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Sleep Treatment Outcome Predictors (STOP) Pilot Study: A randomised controlled trial examining predictors of change of insomnia symptoms and associated traits following cognitive behavioural therapy for insomnia in an unselected sample

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Abstract

Introduction: Cognitive behavioural therapy for insomnia (CBT-I) leads to insomnia symptom improvements in a substantial proportion of patients. However, not everyone responds well to this treatment and it is unclear what determines individual differences in response. The broader aim of this work is to examine to what extent response to CBT-I is due to genetic and environmental factors. The purpose of this pilot study is to examine feasibility of a design to test hypotheses focusing on an unselected sample, i.e. without selection on insomnia complaints, in order to plan a larger behavioural genetics study where most participants will likely not have an insomnia disorder.

Methods and analysis: A two parallel-group randomised controlled trial (RCT) is being conducted across 3 London universities. Female students (minimum age 18 years) enrolled on a psychology programme at one of the 3 sites were invited to participate. Following baseline assessments, participants were randomly allocated to either the treatment group, where they receive weekly sessions of digital CBT-I for 6 weeks, or the control group, where they complete an online puzzle each week for 6 weeks. Follow up assessments take place mid-intervention (3 weeks), end of intervention (6 weeks), and 6 months after allocation. Primary outcomes will be assessed using descriptive statistics and effect size estimates for intervention effects. Secondary outcomes will be analysed using multivariate Generalised Estimating Equation (GEE) models.

Ethics and dissemination: The study received ethical approval from the Research Ethics and Integrity sub-committee, Goldsmiths, University of London (application reference: EA 1305). DNA sample collection for the BioResource received ethical approval from the NRES Committee South Central-Oxford (reference number: 15/SC/0388). The results of this work shall be published in relevant peer-reviewed journals and uploaded to the trial registration website as appropriate.

Trial registration: Clinicaltrials.gov (identifier: NCT03062891).

Strengths and limitations

- This study contains a large sample size for a pilot study, and will provide valuable effect size information useful for the planning of future investigations of this topic.
- Stratification on sleep problems was implemented to ensure baseline sleep problems were equal in both groups.
- Recruitment was done using convenience sampling which may lead to some self-selection bias in the sample.
- The online nature of the study makes it difficult to fully assess adherence to the intervention.

Introduction

Insomnia occurs frequently and causes a substantial burden to society [1]. It is estimated that as many as one-third of US adults experience issues with their sleep, and the annual cost of insomnia to the US labour force has been estimated to be approximately $280 billion [2]. Historically, insomnia has been considered as secondary to other psychiatric disorders, such as depression [3,4]. More recently however, it has become clear that insomnia is associated with a wide range of psychiatric conditions and may precede and predict their development and severity [5–7].

Cognitive behavioural therapy (CBT) has been shown to be an effective treatment for insomnia [8,9]. Consequently, the American College of Physicians now recommends CBT for insomnia (referred to from hereonin as CBT-I) as the first choice treatment for chronic insomnia [10]. CBT-I is now more accessible than ever due to the development of automated online programmes which have shown promising effectiveness [11–13]. A randomised controlled trial of 164 participants meeting DSM-5 criteria for insomnia disorder showed significant post-treatment improvements in insomnia symptoms and sleep efficiency, for those participants assigned to a digital CBT-I group compared to a placebo [11]. These results were largely maintained at an 8-week follow-up. Following this, a meta-analysis of 15 randomised controlled trials investigating digital CBT-I found across all studies a significant improvement in sleep efficiency (7.2%) following digital CBT-I compared with baseline, and a significant drop on the insomnia severity index, bringing patients to a sub-threshold level of insomnia [13]. This reduction in insomnia symptom severity was also accompanied by a significant drop in symptoms of depression, suggesting CBT-I may also be effective for problems associated with insomnia [14].

Despite the demonstrated effectiveness of CBT-I, some individuals fail to respond to treatment. It has been suggested that CBT-I can significantly reduce symptoms of insomnia in around 70% of patients, meaning 30% of patient s show no improvement in symptoms [15]. Understanding the reasons why people either respond or do not respond to treatment holds promise of improving or tailoring current treatments for insomnia.

Investigations of predictors of treatment response to CBT applied to other conditions, such as anxiety, have shown a wide range of demographic, clinical, genetic, and epigenetic factors influence response to CBT treatment for anxiety [16–19]. Genetic predictors of treatment outcome are still unclear however. Whilst some studies have reported specific genetic markers for intervention outcome in disorders such as post-traumatic stress disorder (PTSD) [20], panic disorder [21], and social anxiety disorder [22], these findings have not always been replicated [23,24]. Whilst individually, any genetic predictor is likely to only explain a small proportion of variance in treatment outcome, understanding these multiple factors and their interactions may serve an important role in improving the outcome of therapy. The aim of this pilot study is to test the feasibility of running a larger-scale study of predictors of treatment outcome for CBT-I within a twin design, where not all participants will have insomnia.

Primary objectives

1. Sleep improvement after CBT-I in an unselected sample

To date, studies examining CBT-I have done so in the context of improving symptoms in patients diagnosed with insomnia disorder [11]. However, we plan to include both

participants with and without insomnia in the main study. In particular, as our future study is likely to focus on *twin pairs* it is inevitable that at least some of the participants in that study will not have insomnia (e.g. one participant may have insomnia but their co-twin might not). We are therefore interested to see the extent to which CBT-I has an effect in an unselected sample i.e. participants with and without an insomnia disorder. This pilot aims to establish the distributional properties of individual differences in change score on measures such as the Sleep Condition Indicator (SCI) and Pittsburgh Sleep Quality Index (PSQI) [25,26] as a result of the CBT-I intervention. The outcome of this will be used to assess the feasibility of running a larger behavioural genetics study in the future investigating genetic predictors of CBT-I outcome in an unselected sample. As we are primarily interested in change in insomnia symptoms, the SCI will be our main outcome measure for this objective (see Measures for detail).

2. Participation rate and treatment acceptability

The second aim of the study is to assess the feasibility of a digital CBT-I intervention study in a non-clinical group. For example, will participants without insomnia be willing to complete a 6-week online programme aimed at improving sleep? As such we will be closely monitoring participation (the proportion of participants who are willing to take part in the study) and drop-out rates (the percentage of participants who sign-up to the study and drop out before the end of the study). We will also examine treatment acceptability. Whilst psychological interventions to treat insomnia such as CBT-I have been rated highly by patients with regards to how acceptable they find the treatment [27,28], it is important for this study to investigate whether participants who do not necessarily have a sleep disorder, find CBT-I an acceptable treatment. This will be assessed using an adapted version of the

Treatment Acceptability Questionnaire (TAQ) [29], for more information see the Measures section.

Secondary aims

3. Factors predicting treatment outcome

We will collect data on factors that may predict treatment outcome, and will be able to use the data collected to estimate effect sizes for various predictors which will be useful in power calculations to estimate the sample size for a larger future behavioural genetics study. Furthermore, by including these measures in the pilot study it will allow us to assess the feasibility of administering a large battery of questionnaires to participants in addition to completing the digital CBT-I/puzzles.

Based on previous work into predictors of treatment outcome in CBT for anxiety [16–19], a wide range of demographic, clinical, and genetic predictors such as potential single nucleotide polymorphisms (SNP) and polygenic risk scores of response to digital CBT-I will be investigated (see Measures section for more details), for producing an estimated effect size that will be helpful in the planning of a larger study.

4. Sleep quality and implications for associated variables

Sleep quality is known to be associated with a number of other variables, such as anxiety and depression [30]. As such, one outcome of improving sleep quality through CBT-I could be an improvement of symptoms in associated variables. For example, in a meta-analysis of digital CBT-I RCT studies, it was found that digital CBT-I significantly reduced depression severity [14]. As such, digital CBT-I holds the promise of not only improving sleep problems themselves, but also the variables commonly associated with them.

Our focus here is to obtain an approximate effect size for any effect that can be used in designing a more substantial study – but we note that we may not have power to report significant effects in the context of this pilot work.

Exploratory aims of the pilot study

5. Genetic predictors of treatment outcome

We will perform preliminary analysis on possible genetic predictors of digital CBT-I treatment outcome to help in the development of hypotheses for a larger genetics study in the future. The samples will be genotyped on the Psychiatric Genomics Consortium customised HumanCoreExome-24+ v1.1 beadchip from Illumina. This beadchip retains a GWAS backbone, exome beadchip content and an additional ~50K psychiatric relevant variants. We will also perform exploratory investigations on the genetic data in relation to exploratory aims 7 & 8 (see below).

6. Mechanisms mediating improvements in insomnia

Assuming enough variation in appropriate measures, we will investigate whether factors such as pre-sleep arousal, cognitions about sleep, chronotype, and specific sleep disturbances mediate CBT-I outcome in an unselected sample.

7. Improvement in sleep paralysis episodes following CBT-I

Sleep paralysis is an unusual but relatively common condition involving a period of inability to perform voluntary movements at either sleep onset or upon awakening [31], with an estimated prevalence of up to 30% [32,33]. If enough participants with sleep paralysis are

included in our sample, we will assess the feasibility and effectiveness of digital CBT-I in the patient groups in terms of reducing the number of episodes, as well as associated fear and hallucinations.

8. Variables associated with exploding head syndrome

Exploding head syndrome is an unusual experience, characterised by hearing loud noises (e.g. an explosion or gunshot) in one's head at either wake-sleep or sleep-wake transitions [31]. If enough participants with exploding head syndrome are included in our study, we shall look at potentially associated variables such as insomnia symptoms, stress, and psychopathology.

Methods and analysis

Design

The study is a two-group parallel randomised controlled trial in which the intervention group will receive a digital CBT-I intervention, and the control group will receive a weekly online puzzle. See the intervention section for more details.

Participants are female students (both undergraduate and postgraduate) completing a psychology programme at one of three London universities (for full details see the trial registration). After completing the baseline assessment online via the Qualtrics system, participants were randomly allocated to either the CBT-I or puzzles group. Three weeks later, participants complete a second online assessment, and then a third online assessment 6 weeks after the start of the study. Finally, a follow-up online assessment will be carried out 6 months after group allocation. Participants were also invited to give a DNA sample at the

start of data collection. While we have limited statistical power to look at genetic predictors of treatment outcomes in the pilot study, these samples could be pooled with other data collected in the future, and also provide a useful opportunity for our collaborators to collect data for another ongoing research initiative (NIHR BioResource for Mental Health). See **Figure 1** for a detailed outline of the study timeline. A completed SPIRIT checklist and World Health Organisation (WHO) trial registration data set can be found in the **supplementary materials**.

Inclusion and exclusion criteria

Only females are eligible for participation. This is because the majority of the students on the psychology courses are female, and so adding males would create heterogeneity but without sufficient power to examine this further. Furthermore, only individuals enrolled in a psychology course from one of 3 London universities were recruited due to reasons of convenience. We focused our recruitment efforts on first year students in particular, as it is possible that a small number of students in other years may have already taken part in studies using the same digital CBT-I platform [35]. In order to address this point explicitly, in the questionnaires given to participants, they were asked if they have had any experience with Sleepio before taking part in this study.

Participant recruitment

Participants were recruited to the study using a two-step procedure. Initially, potential participants were contacted via an e-mail providing the study information, specific instructions as to the nature of the recruitment day, and contact information.

The second stage of recruitment involved a series of recruitment days at the three 3 sites. These recruitment days were timed to coincide with classes that potential participants were present at, to make it more likely that they would be in university. At sign-up, participants were given a paper copy of the information sheet and were given the option to ask any questions about the nature of the study. After confirming that they were happy to take part in the study, all participants were asked to give informed consent, provide a DNA sample (see DNA sample collection), and were assigned a unique participant ID number which was used for future assessments. To allow the participation of individuals who wished to take part in the study but were unable to sign-up in person, participants were given the option to contact the research team directly by e-mail in order to arrange providing consent to take part in the study.

Participants will be rewarded for their time, either in the form of course credits (offered credits + £5 online gift voucher) or online shopping voucher (£40), awarded to them upon completion of the study.

