16 (8.77)	48.62 (9.02)	45.31 (8.88)
Adjusted Difference (C.I.)*	0.99 (0.23, 1.76)		2.58 (1.79, 3.38)		2.93 (2.11, 3.75)	
p-value	0.0107		<0.0001		<0.0001	

* Linear mixed effects model adjusted for age, sex, Partner status, height, employment status, smoking status, exercise status, history of heart disease, cancer and other comorbidities, week and interaction of week with randomisation, and including a random effect at the individual-level.

A further sensitivity analysis was performed whereby missingness was assumed to be related to the outcome. The last observation carried forward method of imputation was used, where the last available measurement for a participant was imputed for all further missing measurements of that participant. The results are shown in Table 44. The treatment effects are still statistically significant at all time points, but the effect sizes are smaller.

TABLE 44 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN WEMWBS SCORE BETWEEN THE TWO GROUPS WHEN THE MISSING DATA ARE IMPUTED USING LAST OBSERVATION CARRIED FORWARD

	WEMWBS 4 Weeks		WEMWBS 8 Weeks		WEMWBS 24 Weeks	
	Sleepio N=853	TAU N=858	Sleepio N=853	TAU N=858	Sleepio N=853	TAU N=858
Unadjusted Mean (Standard Deviation)	44.40 (8.41)	43.88 (8.09)	45.58 (8.84)	44.15 (8.47)	45.88 (8.91)	44.19 (8.62)
Adjusted Difference (C.I.)*	0.61 (0.08;1.13)		1.51 (0.99; 2.04)		1.77 (1.24; 2.29)	
p-value	0.0237		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

3.7.1.3 GSII Rank 1

The missing data mechanism was explored by means of a pattern mixture model. The results are displayed in Figure 11. If participants with a GSII rank 1 VAS score missing at 8 weeks in the Sleepio group had an average score of 5 less than those who were not missing, the treatment effect would still have been statistically significant between the two groups. If participants with a missing outcome in the control group had an average GSII rank 1 VAS score of 5 or less greater than those who were not missing, the estimated treatment effect would still be statistically significant.

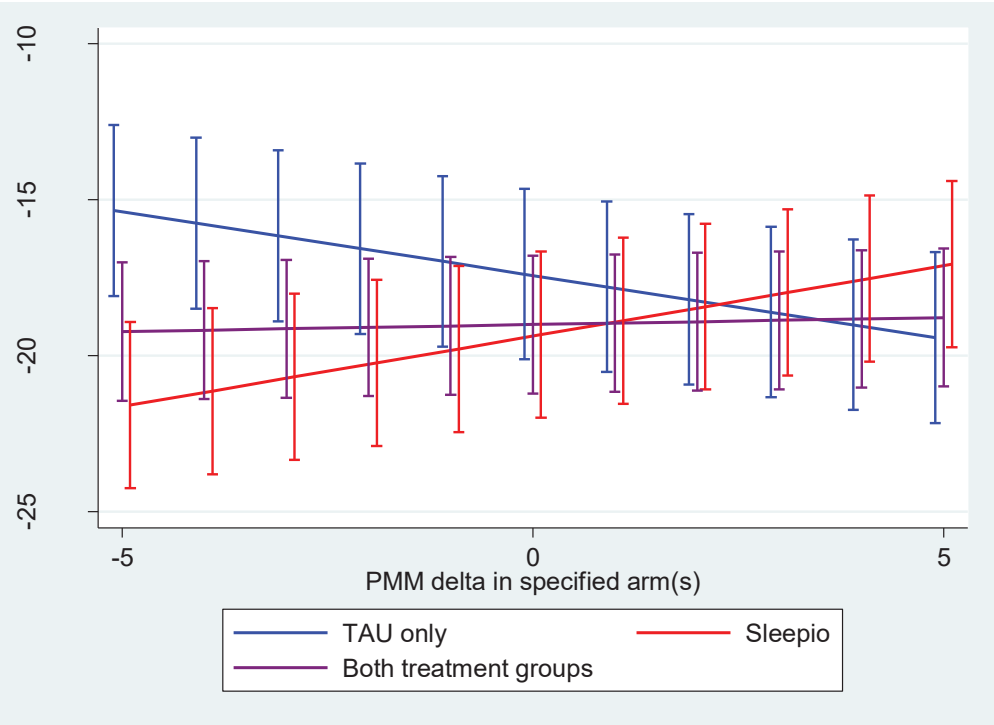

FIGURE 11 PATTERN MIXTURE MODEL RESULTS FOR THE GSII VAS SCORE FOR RANK 1 AT 8 WEEKS

A sensitivity analysis was performed including baseline covariates which were found to be predictive of missingness at 8 weeks. The results are shown in Table 45. The estimated treatment effects are very close to those from the main analysis (Table 20).

TABLE 45 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN GSII (3A) SCORE BETWEEN THE TWO TREATMENT GROUPS WHEN SEX, PARTNER STATUS, HEIGHT, EMPLOYMENT STATUS, SMOKING STATUS, EXERCISE STATUS, HISTORY OF HEART DISEASE, CANCER AND OTHER COMORBIDITIES ARE INCLUDED AS COVARIATES

	GSII 4 Weeks		GSII 8 Weeks		GSII 24 Weeks	
	Sleepio N=546	TAU N=546	Sleepio N=467	TAU N=509	Sleepio N=409	TAU N=492
Unadjusted Mean (Standard Deviation)	60.69 (26.20)	69.80 (23.64)	46.87 (29.90)	65.68 (25.86)	43.78 (31.25)	63.33 (27.26)
Adjusted Difference (C.I.)*	-8.69 (-11.80, -5.57)		-17.65 (-20.90, 14.39)		-18.88 (-22.24, -15.52)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for age, sex, Partner status, height, employment status, smoking status, exercise status, history of heart disease, cancer and other comorbidities, week and interaction of week with randomisation, and including a random effect at the individual-level.

A further sensitivity analysis was performed whereby missingness was assumed to be related to the outcome. The last observation carried forward method of imputation was used, where the last available measurement for a participant was imputed for all further missing measurements of that participant. The results are shown in Table 46. The treatment effects are still statistically significant at all time points, but the effect sizes are smaller.

TABLE 46 LINEAR MIXED EFFECTS MODEL RESULTS FOR THE DIFFERENCE IN THE CHANGE IN GSII RANK 1 VAS SCORE BETWEEN THE TWO GROUPS WHEN THE MISSING DATA ARE IMPUTED USING LAST OBSERVATION CARRIED FORWARD

	GSII Item A 4 Weeks		GSII Item A 8 Weeks		GSII Item A 24 Weeks	
	Sleepio N=853	**TAU N=858**	**Sleepio N=853**	**TAU N=858**	**Sleepio N=853**	**TAU N=858**
Unadjusted Mean (Standard Deviation)	70.93 (26.12)	76.41 (22.23)	62.74 (31.44)	72.95 (24.54)	60.49 (32.69)	71.36 (25.70)
Adjusted Difference (C.I.)*	-5.81 (-8.25, -3.39)		-10.55 (-12.98, -8.12)		-11.21 (-13.64, -8.79)	
p-value	<0.0001		<0.0001		<0.0001	

* Linear mixed effects model adjusted for baseline score, week and interaction of week with randomisation, and including a random effect at the individual-level.

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