Randomisation and study automation

After collection of baseline data, participants were randomly allocated to either the CBT-I group or the puzzles group. A member of the research team randomised eligible participants using the blockrand package for R [36]. Participants were stratified based upon age, sleep problems and study site. Stratification on age was performed to assure similar age distributions in both groups. Stratification on sleep problems was implemented to avoid the possibility of a disproportionate number of participants with sleep problems being randomly allocated to the same group. Stratification for study site was implemented to avoid an unnecessary delay between completing the first questionnaire and being allocated to a group.

An automated e-mail was sent to participants to inform them of which group they had been assigned. Those in the CBT-I group were given further information as to the nature of the programme (see Digital CBT-I) as well as a unique code needed to log into the website. Those in the puzzles group were given information as to the nature of the tasks that they were required to complete (see Puzzles). Participants were not able to change groups once they have been allocated.

Intervention

Digital CBT-I

CBT-I participants received 6 weekly CBT-I sessions delivered by an animated 'virtual therapist' (The Prof) via the online platform 'Sleepio' (http://www.sleepio.com). The programme comprises a fully automated media-rich web application, driven dynamically by baseline, adherence, performance and progress data, and provides additional access to elements such as an online library with background information, a community of fellow users, and support, prompts and reminders sent by e-mail.

The Sleepio programme covers behavioural (e.g., sleep restriction, stimulus control) and cognitive (e.g., putting the day to rest, thought restructuring, imagery, articulatory suppression, paradoxical intention, mindfulness) strategies, as well as additional relaxation strategies (progressive muscle relaxation and autogenic training) and advice on lifestyle and bedroom factors (sleep hygiene). The intervention was based upon a previously validated manual [37–39]. Sleepio has been shown to improve sleep and associated daytime functioning in adults diagnosed with insomnia disorder [11].

Puzzles

Participants in the control group were sent weekly puzzles to complete within Qualtrics. Each puzzle was designed to be cognitively engaging, and time taken to complete a puzzle has been matched as closely as possible to the time taken to complete one session of digital CBT-I. Puzzles were sent directly to participants via automated distribution e-mails sent at 7 day intervals. In order to track whether participants were completing the puzzles, they were required to enter their participant ID number at the start of each puzzle. The types of puzzles administered to participants included word searches, crosswords, and lateral thinking problems.

Data Collection

DNA sample collection

This project was conducted in collaboration with the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) BioResource for Mental and Neurological Health in London as part of a national NIHR initiative to build up a central library of information (or "BioBank)" about people's health.

In this study, we obtained saliva samples from our participants after obtaining consent during the recruitment days. Samples were collected by a researcher from the BioResource team in compliance with their ethically approved protocol. The BRC is the custodian of the samples received. On receipt, samples were logged and prepared for extraction of DNA. The BRC ensures that genetic samples are processed in accordance with strict health and safety guidelines and under the requirements of the Human Tissue Act (HTA). King's College

London holds a HTA license, number: 12293. All samples are stored in tubes labelled with a barcode that includes the participant number. The link between the participant ID and de-identified data is kept in a secure folder. The DNA samples collected as part of this study are stored by the BRC for future analysis and hypothesis testing with appropriate ethical approval in the future, and under existing BRC BioResource approvals.

Wave 1 data collection

Eligible participants were given the option of completing the baseline survey online after signing up. Participants were encouraged to complete the survey within one week from sign-up. Paper copies were made available for participants who had problems with their device or internet access.

Participants completed all measures, as shown in **Table 1**. Participants had the option to leave out any question. The survey took 30-40 minutes to complete. At the end the survey, participants were reminded that they would be contacted with regards to future data collection.

Waves 2-4 data collection

The second, third, and fourth waves of data collection will be carried out 3 weeks, 6 weeks, and 6 months following the allocation of participants to groups. These time points correspond to mid-intervention, end-of-intervention, and post-intervention follow-up time points respectively (see Figure 1 for more detail). Automated e-mails distributed by Qualtrics will be sent to participants at the designated intervals. Not all measures are assessed at all waves, as shown in **Table 1**. Follow-up emails to non-responders will be sent each week to participants who fall behind on their tasks (i.e. CBT-I, puzzles, or surveys).

Measures

Descriptions for all measures used are provided below. For waves 2-4 some measures were adapted to ask participants to consider their answers with reference to the last 2 weeks (unless otherwise stated below), in order to ensure participants were considering only the time since the last wave of data collection when responding. Full details on each measure used can be found in the **supplementary materials**.

Demographic information was collected at baseline. At the start of each survey, participants were asked to indicate whether it was currently term time, exam time, or holiday time. At wave 2, participants in the Sleepio group indicated whether they had ever used Sleepio before.

Sleep measures

Insomnia symptoms – *Sleep Condition Indicator* (SCI) [25]. An 8-item measure assessing symptoms of insomnia, used to identify insomnia symptoms in community samples [40].

Sleep Quality – *Pittsburgh Sleep Quality Index (PSQI)* [26]. An 18-item questionnaire assessing 7 components of sleep quality and disturbances, which also yields a global score of sleep quality. The scale has been shown to be reliable and valid in assessing sleep quality in adult community samples [41].

Trauma-related sleep disturbances – *Pittsburgh Sleep Quality Index Addendum* [42]. Assesses frequency of 7 sleep disturbances typically related to trauma. The measure has been validated for use in assessing these disturbances [42,43].

Pre-sleep-arousal – *Pre-sleep Arousal Scale* [44]. Measures symptoms of cognitive (8 items) and somatic (8 items) arousal experienced around bedtime. It is has been validated with respect to objective measures of pre-sleep arousal [45,46].

Cognitions about sleep – *Dysfunctional Beliefs About Sleep Scale (DBAS)* [47]. A 10-item questionnaire that includes items about sleep-disruptive cognitions such as faulty beliefs, worry, and attentional bias. The measure has shown to be reliable [48].

Chronotype – *Munich Chronotype Questionnaire (MCTQ)* [49]. Chronotype is estimated as the midpoint of sleep on workdays and work-free days minus half of the difference between sleep duration on work-free days and average sleep duration of the work to control for sleep debt (i.e. the midpoint of sleep on work-free days, corrected for sleep duration). The MCTQ is a reliable and valid measure of chronotype [50,51].

Sleep paralysis – *Waterloo Unusual Experiences Questionnaire (WUSEQ*) [52]. Items from the WUSEQ were used to assess the frequency of sleep paralysis and associated hallucinations. The measure is valid and reliable in healthy student samples [53,54].

Sleep paralysis – *Fearful Isolated Sleep Paralysis Interview (FISPI)* [55]. Two items from this measure were adapted to measure the amount of fear/distress typically caused by sleep paralysis episodes, and how much interference with waking life episodes have caused. The

FISPI has been used as a valid and reliable measure of sleep paralysis in university samples [56].

Exploding head syndrome – *Munich Parasomnia Screening (MUPS)* [57]. Lifetime prevalence of exploding head syndrome was measure using a single item from the MUPS.

Psychopathology and well-being measures

Anxiety symptoms – *State Trait Anxiety Index (STAI)* [58]. The STAI assesses both state (20 items) and trait (20 items) levels of anxiety, and is a valid and reliable measure of anxiety symptoms [59].

Depressed mood – *Mood and Feelings Questionnaire (MFQ)* [60]. Depressed mood was measured using the 13-item MFQ. This has been shown to be a valid measure of depressed mood.

ADHD symptomatology – Bespoke measure examined 18 symptoms of ADHD according to DSM-5 criteria [61]. This is a valid and reliable measure of ADHD symptoms, and has been previously used to in young adults to assess ADHD symptomatology in the context of sleep quality [62].

Psychotic experiences – *Specific Psychotic Experiences Questionnaire (SPEQ)* [63]. Sub-scales relating to paranoia [64], hallucinations [65], and cognitive disorganisation [66] were used as they are strongly related with sleep disturbances [67]. The scale has been shown to have good reliability and validity [63].

Positive mental health – *Positive Mental Health Scale (PMH)* [68]. Positive aspects of health and life experiences were assessed using a 9-item questionnaire.

Life stress – *Perceived Stress Scale (PSS)* [69]. Life stress was measured with a 10-item measure. A review of articles assessing the psychometric properties of the PSS found the measure to be a reliable and valid measure of life stress [70].

Exposure to threatening events – *List of Threatening Experiences (LTE)* [71,72]. Participants were asked to indicate whether they had experienced any threatening events from a list of 24. The LTE has been shown to have high reliability and be a valid measure of exposure to potentially threatening experiences [73].

Lifestyle measures

At each wave, participants were asked about their sleeping arrangements [74], and alcohol [75] and caffeine intake [76]. Cigarette [75] and electronic (e) cigarette usage [77–79] were assessed at baseline.

Treatment acceptability

The 6-item *Treatment Acceptability Questionnaire (TAQ)* [29] asked specific questions regarding the degree to which they found the treatment acceptable, ethical, and effective. There were also specific questions about the nature of the virtual therapist. Only participants in the Sleepio group received the TAQ.

Sample size

For this study, the target is to have 200 participants, which should provide power to examining our primary research questions. Though we plan to over recruit to account for some attrition throughout the study. Power analyses are often conducted using hypothesised effect sizes based on mean differences (e.g. before and after treatment). However, as this is a pilot for a future behavioural genetics study, the main statistic of interest is not mean differences, but individual differences (i.e. variances). As one of the aims of this pilot study is to assess whether it is possible to observe enough variation in the difference scores of the treatment group to embark upon a bigger population twin study where the main aim will be to decompose observed variance into additive genetic (A), common (shared) environmental (C), and non-shared environmental (E) components.

Statistical analysis

Primary objectives

1. CBT-I in an unselected sample

The aim is to examine variation in response to CBT-I (i.e. variation in the change score of self-reported insomnia symptoms and sleep quality, as measured by the SCI and PSQI). This aim will be achieved by calculating a change score in insomnia symptoms/sleep quality (SCI/PSQI) by comparing pre- and post-CBT-I and reporting descriptive statistics for this measure. This will also be conducted for the group given puzzles, where we would expect less variation in sleep quality over time. Given the anticipated group sizes (100 per group) it is likely we will be able to detect a treatment difference between groups with an unadjusted effect size of 0.46.

2. Participation rate and treatment acceptability

Evaluation of participation rate and treatment acceptability will be based on the descriptive statistics i.e. percentage of participants who sign up to the study, percentage of participants who complete the study, and mean scores on treatment acceptability questionnaire. No formal statistical tests shall be performed.

Secondary objectives

3 & 4. Factors predicting treatment outcome and sleep quality and implications for associated variables

We will test which measures at baseline are moderators of longitudinal outcome of change scores in insomnia symptoms with multivariate Generalised Estimating Equation (GEE) models using Akaike/Bayesian information criterion (A/BIC) criteria to select an optimal model with predictors of insomnia symptoms/sleep quality derived. All models will be run in Stata and control for covariates (e.g. age) and the non-independence of sibling-pair data. Missing data shall be accounted for using maximum likelihood or multiple imputation procedures.

Ethics, consent, confidentiality, and data security

All stages of the study received ethical approval from the Research Ethics and Integrity sub-committee at Goldsmiths, University of London (application reference: EA 1305). DNA sample collection for the BioResource received ethical approval from the NRES Committee South Central-Oxford (reference number: 15/SC/0388). All participants were asked to provide informed consent before participating. A sample consent form is provided in the

supplementary materials. It was made explicit that participation in the study is voluntary, that participants can choose not to answer questions if they do not want to, that they had the right to withdraw from the study at any point, and that their data would remain confidential. Participants were informed of the intention to publish results from this study using their data, and agreed to this in the informed consent. Copies of questionnaire booklets given to participants are not publically available due to copyright restrictions on some of the measures.

All identifying information is stored in a password protected document. Survey responses are automatically stored in Qualtrics. No identifying information is stored with response data. Data in Qualtrics is secured using industry best standards (https://www.qualtrics.com/security-statement/). At the end of data collection, datafiles for each wave of the study shall be downloaded off of Qualtric's servers and stored in SPSS. At this point, the datafiles will be removed from Qualtrics. Only researchers directly involved in the analysis of data will have access to participant data. The final, anonymised datasets from each wave of the study shall be available upon reasonable request from the corresponding author upon completion of the study.

Dissemination of findings

Results of this trial will be disseminated primarily via peer-reviewed journal publications. It is expected that the primary, secondary, and exploratory aims 5 and 6 of this study will be reported in a single publication. Other findings of exploratory aims will be published separately. The results of this study will also be available on the ClinicalTrials.gov website when they become available.

Competing interests

The position of AIL at the University of Oxford is funded by Big Health Ltd, the company behind the digital CBT-I program evaluated in this study. CAE is the co-founder and CMO of Big Health Ltd and holds shares in Big Health Ltd. AMG has provided guidance and educational content for a freely available educational website focused on infant sleep. This website is partially supported by Johnson and Johnson, but they do not have any influence over content and do not advertise on it. She also contributes to BBC Focus Magazine.

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Author contributions

Study conception and design: TCE, FR, HMSZ, RK, CAE, JH, MH, AMG

Acquisition of data: DD, HMSZ, RK, AIL, IB, SD, AR, AMG

Future analysis of data: DD, FR, SD

Preparation of manuscript: All authors

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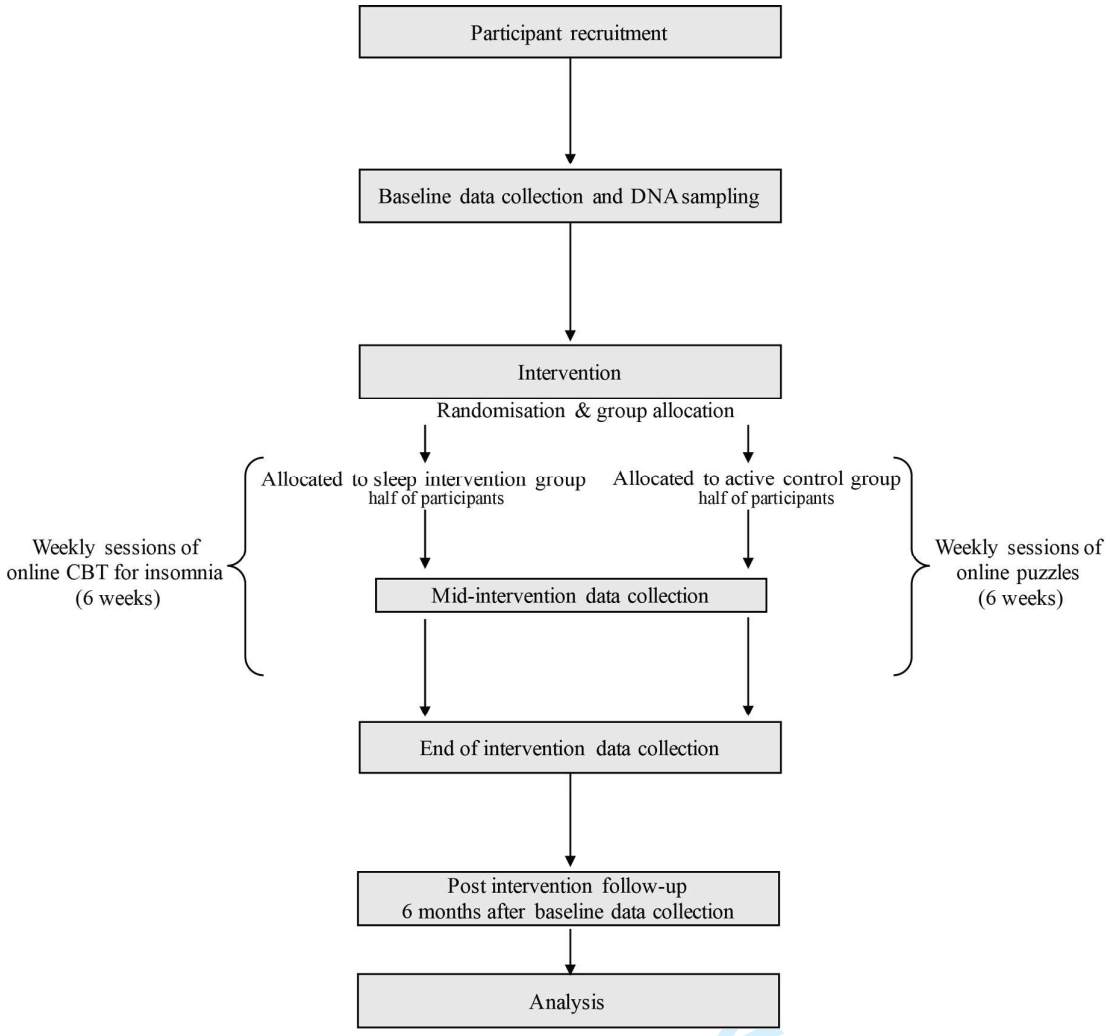

Figure 1. Flowchart of study timeline

Table 1. Schedule of enrolment, interventions, and assessments made at each wave

	Measures	Enrolment	Wave 1 Baseline	Allocation	Wave 2 (3 weeks) Mid-assessment	Wave 3 (6 weeks) End-assessment	Wave 4 (6 months) Follow-up
Enrolment							
Eligibility screening		X					
Informed consent		X					
Saliva DNA sample		X					
Allocation				X			
Interventions							
CBT-I					X	X	
Puzzles					X	X	
Assessments							
Demographics			X				
Medical history			X				
Weight and height			X			X	X
Time of year			X		X	X	X
Sleep measures	SCI		X		X	X	X
	PSQI		X		X	X	X
	PSQI-A		X			X	X
	PSAS		X		X	X	X
	DBAS		X		X	X	X
	MCTQ		X			X	X
	WUSEQ		X			X	X
	FISPI		X			X	X
	MUPS		X				
Well-being measures	STAI		X		X	X	X
	MFQ		X		X	X	X
	ADHD		X			X	X

	SPEQ	X		X	X
	PMH	X	X	X	X
	PSS	X	X	X	X
	LTE	X	X	X	X
Lifestyle measures	Sleeping arrangements	X	X	X	X
	Alcohol intake	X	X	X	X
	Caffeine intake	X	X	X	X
	Smoking behaviour	X			
	Vaping behaviour	X			
Treatment acceptability	TAQ[1]		X	X	

PSQI = Pittsburgh Sleep Quality Index, SCI = Sleep Condition Indicator, PSQI-A = Pittsburgh Sleep Quality Index – Addendum, PSAS = Pre-sleep Arousal Scale, DBAS = Dysfunctional Beliefs About Sleep Scale, MCTQ = Munich Chronotype Questionnaire WUSEQ = Waterloo Unusual Experiences Scale, FISPI = Fearful Isolated Sleep Paralysis Interview, MUPS = Munich Parasomnia Screening, STAI = State/Trait Anxiety Index, MFQ = Moods and Feelings Questionnaire, ADHD = Attention Deficit Hyperactivity Disorder, SPEQ = Specific Psychotic Experiences Questionnaire (paranoia, hallucinations, and cognitive disorganisation sub-scales), PMH = Positive Mental Health Scale, PSS = Perceived Stress Scale, LTE = List of Threatening Experiences.

[1] Only administered to the Sleepio group.

Details of measures

Demographics

Questions were asked regarding the participant's age, date of birth, sex, and ethnicity at the start of the study. They were also asked to report on educational attainment e.g. the number of secondary school education exams taken (General Certificate of Secondary Education (GCSE)/A-levels or international equivalents), and specific grades received during A-level exams or their non-UK equivalent. Participants were also asked to indicate other qualifications received, as well as number of bachelors (e.g. BSc/BA), masters (e.g. MSc), and doctoral degrees (e.g. PhD).

Weight and height

Participants were asked to report their weight either in kilograms or stone. They were also asked to report their height in either centimetres or feet and inches.

Medical history

Participants were asked to rate how good they thought their health was generally, on a 5-point scale ranging from excellent to poor. They were asked whether they had ever been diagnosed by a medical professional with any mood disorders e.g. "*Anxiety or panic disorder"* or nervous system problems e.g. *"Schizophrenia"*. For each illness, they can select either yes or no. If a participant is currently diagnosed with any other psychological or physical illnesses not listed, they were asked to list them.

Use of either prescription medications, and/or use of over the counter, alternative medications, vitamins, minerals, herbal, or other supplements over the last 6 months was assessed by either answering yes, no, or don't know. If a participant has been using any of these, they were asked to name the substances being taken, the reason for use, and whether they took it regularly or occasionally.

Term, exam, or holiday period

At each wave participants were asked: *"At the moment, is it…"*, and chose one of 3 responses. These were: term time, exam time, or holiday time.

Sleep measures

Sleep Condition Indicator (SCI) [1] – In this 8-item questionnaire, participants consider a typical night in the last month and rate various aspects of their sleep including sleep onset, awakenings, perceived sleep quality, the effect of poor sleep on various aspects of life, and the length of their sleep. Higher scores are indicative of better sleep, and scores <= 16 indicate probable insomnia disorder. The SCI is valid, reliable and sensitive to change in insomnia severity [1]. It has been used to identify insomnia symptoms in community samples [2].

Pittsburgh Sleep Quality Index (PSQI) [3] – The PSQI is an 18-item questionnaire assessing 7 components of sleep quality and disturbances (subjective sleep quality, sleep efficiency, sleep disruption, use of sleeping medications, and daytime dysfunction). The scale yields an overall 'global' score of sleep quality, as well as component scores for each of the 7 facets of sleep quality and disturbances assessed, with a higher score indicating greater sleep problems. The

scale has been shown to be reliable and valid in assessing sleep quality in adult community samples [4].

Pittsburgh Sleep Quality Index Addendum (PSQI-A) [5] – Items included in this measure assess sleep disturbances typically related to trauma (disruptive nocturnal behaviours). The frequency of 7 disruptive nocturnal behaviours (e.g. memories or nightmares of a traumatic experience) are assessed with the PSQI-A. The frequency of each disruptive nocturnal behaviour is assessed on a scale ranging from never to 5-7 nights per week, with higher scores indicating a higher frequency of disruptive nocturnal behaviours. The PSQI-A has been shown to be a valid and reliable measure of sleep disturbances related to trauma [5,6].

Pre-sleep Arousal Scale (PSAS) [7] – The PSAS is a 16-item questionnaire measuring symptoms of cognitive (8 items e.g. intrusive thoughts) and somatic (8 items e.g. sweating) arousal experienced around bedtime. Each item is answered on a 5-point scale ranging from not at all to extremely. The scores from each item are summed to create a pre-sleep arousal score for both cognitive (PSAS-C) and somatic (PSAS-S) pre-sleep arousal. For both sub-scales, higher scores indicate greater levels of pre-sleep arousal. The PSAS has been shown to be a valid measure of pre-sleep arousal, and is comparable with objective measures of pre-sleep arousal [8,9].

Dysfunctional Beliefs About Sleep Scale (DBAS-10) [10] – This measure includes questions about sleep-disruptive cognitions such as faulty beliefs, worry, and attentional bias. There are a total of 10 items, and each is answered on a 5-point scale ranging from not at all to extremely. A global score is calculated based on all 10 items, with higher scores indicating higher levels of

dysfunctional beliefs about sleep. Three sub-scales can also be calculated, relating to: 1 – beliefs about the immediate negative consequences of insomnia, 2 – beliefs about the long-term negative consequences of insomnia, and 3 – beliefs about the need to try harder to sleep. The measure has been shown to be a reliable measure of cognitions about sleep [11].

Munich Chronotype Questionnaire (MCTQ) [12] – The MCTQ is a 14-item questionnaire focused primarily on sleep timing, with questions assessing the regularity of one's work schedule, number of workdays per week, sleep timing on workdays and work-free days, and use of an alarm clock on workdays and work-free days. Chronotype is estimated as the midpoint of sleep on workdays and work-free days minus half of the difference between sleep duration on work-free days and average sleep duration of the work to control for sleep debt (i.e. the midpoint of sleep on work-free days, corrected for sleep duration). Importantly, chronotype can only be calculated when individuals do not use an alarm clock on work-free days. The MCTQ is a reliable and valid measure of chronotype [13,14].

Waterloo Unusual Experiences Questionnaire (WUSEQ) [15] – Items for the WUSEQ were used to assess the frequency of sleep paralysis and associated hallucinations. Frequency of sleep paralysis was assessed via the item *"Sometimes when falling asleep or when waking from sleep, I experience a brief period during which I am unable to move, even though I am awake and conscious of my surroundings"*. This is answered on a 7-point scale ranging from never to several times a week. Those who indicated experiencing sleep paralysis at least once are asked follow-up questions about the frequency with which they experience associated hallucinations, on a 4-point scale from never to always. Three categories of sleep paralysis hallucinations are

assessed: intruder, incubus and vestibular-motor [16]. The WUSEQ has been shown to be valid and reliable measure of sleep paralysis frequency and associated hallucinations in healthy student samples [16,17].

Fearful Isolated Sleep Paralysis Interview (FISPI) [18] – Two items from the FISPI were included to assess the amount of fear/distress typically caused by sleep paralysis episodes, and how much interference with waking life sleep paralysis episodes have caused. For each item, participants respond on a scale from none, to very severe. Only participants who report experiencing at least one episode of sleep paralysis will answer these items. The FISPI has been used as a valid and reliable measure of sleep paralysis in university samples [19].

Munich Parasomnia Screening (MUPS) [20] – The lifetime prevalence of exploding head syndrome was measured using a single item from the MUPS. Participants are asked if they had ever noticed the following behaviour: *"When falling asleep or waking, perceiving a loud bang, a sound similar to a bang (e.g. door bang), or having the sensation of an "explosion in the head"".* This item was answered on a scale ranging from never observed, to very frequently (every/almost every night). The MUPS is a valid measure for recognising nocturnal behaviours and parasomnias [20].

Psychopathology and well-being measures

State Trait Anxiety Index (STAI) [21] – The STAI assesses both state and trait levels of anxiety. *State* anxiety was measured using 20 items in which participants were asked to rate the way that

they feel at the present moment (e.g. *"I feel calm", "I am presently worrying over possible misfortunes"*). Each item was assessed on a scale ranging from not at all, to very much so. Higher scores are indicative of greater state anxiety. *Trait* anxiety was measured using 20 items in which participants were asked rate the extent to which they generally feel (e.g., *"I make decisions easily", "I worry too much over something that really doesn't matter"*), on a scale ranging from not at all, to very much so. Higher scores are indicative of greater trait anxiety. The STAI has been shown to be a reliable and valid measure of anxiety symptoms [22].

Mood and Feelings Questionnaire (MFQ) [23] – Depressed mood was measured using the 13-item MFQ. Participants rated the way that they had felt or acted during the past two weeks (e.g. *"I felt miserable and unhappy"*, *"I found it hard to think properly or concentrate"*) on a 3-point scale (not true, sometimes, true). A higher score is indicative of a higher depressed mood over the last 2 weeks. This has been shown to be a valid measure of depressed mood [24].

ADHD – This bespoke measure examined symptoms of attention deficit hyperactivity disorder (ADHD) according to DSM-5 criteria [25]. Participants were asked about 18 symptoms of ADHD according to DSM-5 criteria. Each item is responded as either a yes or no answer. A higher score is indicative of greater ADHD symptomatology. This is a valid and reliable measure of ADHD symptoms, and has been previously used to in young adults to assess ADHD symptomatology in the context of sleep quality [26].

Specific Psychotic Experiences Questionnaire (SPEQ) [27] – The SPEQ measures 6 facets of psychotic experiences. For this study, sub-scales relating to paranoia [28], hallucinations [29],

and cognitive disorganisation [30] were used. These sub-scales were selected based upon prior work showing that these 3 aspects of psychotic experiences are most strongly associated with sleep disturbances in a community sample [31]. As space for questionnaire measures was limited, the 5-highest loading items from each of the 3 sub-scales were selected for inclusion [27]. The paranoia and hallucinations sub-scales were scored on a scale ranging from not at all, to daily, whilst items on the cognitive disorganisation subscale were scored as either yes or no. On all scales, a higher score reflected greater frequency of psychotic experiences. The scale has been shown to have good reliability and validity [27].

Positive Mental Health Scale (PMH) [32] – Positive mental health was assessed using the 9-item PMH. The scale assesses positive aspects of health and life experiences (e.g. *"I am often carefree and in good spirits"*, and *"I am in good physical and emotional condition"*). Each item was answered on a 4-point scale ranging from do not agree to agree. An overall mean score is derived, with a higher score indicating greater positive mental health. The reliability and validity of the measure has been shown to be good [32].

Perceived Stress Scale (PSS) [33] – This 10-item scale was used to measure stress. Participants rated the extent to which they had felt and thought in a certain way over the past month (e.g. *"How often have you felt confident about your ability to handle your personal problems"*), on a scale ranging from never to very often. All items are summed to create an overall score with higher scores indicating a greater level of perceived stress over the past month. A review of articles assessing the psychometric properties of the PSS found the measure to be a reliable and valid measure of life stress [34].

List of Threatening Experiences (LTE) [35,36] – Participants were asked to indicate whether they had experienced any threatening life events from a list of 24. Example events include: *"Been in hospital with a serious illness or injury"*, *"Death of a child or spouse"*, and *"Been sacked from a job"*. For each event, participants were asked to indicate whether they had experienced it recently, answering either yes or no. Scores are summed to create an overall exposure to threatening life events score, with a higher score indicating exposure to a greater number of different threatening events. The LTE has been shown to have high reliability and be a valid measure of exposure to potentially threatening experiences [37].

Lifestyle measures

Sleeping arrangements – Participants were asked 2 questions relating to their sleeping arrangements. They were: 1 – *"During the past month, who usually sleeps in the same room as you"*, and 2: *"During the past month, who usually sleeps in the same bed as you"*. Responses options for both items were: nobody, partner, baby/child, other. These items have been used previous work examining sleep in a healthy sample [38].

Alcohol intake [39] – This was assessed by four items: 1 – *"Do you drink?"* (scored as either yes or no), 2 – *"When you have an alcoholic drink, how many drinks do you have?"* (scale ranged from 1 to 8 or more, with one alcoholic drink being ½ pint of beer or lager/one glass of wine/one glass of spirits/one alcopop), 3 – *"How often do you have an alcoholic drink?"* (scale ranged from once or twice a year to almost every day), and 4 – *"During the last 30 days, how many times did you have five or more alcoholic drinks on the same occasion"* (scale included: four or

more times, three times, twice, once, I have not had five or more drinks on the same occasion in the past month, I have never had five or more drinks on the same occasion). Using items 2 – 4, average alcohol intake in terms of units of alcohol consumed per week can be calculated.

Caffeine intake [40]– The number of caffeinated drinks consumed per day for the last month was assessed. The drinks included were freshly brewed coffee (one shot espresso = one cup), instant coffee, caffeinated tea, and caffeinated soft drinks. The number of each drink type consumed ranged from 0, to 8 or more. The number of each drink type consumed is then recoded to reflect the amount of caffeine present in each type of drink, in order to calculate a score of total caffeine intake.

Smoking behaviour [39] – Three items were used to assess smoking behaviour: 1 – *"Do you smoke?"* (scored as yes, no, or used to but have given up), 2 – *"How often do you smoke cigarettes?"* (scale ranging from every day to once a month), and 3 – *"On the days that I do smoke, I smoke ... cigarettes"* (response options are: 1-5, 6-10, 11-15, 15-20, more than 20). The latter two questions are then used to calculate the number of cigarettes smoked per week.

Vaping behaviour – A bespoke measure of electronic (e) cigarette usage was used based on items from previous studies of e-cigarette usage [41–43]. Usage is assessed using 6 items: 1 – *"Do you use an electronic cigarette (e-cigarette)?"* (scored as either yes or no), 2 – *"How many days have you used an e-cigarette in the past two weeks?"*, 3 – *"Each time you use the e-cigarette, how many puffs do you inhale?"*, 4 – *"What strength of e-cigarette liquid do you use?"* (options are: 0 mg/l, 6 mg/ml, 12 mg/ml, 16mg/ml, 18 mg/ml, 26 mg/ml, other, don't know), 5 – *"How*

many cartridges/refills do you use per day?", and 6 – *"How long does a refill/cartridge typically last (hours)?"*.

Treatment acceptability

Treatment Acceptability Questionnaire (TAQ) [44] – The TAQ is a 6-item measure assessing the treatment acceptability of psychological treatments for adult populations. Participants in the digital CBT-I group are asked the degree to which they find the treatment acceptable, ethical, effective, and likelihood of negative side effects on a 7-point scale, with a lower number indicating lower treatment acceptability. They are also asked two questions specifically about the nature of the therapist, regarding how knowledgeable and trustworthy participants judge them to be. These items are answered using the same 7-point scale, and were adapted for use with a virtual CBT-I therapist used in this study. The measure has been shown to be reliable and valid [44].

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PARTICIPANT INFORMATION SHEET

You are invited to take part in a study which will use cognitive behavioural therapy (CBT) to improve your sleep. The purpose of this information sheet is to tell you about the study, and what will be involved if you decide to participate. **Please note that you do not need to have a sleep disorder in order to take part. We are inviting all psychology students who are female to participate in this study.**

BACKGROUND INFORMATION

CBT-I

CBT is an extremely effective treatment for disturbed sleep – particularly insomnia. Insomnia is a common problem involving trouble falling asleep, staying asleep, or getting quality sleep. CBT for insomnia (CBT-I) aims to improve sleep habits and behaviours by identifying and changing the thoughts and the behaviours that are negatively affecting sleep. SLEEPIO - which was developed by Professor Colin Espie, University of Oxford – is an online course and has therefore made this treatment far more accessible. SLEEPIO is the programme which is used in this study to help improve sleep, and one study found that 70% of individuals who use this programme showed long term improvements. **We plan to use this programme with an unselected sample, to see if those without sleep problems will also be willing to complete the programme and will experience benefits.**

Predictors of Treatment Outcome

It is important to look at predictors of treatment outcome to be able to improve and tailor treatments for individuals. One of our team, Professor Thalia Eley, King's College, London, has worked on ground-breaking work predicting CBT treatment outcome for anxiety in children focusing on demographic (e.g. sex) and clinical (e.g. comorbidity/ severity) risks but most uniquely genetic and epigenetic risks. **We also plan to look at predictors of treatment outcomes in the current study.**

THE STUDY

In this study, you will be asked to complete a set of questionnaires which measure sleep, behavioural and emotional issues as well as physical attributes such as health, weight and lifestyle. You will also be asked to provide a sample of your DNA (e.g. by providing saliva) by the UK biobank. Please note, they will also ask you to take part in their study (and will provide you with separate information and ethics form should you decide to participate). In this study, you will then be randomly allocated into one of two conditions, one of which will require you to take part in an online CBT programme called SLEEPIO which will take six weeks to complete. In the other group you will be asked to complete puzzles each week for six weeks. Please note that all those allocated into the latter group will be offered access to SLEEPIO at the end of the study should that appeal.

Three weeks, six weeks and six months after being allocated into your group you will be asked to complete further online questionnaires to assess your sleep, behavioural and emotional difficulties

TIME COMMITMENT

The study would require you to participate in a 6 week course (with brief weekly sessions and to keep a sleep diary) or to complete puzzles once a week for six weeks, as well as follow-up questionnaires. Participants would acquire insight into CBT; useful information to improve your sleep. After completing all four waves of data collection (with the final wave six months after starting the study), you shall receive a £40 Amazon gift card as a reward.

PARTICIPANTS' RIGHTS

You have the right to have your questions about the procedures answered (unless answering these questions would interfere with the study's outcome). If you have any questions as a result of reading this information sheet, you should ask the researcher before the study begins. Participation is entirely optional. You have the right to omit or refuse to answer or respond to any question.

If we publish data from this study, this will be done so anonymously so that it will not be possible to identify you from the report.

You may decide to withdraw from the research study at any time without explanation. You have the right to ask that any data you have supplied up to that point be withdrawn/ destroyed.

CONFIDENTIALITY/ANONYMITY

Your data will be kept confidential within the research team or with carefully selected bona fide researchers. We are likely to publicly present and publish the data – but you will not be identifiable during this process. Your data will be anonymised – meaning that the data collected from you will not be stored with personal data from which you could be easily identified such as your name, address and email. Once anonymised, these data may be made available to researchers via accessible data repositories and possibly used for novel purposes. Up until that point you can decide not to remove your data from inclusions in analyses.

FEEDBACK & CONTACT

You will not be given individual results from the testing. Information on the progress of the research will be widely available and we will be happy to give out this general information upon request. Professor Alice Gregory is leading this study and will be glad to answer your questions about this study at any time. You may contact her at Email: A.Gregory@gold.ac.uk.

INFORMED CONSENT FORM

PREDICTORS OF ONLINE CBT-I OUTCOME AND INFLUENCE ON ASSOCIATED PHENOTYPES

By checking the boxes below, you are agreeing that:

- ☐ You have read and understood the participant information sheet
- ☐ You have had the opportunity to ask questions about your participation which have been answered to your satisfaction
- ☐ You are taking part in this study voluntarily (without coercion) and understand you can withdraw at any point without explanation.
- ☐ Anonymised data may be shared in public research repositories
- ☐ You agree to have your details passed onto the UK biobank, who will contact you in order to obtain a DNA sample (and will invite you to be involved in their study)
- ☐ You agree to be contacted about other research projects
- ☐ You agree for the researchers to access to your exam results for the purposes of this study
- ☐ You are 18 years of age or older

_____

Participant's Name (Printed)*

_____ _____

Participant's signature* Date

_____ _____

Participant's email address Participant's telephone number

_____

Participant's address

SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	See supplementary
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	See corresponding author
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	13
Objectives	7	Specific objectives or hypotheses	5-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Figure 1, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-18, Table 1, supplementary
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20-21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20-21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13-14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set – The STOP Study

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	Clinicaltrials.gov. Identifier: NCT03062891
Date of registration in primary registry	5th December 2016
Secondary identifying numbers	NA
Source(s) of monetary or material support	Biomedical Research Centre (BRC) BioResource
Primary sponsor	King's College London
Secondary sponsor(s)	NA
Contact for public queries	Alice M. Gregory Department of Psychology Goldsmiths, University of London London, UK, SE14 6NW Email: a.gregory@gold.ac.uk Telephone: +1 541 346 4075
Contact for scientific queries	Alice M. Gregory Department of Psychology Goldsmiths, University of London London, UK, SE14 6NW Email: a.gregory@gold.ac.uk Telephone: +1 541 346 4075
Public title	The STOP Pilot Study (Sleep Treatment Outcome Predictors)
Scientific title	Sleep Treatment Outcome Predictors (STOP) Pilot Study: A randomised controlled trial examining

DATA CATEGORY	INFORMATION
	predictors of changes of insomnia symptoms and associated traits following cognitive behavioural therapy for insomnia in an unselected sample
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Symptoms of insomnia
Intervention(s)	Treatment: Online CBT for insomnia (CBT-I). CBT-I participants will receive six weekly sessions delivered by an animated 'virtual therapist (The Prof) via the online platform 'Sleepio'. The programme comprises a fully automated media-rich web application, driven dynamically by baseline, adherence, performance and progress data, and provides additional access to elements such as an online library with background information, a community of fellow users, and support, prompts and reminders sent by e-mail. Control: Puzzles. Each week participants will be sent a puzzle to complete online (e.g. logic puzzles, crosswords etc.). The puzzles have been designed to be cognitively engaging an take a similar amount of time to one session of Sleepio (20-25 minutes).
Key inclusion and exclusion criteria	Inclusion: Female, aged 18+, psychology student (undergraduate or postgraduate) at one of the three study sites. Exclusion: Male, Under 18, not a psychology student at one of the three study sites.
Study type	Interventional Allocation: randomized (stratified by baseline insomnia symptoms) Intervention model: parallel assignment Masking: No masking Primary purpose: treatment
Date of first enrolment	18th November 2016

Open access: first published as 10.1136/bmjopen-2017-017177 on 1 December 2017. Downloaded from

DATA CATEGORY	INFORMATION
Target sample size	240
Recruitment status	197 participants recruited into the study. Waves 1-3 at various stages of completion. Wave 4 to begin July 2017.
Primary outcome(s)	1. Improvement in sleep problems following online CBT as indicated by changes in insomnia symptoms and subjective sleep quality. 2. Assessment of treatment acceptability of the CBT-I in an unselected sample. 3. Participation and drop-out rates.
Key secondary outcomes	1. Predictors of response to treatment outcome. Specific predictors being: anxiety, depression, ADHD symptoms, psychotic experiences, positive mental health, stress, and threatening life events. Main statistic of interest will be effect size. 2. Improvement in sleep problems through CBT-I to be associated with improvement of symptoms in other variables. Specifically: anxiety, depression, ADHD symptoms, psychotic experiences, positive mental health, stress, and threatening life events. Main statistic of interest will be effect size.

BMJ Open

Sleep Treatment Outcome Predictors (STOP) Pilot Study: A protocol for a randomised controlled trial examining predictors of change of insomnia symptoms and associated traits following cognitive behavioural therapy for insomnia in an unselected sample

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-017177.R1
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Sleep Treatment Outcome Predictors (STOP) Pilot Study: A protocol for a randomised controlled trial examining predictors of change of insomnia symptoms and associated traits following cognitive behavioural therapy for insomnia in an unselected sample

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Abstract

Introduction: Cognitive behavioural therapy for insomnia (CBT-I) leads to insomnia symptom improvements in a substantial proportion of patients. However, not everyone responds well to this treatment and it is unclear what determines individual differences in response. The broader aim of this work is to examine to what extent response to CBT-I is due to genetic and environmental factors. The purpose of this pilot study is to examine feasibility of a design to test hypotheses focusing on an unselected sample, i.e. without selection on insomnia complaints, in order to plan a larger behavioural genetics study where most participants will likely not have an insomnia disorder.

Methods and analysis: A two parallel-group randomised controlled trial (RCT) is being conducted across 3 London universities. Female students (minimum age 18 years) enrolled on a psychology programme at one of the 3 sites were invited to participate. The target number of participants to be recruited is 240. Following baseline assessments, participants were randomly allocated to either the treatment group, where they received weekly sessions of digital CBT-I for 6 weeks, or the control group, where they completed an online puzzle each week for 6 weeks. Follow up assessments have taken place mid-intervention (3 weeks) and end of intervention (6 weeks). A 6 month follow up assessment will also occur. Primary outcomes will be assessed using descriptive statistics and effect size estimates for intervention effects. Secondary outcomes will be analysed using multivariate Generalised Estimating Equation (GEE) models.

Ethics and dissemination: The study received ethical approval from the Research Ethics and Integrity sub-committee, Goldsmiths, University of London (application reference: EA 1305). DNA sample collection for the BioResource received ethical approval from the NRES Committee South Central-Oxford (reference number: 15/SC/0388). The results of this work shall be published in peer-reviewed journals

Trial registration: Clinicaltrials.gov (identifier: NCT03062891).

Strengths and limitations

- This study contains a large sample size for a pilot study, and will provide valuable effect size information useful for the planning of future investigations of this topic.
- Stratification on sleep problems was implemented to ensure baseline sleep problems were equal in both groups.
- Recruitment was done using convenience sampling which may lead to some self-selection bias in the sample.
- The online nature of the study makes it difficult to fully assess adherence to the intervention.

Introduction

Insomnia occurs frequently and causes a substantial burden to society [1]. It is estimated that as many as one-third of US adults experience issues with their sleep, and the annual cost of insomnia to the US labour force has been estimated to be approximately $280 billion [2]. Historically, insomnia has been considered as secondary to other psychiatric disorders, such as depression [3,4]. More recently however, it has become clear that insomnia is associated with a wide range of psychiatric conditions and may precede and predict their development and severity [5–7].

Cognitive behavioural therapy (CBT) has been shown to be an effective treatment for insomnia [8,9]. Consequently, the American College of Physicians now recommends CBT for insomnia (referred to from hereonin as CBT-I) as the first choice treatment for chronic insomnia [10]. CBT-I is now more accessible than ever due to the development of automated online programmes which have shown promising effectiveness [11–13]. A randomised controlled trial of 164 participants meeting DSM-5 criteria for insomnia disorder showed significant post-treatment improvements in insomnia symptoms and sleep efficiency, for those participants assigned to a digital CBT-I group compared to a placebo [11]. These results were largely maintained at an 8-week follow-up. Following this, a meta-analysis of 15 randomised controlled trials investigating digital CBT-I found across all studies a significant improvement in sleep efficiency (7.2%) following digital CBT-I compared with baseline, and a significant drop on the insomnia severity index, bringing patients to a sub-threshold level of insomnia [13]. This reduction in insomnia symptom severity was also accompanied by a significant drop in symptoms of depression, suggesting CBT-I may also be effective for problems associated with insomnia [14].

Despite the demonstrated effectiveness of CBT-I, some individuals fail to respond to treatment. It has been suggested that CBT-I can significantly reduce symptoms of insomnia in around 70% of patients, meaning 30% of patient s show no improvement in symptoms [15]. Understanding the reasons why people either respond or do not respond to treatment holds promise of improving or tailoring current treatments for insomnia.

Investigations of predictors of treatment response to CBT applied to other conditions, such as anxiety, have shown a wide range of demographic, clinical, genetic, and epigenetic factors influence response to CBT treatment for anxiety [16–19]. Genetic predictors of treatment outcome are still unclear however. Whilst some studies have reported specific genetic markers for intervention outcome in disorders such as post-traumatic stress disorder (PTSD) [20], panic disorder [21], and social anxiety disorder [22], these findings have not always been replicated [23,24]. Whilst individually, any genetic predictor is likely to only explain a small proportion of variance in treatment outcome, understanding these multiple factors and their interactions may serve an important role in improving the outcome of therapy. The aim of this pilot study is to test the feasibility of running a larger-scale study of predictors of treatment outcome for CBT-I within a twin design, where not all participants will have insomnia.

Primary objectives

1. Sleep improvement after CBT-I in an unselected sample

To date, studies examining CBT-I have done so in the context of improving symptoms in patients diagnosed with insomnia disorder [11]. However, we plan to include both

participants with and without insomnia in the main study. In particular, as our future study is likely to focus on *twin pairs* it is inevitable that at least some of the participants in that study will not have insomnia (e.g. one participant may have insomnia but their co-twin might not). We are therefore interested to see the extent to which CBT-I has an effect in an unselected sample i.e. participants with and without an insomnia disorder. This pilot aims to establish the distributional properties of individual differences in change score on measures such as the Sleep Condition Indicator (SCI) and Pittsburgh Sleep Quality Index (PSQI) [25,26] as a result of the CBT-I intervention. The outcome of this will be used to assess the feasibility of running a larger behavioural genetics study in the future investigating genetic predictors of CBT-I outcome in an unselected sample. As we are primarily interested in change in insomnia symptoms, the SCI will be our main outcome measure for this objective (see Measures for detail).

2. Participation rate and treatment acceptability

The second aim of the study is to assess the feasibility of a digital CBT-I intervention study in a non-clinical group. For example, will participants without insomnia be willing to complete a 6-week online programme aimed at improving sleep? As such we will be closely monitoring participation (the proportion of participants who are willing to take part in the study) and drop-out rates (the percentage of participants who sign-up to the study and drop out before the end of the study). We will also examine treatment acceptability. Whilst psychological interventions to treat insomnia such as CBT-I have been rated highly by patients with regards to how acceptable they find the treatment [27,28], it is important for this study to investigate whether participants who do not necessarily have a sleep disorder, find CBT-I an acceptable treatment. This will be assessed using an adapted version of the

Treatment Acceptability Questionnaire (TAQ) [29], for more information see the Measures section.

Secondary aims

3. Factors predicting treatment outcome

We will collect data on factors that may predict treatment outcome, and will be able to use the data collected to estimate effect sizes for various predictors which will be useful in power calculations to estimate the sample size for a larger future behavioural genetics study. Furthermore, by including these measures in the pilot study it will allow us to assess the feasibility of administering a large battery of questionnaires to participants in addition to completing the digital CBT-I/puzzles.

Based on previous work into predictors of treatment outcome in CBT for anxiety [16–19], a wide range of demographic, clinical, and genetic predictors such as potential single nucleotide polymorphisms (SNP) and polygenic risk scores of response to digital CBT-I will be investigated (see Measures section for more details), for producing an estimated effect size that will be helpful in the planning of a larger study.

4. Sleep quality and implications for associated variables

Sleep quality is known to be associated with a number of other variables, such as anxiety and depression [30]. As such, one outcome of improving sleep quality through CBT-I could be an improvement of symptoms in associated variables. For example, in a meta-analysis of digital CBT-I RCT studies, it was found that digital CBT-I significantly reduced depression severity [14]. As such, digital CBT-I holds the promise of not only improving sleep problems themselves, but also the variables commonly associated with them.

Our focus here is to obtain an approximate effect size for any effect that can be used in designing a more substantial study – but we note that we may not have power to report significant effects in the context of this pilot work.

Exploratory aims of the pilot study

5. Genetic predictors of treatment outcome

We will perform preliminary analysis on possible genetic predictors of digital CBT-I treatment outcome to help in the development of hypotheses for a larger genetics study in the future. The samples will be genotyped on the Psychiatric Genomics Consortium customised HumanCoreExome-24+ v1.1 beadchip from Illumina. This beadchip retains a GWAS backbone, exome beadchip content and an additional ~50K psychiatric relevant variants. We will also perform exploratory investigations on the genetic data in relation to exploratory aim 8 (see below).

6. Mechanisms mediating improvements in insomnia

Assuming enough variation in appropriate measures, we will investigate whether factors such as pre-sleep arousal, cognitions about sleep, chronotype, and specific sleep disturbances mediate CBT-I outcome in an unselected sample.

7. Improvement in sleep paralysis episodes following CBT-I

Sleep paralysis is an unusual but relatively common condition involving a period of inability to perform voluntary movements at either sleep onset or upon awakening [31], with an estimated prevalence of up to 30% [32,33]. If enough participants with sleep paralysis are

included in our sample, we will assess the feasibility and effectiveness of digital CBT-I in the patient groups in terms of reducing the frequency of episodes, as well as associated fear and hallucinations.

8. Variables associated with exploding head syndrome

Exploding head syndrome is an unusual experience, characterised by hearing loud noises (e.g. an explosion or gunshot) in one's head at either wake-sleep or sleep-wake transitions [31]. If enough participants with exploding head syndrome are included in our study, we shall look at potentially associated variables such as insomnia symptoms, stress, and psychopathology.

Methods and analysis

Study dates

Recruitment for the study started November 2016, and data will have finish being collected by the end of September 2017. The study was retrospectively registered on 5th December 2016. The reason the trial was registered retrospectively was due to very restricted limitations on when participants could be recruited (see Participant recruitment). Unfortunately, the trial was not registered until after the first recruitment dates had passed. Rather than lose potential recruiting opportunities, we decided to register the trial retrospectively.

Design

The study is a two-group parallel randomised controlled trial in which the intervention group will receive a digital CBT-I intervention, and the control group will receive a weekly online puzzle. See the intervention section for more details.

Participants are female students (both undergraduate and postgraduate) completing a psychology programme at one of three London universities (for full details see the trial registration). After completing the baseline assessment online via the Qualtrics system, participants were randomly allocated to either the CBT-I or puzzles group. Three weeks later, participants completed a second online assessment, and then a third online assessment 6 weeks after the start of the study. Finally, a follow-up online assessment will be carried out 6 months after group allocation. Participants were also invited to give a DNA sample at the start of data collection. While we have limited statistical power to look at genetic predictors of treatment outcomes in the pilot study, these samples could be pooled with other data collected in the future, and also provide a useful opportunity for our collaborators to collect data for another ongoing research initiative [34]. See **Figure 1** for a detailed outline of the study timeline. A completed SPIRIT checklist and World Health Organisation (WHO) trial registration data set can be found in **Supplementary files 1 and 2**.

Inclusion and exclusion criteria

Only females were eligible for participation. This is because the majority of the students on the psychology courses are female, and so adding males would create heterogeneity but without sufficient power to examine this further. Furthermore, only individuals enrolled in a psychology course from one of 3 London universities were recruited due to reasons of convenience. We focused our recruitment efforts on first year students in particular, as it is possible that a small number of students in other years may have already taken part in studies using the same digital CBT-I platform [35]. In order to address this point explicitly, in the questionnaires given to participants, they were asked if they have had any experience with Sleepio before taking part in this study.

Participant recruitment

Participants were recruited to the study using a two-step procedure. Initially, potential participants were contacted via an e-mail that provided the study information, specific instructions as to the nature of the recruitment day, and contact information.

The second stage of recruitment involved a series of recruitment days at the three 3 sites. These recruitment days were timed to coincide with classes that potential participants were present at, to make it more likely that they would be in university. At sign-up, participants were given a paper copy of the information sheet and were given the option to ask any questions about the nature of the study. After confirming that they were happy to take part in the study, all participants were asked to give informed consent, provide a DNA sample (see DNA sample collection), and were assigned a unique participant ID number which was used for future assessments. To allow the participation of individuals who wished to take part in the study but were unable to sign-up in person, participants were given the option to contact the research team directly by e-mail in order to arrange providing consent to take part in the study.

Participants will be rewarded for their time, either in the form of course credits (offered credits + £5 online gift voucher) or online shopping voucher (£40), awarded to them upon completion of the study.

Randomisation and study automation

After collection of baseline data, participants were randomly allocated to either the CBT-I group or the puzzles group. A member of the research team randomised eligible participants

using the blockrand package for R [36]. Participants were stratified based upon age, sleep problems, and study site. Stratification on age was performed to assure similar age distributions in both groups. Stratification on sleep problems was implemented to avoid the possibility of a disproportionate number of participants with sleep problems being randomly allocated to the same group. Stratification for study site was implemented to avoid an unnecessary delay between completing the first questionnaire and being allocated to a group.

An automated e-mail was sent to participants to inform them of which group they had been assigned. Those in the CBT-I group were given further information as to the nature of the programme (see Digital CBT-I) as well as a unique code needed to log into the website. Those in the puzzles group were given information as to the nature of the tasks that they were required to complete (see Puzzles). Participants were not able to change groups once they have been allocated.

Intervention

Digital CBT-I

CBT-I participants received 6 weekly CBT-I sessions delivered by an animated 'virtual therapist' (The Prof) via the online platform 'Sleepio' (http://www.sleepio.com). The programme comprised a fully automated media-rich web application, driven dynamically by baseline, adherence, performance and progress data, and provides additional access to elements such as an online library with background information, a community of fellow users, and support, prompts and reminders sent by e-mail.

The Sleepio programme covers behavioural (e.g., sleep restriction, stimulus control) and cognitive (e.g., putting the day to rest, thought restructuring, imagery, articulatory suppression, paradoxical intention, mindfulness) strategies, as well as additional relaxation strategies (progressive muscle relaxation and autogenic training) and advice on lifestyle and bedroom factors (sleep hygiene). As part of the intervention, participants filled in a daily sleep diary. The intervention was based upon a previously validated manual [37–39]. Sleepio has been shown to improve sleep and associated daytime functioning in adults diagnosed with insomnia disorder [11].

Puzzles

Participants in the control group were sent weekly puzzles to complete within Qualtrics. Each puzzle was designed to be cognitively engaging, and time taken to complete a puzzle has been matched as closely as possible to the time taken to complete one session of digital CBT-I. Puzzles were sent directly to participants via automated distribution e-mails sent at 7 day intervals. In order to track whether participants were completing the puzzles, they were required to enter their participant ID number at the start of each puzzle. The types of puzzles administered to participants included word searches, crosswords, and lateral thinking problems.

Data Collection

DNA sample collection

This project was conducted in collaboration with the National Institute for Health Research (NIHR) Biomedical Research Centre (BRC) BioResource for Mental and Neurological

Health in London as part of a national NIHR initiative to build up a central library of information (or "BioBank)" about people's health.

In this study, we obtained saliva samples from our participants after obtaining consent during the recruitment days. Samples were collected by a researcher from the BioResource team in compliance with their ethically approved protocol. The BRC is the custodian of the samples received. On receipt, samples were logged and prepared for extraction of DNA. The BRC ensured that genetic samples were processed in accordance with strict health and safety guidelines and under the requirements of the Human Tissue Act (HTA). King's College London holds a HTA license, number: 12293. All samples are stored in tubes labelled with a barcode that includes the participant number. The link between the participant ID and de-identified data is kept in a secure folder. The DNA samples collected as part of this study are stored by the BRC for future analysis and hypothesis testing with appropriate ethical approval in the future, and under existing BRC BioResource approvals.

Wave 1 data collection

Eligible participants were given the option of completing the baseline survey online after signing up. Participants were encouraged to complete the survey within one week from sign-up. Paper copies were made available for participants who had problems with their device or internet access.

Participants completed all measures, as shown in **Table 1**. Participants had the option to leave out any question. The survey took 30-40 minutes to complete. At the end the survey, participants were reminded that they would be contacted with regards to future data collection.

Waves 2-4 data collection

The second and third, waves of data collection were carried out 3 weeks and 6 weeks following allocation. The fourth wave will be carried out 6 months following the allocation of participants to groups. These time points correspond to mid-intervention, end-of-intervention, and post-intervention follow-up time points respectively (see Figure 1 for more detail). Automated e-mails distributed by Qualtrics will be sent to participants at the designated intervals. Not all measures are assessed at all waves, as shown in **Table 1**. Follow-up emails to non-responders will be sent each week to participants who fall behind on their tasks (i.e. CBT-I, puzzles, or surveys).

Measures

Descriptions for all measures used are provided below. For waves 2-4 some measures were adapted to ask participants to consider their answers with reference to the last 2 weeks (unless otherwise stated below), in order to ensure participants were considering only the time since the last wave of data collection when responding. Full details on each measure used can be found in **Supplementary File 3**.

Demographic information was collected at baseline. At the start of each survey, participants were asked to indicate whether it was currently term time, exam time, or holiday time. At wave 2, participants in the Sleepio group indicated whether they had ever used Sleepio before.

Sleep measures

Insomnia symptoms – *Sleep Condition Indicator* (SCI) [25]. An 8-item measure assessing symptoms of insomnia, used to identify insomnia symptoms in community samples [40].

Sleep Quality – *Pittsburgh Sleep Quality Index (PSQI)* [26]. An 18-item questionnaire assessing 7 components of sleep quality and disturbances, which also yields a global score of sleep quality. The scale has been shown to be reliable and valid in assessing sleep quality in adult community samples [41].

Trauma-related sleep disturbances – *Pittsburgh Sleep Quality Index Addendum* [42]. Assesses frequency of 7 sleep disturbances typically related to trauma. The measure has been validated for use in assessing these disturbances [42,43].

Pre-sleep-arousal – *Pre-sleep Arousal Scale* [44]. Measures symptoms of cognitive (8 items) and somatic (8 items) arousal experienced around bedtime. It is has been validated with respect to objective measures of pre-sleep arousal [45,46].

Cognitions about sleep – *Dysfunctional Beliefs About Sleep Scale (DBAS)* [47]. A 10-item questionnaire that includes items about sleep-disruptive cognitions such as faulty beliefs, worry, and attentional bias. The measure has shown to be reliable [48].

Chronotype – *Munich Chronotype Questionnaire (MCTQ)* [49]. Chronotype is estimated as the midpoint of sleep on workdays and work-free days minus half of the difference between sleep duration on work-free days and average sleep duration of the work to control for sleep debt (i.e. the midpoint of sleep on work-free days, corrected for sleep duration). The MCTQ is a reliable and valid measure of chronotype [50,51].

Sleep paralysis – *Waterloo Unusual Experiences Questionnaire (WUSEQ*) [52]. Items from the WUSEQ were used to assess the frequency of sleep paralysis and associated hallucinations. The measure is valid and reliable in healthy student samples [53,54].

Sleep paralysis – *Fearful Isolated Sleep Paralysis Interview (FISPI)* [55]. Two items from this measure were adapted to measure the amount of fear/distress typically caused by sleep paralysis episodes, and how much interference with waking life episodes have caused. The FISPI has been used as a valid and reliable measure of sleep paralysis in university samples [56].

Exploding head syndrome – *Munich Parasomnia Screening (MUPS)* [57]. Lifetime prevalence of exploding head syndrome was measure using a single item from the MUPS.

Psychopathology and well-being measures

Anxiety symptoms – *State Trait Anxiety Index (STAI)* [58]. The STAI assesses both state (20 items) and trait (20 items) levels of anxiety, and is a valid and reliable measure of anxiety symptoms [59].

Depressed mood – *Mood and Feelings Questionnaire (MFQ)* [60]. Depressed mood was measured using the 13-item MFQ. This has been shown to be a valid measure of depressed mood.

ADHD symptomatology – Bespoke measure examined 18 symptoms of ADHD according to DSM-5 criteria [61]. This is a valid and reliable measure of ADHD symptoms, and has been

previously used to in young adults to assess ADHD symptomatology in the context of sleep quality [62].

Psychotic experiences – *Specific Psychotic Experiences Questionnaire (SPEQ)* [63]. Sub-scales relating to paranoia [64], hallucinations [65], and cognitive disorganisation [66] were used as they are strongly related with sleep disturbances [67]. The scale has been shown to have good reliability and validity [63].

Positive mental health – *Positive Mental Health Scale (PMH)* [68]. Positive aspects of health and life experiences were assessed using a 9-item questionnaire.

Life stress – *Perceived Stress Scale (PSS)* [69]. Life stress was measured with a 10-item measure. A review of articles assessing the psychometric properties of the PSS found the measure to be a reliable and valid measure of life stress [70].

Exposure to threatening events – *List of Threatening Experiences (LTE)* [71,72]. Participants were asked to indicate whether they had experienced any threatening events from a list of 24. The LTE has been shown to have high reliability and be a valid measure of exposure to potentially threatening experiences [73].

Lifestyle measures

At each wave, participants were asked about their sleeping arrangements [74], and alcohol [75] and caffeine intake [76]. Cigarette [75] and electronic (e) cigarette usage [77–79] were assessed at baseline.

Treatment acceptability

The 6-item *Treatment Acceptability Questionnaire (TAQ)* [29] asked specific questions regarding the degree to which they found the treatment acceptable, ethical, and effective. There were also specific questions about the nature of the virtual therapist. Only participants in the Sleepio group received the TAQ.

Sample size

For this study, the target was to have 200 participants, which should provide power to examining our primary research questions. Though we plan to over recruit to account for some attrition throughout the study. As such, 240 participants will be recruited. Power analyses are often conducted using hypothesised effect sizes based on mean differences (e.g. before and after treatment). However, as this is a pilot for a future behavioural genetics study, the main statistic of interest is not mean differences, but individual differences (i.e. variances). The decision to recruit 200 participants for this pilot study was mainly based on personal experiences of recruiting undergraduates from our institutions.

Statistical analysis

Primary objectives

1. CBT-I in an unselected sample

The aim is to examine variation in response to CBT-I (i.e. variation in the change score of self-reported insomnia symptoms, as measured by the SCI). To this end we will obtain an effect size for the difference in change scores between the two groups on the SCI scale.

Previous RCTs using the SCI as an outcome measure have observed a large effect size (Cohen's d = 1.50) when comparing baseline score to post-treatment score [11]. It is possible in our sample the effect size will be smaller, given the fact that participants won't necessarily meet insomnia criteria. Nevertheless, a small effect is still expected.

We will then look at differences between groups, by comparing the percentage of participants who finish with SCI scores in different ranges. We will also look how many participants score below and above the suggested cut-off score for probable insomnia symptoms. Previous data suggests a cut-off of 16, with a score below that meaning probable symptoms of insomnia [25]. Furthermore, we will calculate the percentage of participants in the digital CBT-I group that will be above the mean score of the control group (Cohen's U_3), the percentage of the two groups that overlap, and the probability that one person picked at random from the digital CBT-I group will have a higher score than a person picked at random from the control group (the probability of superiority) [80].

2. Participation rate and treatment acceptability

Evaluation of participation rate and treatment acceptability will be based on the descriptive statistics i.e. percentage of participants who sign up to the study and complete it, the percentage from each group who drop out at each stage, and mean scores on treatment acceptability questionnaire. Ninety-five percent confidence intervals for participation rate and acceptability scores will be calculated, which will show the upper and lower bound values of where the true population parameter will appear. Formal tests will be conducted to compare participant rates between the two groups (chi-square analysis). For treatment acceptability, chi-square tests will test the proportion of participants selecting each response option.

Secondary objectives

3 & 4. Factors predicting treatment outcome and sleep quality and implications for associated variables

We will test which measures at baseline are moderators of longitudinal outcome of change scores in insomnia symptoms with multivariate Generalised Estimating Equation (GEE) models using Akaike/Bayesian information criterion (A/BIC) criteria to select an optimal model with predictors of insomnia symptoms/sleep quality derived. All models will be run in Stata and control for covariates (e.g. age) and the non-independence of sibling-pair data. Missing data shall be accounted for using maximum likelihood or multiple imputation procedures. Due to the small sample size, power may not be sufficient to investigate interaction effects. However, they shall be performed as an exploratory analysis.

Ethics, consent, confidentiality, and data security

All stages of the study received ethical approval from the Research Ethics and Integrity sub-committee at Goldsmiths, University of London (application reference: EA 1305). DNA sample collection for the BioResource received ethical approval from the NRES Committee South Central-Oxford (reference number: 15/SC/0388). All participants were asked to provide informed consent before participating. It was made explicit that participation in the study is voluntary, that participants can choose not to answer questions if they do not want to, that they had the right to withdraw from the study at any point, and that their data would remain confidential. Participants were informed of the intention to publish results from this study using their data, and agreed to this in the informed consent. Copies of questionnaire booklets given to participants are not publically available due to copyright restrictions on some of the measures.

All identifying information is stored in a password protected document. Survey responses are automatically stored in Qualtrics. No identifying information is stored with response data. Data in Qualtrics is secured using industry best standards (https://www.qualtrics.com/security-statement/). At the end of data collection, datafiles for each wave of the study shall be downloaded off of Qualtric's servers and stored in SPSS. At this point, the datafiles will be removed from Qualtrics. Only researchers directly involved in the analysis of data will have access to participant data. The final, anonymised datasets from each wave of the study shall be available upon reasonable request from the corresponding author upon completion of the study.

Dissemination of findings

Results of this trial will be disseminated primarily via peer-reviewed journal publications. It is expected that the primary, secondary, and exploratory aims 5 and 6 of this study will be reported in a single publication. Other findings of exploratory aims will be published separately. The results of this study will also be available on the ClinicalTrials.gov website when they become available.

Strengths and weaknesses of the protocol

A key strength of the study is the use of an online CBT-I intervention. The online feature of this intervention is important as it provides easy access for participants. Furthermore, by using an automated system, there is no need for participants to interact with a CBT therapist during the intervention. This makes it a more efficient programme than face-to-face CBT which means that it is more feasible to administer to a large sample. It also means that everyone gets the same experience. Examining treatment acceptability for digital CBT-I in a

non-selected sample represents a novel investigation that will yield important findings for future researchers wishing to look at this intervention in non-clinical populations. Exploration of potential mechanisms underlying changes in insomnia symptoms is also a strong aspect of this study, as it will contribute to our knowledge of how CBT-I works in reducing symptoms.

Weaknesses include selection bias in the sample. It is possible that those who already suffer from sleep problems (despite not necessarily having an insomnia disorder) are more likely to take part in the study, although recruitment e-mails emphasised that participants did not have to suffer from any sleep problems to take part. Our convenience sample is also not a representative one, meaning that it may be hard to generalise findings to other populations. Relatedly, it is conceivable that psychology students as compared to others, may react differently, and rate the effectiveness differently, to a psychological therapy.

Judging study success

When considering whether the study will be successful (i.e. what results will suggest that a larger, behavioural genetics study is warranted), multiple variables will be considered. These will be the participation rates, treatment acceptability, and effect size. As everything will be looked at together, strict criteria will not be set.

Competing interests

The position of AIL at the University of Oxford is funded by Big Health Ltd, the company behind the digital CBT-I program evaluated in this study. CAE is the co-founder and CMO of Big Health Ltd and holds shares in Big Health Ltd. AMG has provided guidance and educational content for a freely available educational website focused on infant sleep. This website is partially supported by Johnson and Johnson, but they do not have any influence over content and do not advertise on it. She also contributes to BBC Focus Magazine.

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Author contributions

Study conception and design: TCE, FR, HMSZ, RK, AIK, CAE, JH, MH, AMG

Acquisition of data: DD, HMSZ, RK, AIL, IB, SD, AR, AMG

Future analysis of data: DD, FR, SD

Preparation of manuscript: All authors

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Table 1. Schedule of enrolment, interventions, and assessments made at each wave

	Measures	Enrolment	Wave 1 Baseline	Allocation	Wave 2 (3 weeks) Mid-assessment	Wave 3 (6 weeks) End-assessment	Wave 4 (6 months) Follow-up
Enrolment							
Eligibility screening		X					
Informed consent		X					
Saliva DNA sample		X					
Allocation				X			
Interventions							
CBT-I					X	X	
Puzzles					X	X	
Assessments							
Demographics			X				
Medical history			X				
Weight and height			X			X	X
Time of year			X		X	X	X
Sleep measures	SCI		X		X	X	X
	PSQI		X		X	X	X
	PSQI-A		X			X	X
	PSAS		X		X	X	X
	DBAS		X		X	X	X
	MCTQ		X			X	X
	WUSEQ		X			X	X
	FISPI		X			X	X
	MUPS		X				
Well-being measures	STAI		X		X	X	X
	MFQ		X		X	X	X
	ADHD		X			X	X

	SPEQ	X		X	X
	PMH	X	X	X	X
	PSS	X	X	X	X
	LTE	X	X	X	X
Lifestyle measures	Sleeping arrangements	X	X	X	X
	Alcohol intake	X	X	X	X
	Caffeine intake	X	X	X	X
	Smoking behaviour	X			
	Vaping behaviour	X			
Treatment acceptability	TAQ[1]		X	X	

PSQI = Pittsburgh Sleep Quality Index, SCI = Sleep Condition Indicator, PSQI-A = Pittsburgh Sleep Quality Index – Addendum, PSAS = Pre-sleep Arousal Scale, DBAS = Dysfunctional Beliefs About Sleep Scale, MCTQ = Munich Chronotype Questionnaire WUSEQ = Waterloo Unusual Experiences Scale, FISPI = Fearful Isolated Sleep Paralysis Interview, MUPS = Munich Parasomnia Screening, STAI = State/Trait Anxiety Index, MFQ = Moods and Feelings Questionnaire, ADHD = Attention Deficit Hyperactivity Disorder, SPEQ = Specific Psychotic Experiences Questionnaire (paranoia, hallucinations, and cognitive disorganisation sub-scales), PMH = Positive Mental Health Scale, PSS = Perceived Stress Scale, LTE = List of Threatening Experiences.

[1] Only administered to the Sleepio group.

Figure 1 – Flowchart of study timeline

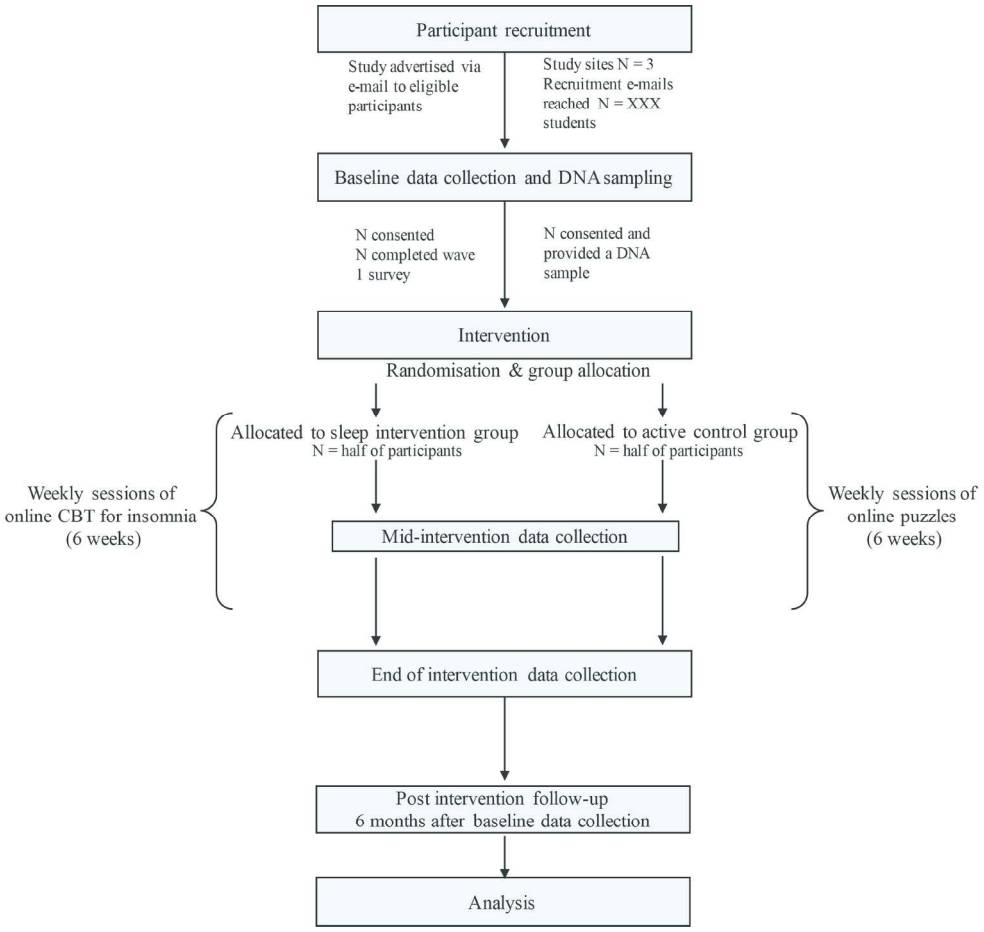

Figure 1 - Flowchart of study timeline

191x176mm (300 x 300 DPI)

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	See supplementary
Protocol version	3	Date and version identifier	N/A
Funding	4	Sources and types of financial, material, and other support	22
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	See corresponding author
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	22
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	N/A

Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4-5
	6b	Explanation for choice of comparators	13
Objectives	7	Specific objectives or hypotheses	5-9
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	9
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	9
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	10
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	12-13
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	N/A
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	10-11, 14
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	5-9
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	14, Figure 1, Table 1

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	19
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	10-11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	11-12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	11-12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	15-18, Table 1, supplementary
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11, 14

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20-21
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	19-20
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N/A
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	N/A
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	N/A
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N/A
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20-21
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	N/A

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	20-21
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	13-14
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20-21
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	22
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	21
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	21-22
	31b	Authorship eligibility guidelines and any intended use of professional writers	22
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

WHO Trial Registration Data Set – The STOP Study

DATA CATEGORY	INFORMATION
Primary registry and trial identifying number	Clinicaltrials.gov. Identifier: NCT03062891
Date of registration in primary registry	5th December 2016
Secondary identifying numbers	NA
Source(s) of monetary or material support	Biomedical Research Centre (BRC) BioResource
Primary sponsor	King's College London
Secondary sponsor(s)	NA
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Public title	The STOP Pilot Study (Sleep Treatment Outcome Predictors)
Scientific title	Sleep Treatment Outcome Predictors (STOP) Pilot Study: A randomised controlled trial examining

DATA CATEGORY	INFORMATION
	predictors of changes of insomnia symptoms and associated traits following cognitive behavioural therapy for insomnia in an unselected sample
Countries of recruitment	United Kingdom
Health condition(s) or problem(s) studied	Symptoms of insomnia
Intervention(s)	Treatment: Online CBT for insomnia (CBT-I). CBT-I participants will receive six weekly sessions delivered by an animated 'virtual therapist (The Prof) via the online platform 'Sleepio'. The programme comprises a fully automated media-rich web application, driven dynamically by baseline, adherence, performance and progress data, and provides additional access to elements such as an online library with background information, a community of fellow users, and support, prompts and reminders sent by e-mail. Control: Puzzles. Each week participants will be sent a puzzle to complete online (e.g. logic puzzles, crosswords etc.). The puzzles have been designed to be cognitively engaging an take a similar amount of time to one session of Sleepio (20-25 minutes).
Key inclusion and exclusion criteria	Inclusion: Female, aged 18+, psychology student (undergraduate or postgraduate) at one of the three study sites. Exclusion: Male, Under 18, not a psychology student at one of the three study sites.
Study type	Interventional Allocation: randomized (stratified by baseline insomnia symptoms) Intervention model: parallel assignment Masking: No masking Primary purpose: treatment
Date of first enrolment	18th November 2016

DATA CATEGORY	INFORMATION
Target sample size	240
Recruitment status	197 participants recruited into the study. Waves 1-3 at various stages of completion. Wave 4 to begin July 2017.
Primary outcome(s)	1. Improvement in sleep problems following online CBT as indicated by changes in insomnia symptoms and subjective sleep quality. 2. Assessment of treatment acceptability of the CBT-I in an unselected sample. 3. Participation and drop-out rates.
Key secondary outcomes	1. Predictors of response to treatment outcome. Specific predictors being: anxiety, depression, ADHD symptoms, psychotic experiences, positive mental health, stress, and threatening life events. Main statistic of interest will be effect size. 2. Improvement in sleep problems through CBT-I to be associated with improvement of symptoms in other variables. Specifically: anxiety, depression, ADHD symptoms, psychotic experiences, positive mental health, stress, and threatening life events. Main statistic of interest will be effect size.

Details of measures

Demographics

Questions were asked regarding the participant's age, date of birth, sex, and ethnicity at the start of the study. They were also asked to report on educational attainment e.g. the number of secondary school education exams taken (General Certificate of Secondary Education (GCSE)/A-levels or international equivalents), and specific grades received during A-level exams or their non-UK equivalent. Participants were also asked to indicate other qualifications received, as well as number of bachelors (e.g. BSc/BA), masters (e.g. MSc), and doctoral degrees (e.g. PhD).

Weight and height

Participants were asked to report their weight either in kilograms or stone. They were also asked to report their height in either centimetres or feet and inches.

Medical history

Participants were asked to rate how good they thought their health was generally, on a 5-point scale ranging from excellent to poor. They were asked whether they had ever been diagnosed by a medical professional with any mood disorders e.g. "*Anxiety or panic disorder"* or nervous system problems e.g. *"Schizophrenia"*. For each illness, they can select either yes or no. If a participant is currently diagnosed with any other psychological or physical illnesses not listed, they were asked to list them.

Use of either prescription medications, and/or use of over the counter, alternative medications, vitamins, minerals, herbal, or other supplements over the last 6 months was assessed by either answering yes, no, or don't know. If a participant has been using any of these, they were asked to name the substances being taken, the reason for use, and whether they took it regularly or occasionally.

Term, exam, or holiday period

At each wave participants were asked: *"At the moment, is it…"*, and chose one of 3 responses. These were: term time, exam time, or holiday time.

Sleep measures

Sleep Condition Indicator (SCI) [1] – In this 8-item questionnaire, participants consider a typical night in the last month and rate various aspects of their sleep including sleep onset, awakenings, perceived sleep quality, the effect of poor sleep on various aspects of life, and the length of their sleep. Higher scores are indicative of better sleep, and scores <= 16 indicate probable insomnia disorder. The SCI is valid, reliable and sensitive to change in insomnia severity [1]. It has been used to identify insomnia symptoms in community samples [2].

Pittsburgh Sleep Quality Index (PSQI) [3] – The PSQI is an 18-item questionnaire assessing 7 components of sleep quality and disturbances (subjective sleep quality, sleep efficiency, sleep disruption, use of sleeping medications, and daytime dysfunction). The scale yields an overall 'global' score of sleep quality, as well as component scores for each of the 7 facets of sleep quality and disturbances assessed, with a higher score indicating greater sleep problems. The

scale has been shown to be reliable and valid in assessing sleep quality in adult community samples [4].

Pittsburgh Sleep Quality Index Addendum (PSQI-A) [5] – Items included in this measure assess sleep disturbances typically related to trauma (disruptive nocturnal behaviours). The frequency of 7 disruptive nocturnal behaviours (e.g. memories or nightmares of a traumatic experience) are assessed with the PSQI-A. The frequency of each disruptive nocturnal behaviour is assessed on a scale ranging from never to 5-7 nights per week, with higher scores indicating a higher frequency of disruptive nocturnal behaviours. The PSQI-A has been shown to be a valid and reliable measure of sleep disturbances related to trauma [5,6].

Pre-sleep Arousal Scale (PSAS) [7] – The PSAS is a 16-item questionnaire measuring symptoms of cognitive (8 items e.g. intrusive thoughts) and somatic (8 items e.g. sweating) arousal experienced around bedtime. Each item is answered on a 5-point scale ranging from not at all to extremely. The scores from each item are summed to create a pre-sleep arousal score for both cognitive (PSAS-C) and somatic (PSAS-S) pre-sleep arousal. For both sub-scales, higher scores indicate greater levels of pre-sleep arousal. The PSAS has been shown to be a valid measure of pre-sleep arousal, and is comparable with objective measures of pre-sleep arousal [8,9].

Dysfunctional Beliefs About Sleep Scale (DBAS-10) [10] – This measure includes questions about sleep-disruptive cognitions such as faulty beliefs, worry, and attentional bias. There are a total of 10 items, and each is answered on a 5-point scale ranging from not at all to extremely. A global score is calculated based on all 10 items, with higher scores indicating higher levels of

dysfunctional beliefs about sleep. Three sub-scales can also be calculated, relating to: 1 – beliefs about the immediate negative consequences of insomnia, 2 – beliefs about the long-term negative consequences of insomnia, and 3 – beliefs about the need to try harder to sleep. The measure has been shown to be a reliable measure of cognitions about sleep [11].

Munich Chronotype Questionnaire (MCTQ) [12] – The MCTQ is a 14-item questionnaire focused primarily on sleep timing, with questions assessing the regularity of one's work schedule, number of workdays per week, sleep timing on workdays and work-free days, and use of an alarm clock on workdays and work-free days. Chronotype is estimated as the midpoint of sleep on workdays and work-free days minus half of the difference between sleep duration on work-free days and average sleep duration of the work to control for sleep debt (i.e. the midpoint of sleep on work-free days, corrected for sleep duration). Importantly, chronotype can only be calculated when individuals do not use an alarm clock on work-free days. The MCTQ is a reliable and valid measure of chronotype [13,14].

Waterloo Unusual Experiences Questionnaire (WUSEQ) [15] – Items for the WUSEQ were used to assess the frequency of sleep paralysis and associated hallucinations. Frequency of sleep paralysis was assessed via the item *"Sometimes when falling asleep or when waking from sleep, I experience a brief period during which I am unable to move, even though I am awake and conscious of my surroundings"*. This is answered on a 7-point scale ranging from never to several times a week. Those who indicated experiencing sleep paralysis at least once are asked follow-up questions about the frequency with which they experience associated hallucinations, on a 4-point scale from never to always. Three categories of sleep paralysis hallucinations are

assessed: intruder, incubus and vestibular-motor [16]. The WUSEQ has been shown to be valid and reliable measure of sleep paralysis frequency and associated hallucinations in healthy student samples [16,17].

Fearful Isolated Sleep Paralysis Interview (FISPI) [18] – Two items from the FISPI were included to assess the amount of fear/distress typically caused by sleep paralysis episodes, and how much interference with waking life sleep paralysis episodes have caused. For each item, participants respond on a scale from none, to very severe. Only participants who report experiencing at least one episode of sleep paralysis will answer these items. The FISPI has been used as a valid and reliable measure of sleep paralysis in university samples [19].

Munich Parasomnia Screening (MUPS) [20] – The lifetime prevalence of exploding head syndrome was measured using a single item from the MUPS. Participants are asked if they had ever noticed the following behaviour: *"When falling asleep or waking, perceiving a loud bang, a sound similar to a bang (e.g. door bang), or having the sensation of an "explosion in the head"".* This item was answered on a scale ranging from never observed, to very frequently (every/almost every night). The MUPS is a valid measure for recognising nocturnal behaviours and parasomnias [20].

Psychopathology and well-being measures

State Trait Anxiety Index (STAI) [21] – The STAI assesses both state and trait levels of anxiety. *State* anxiety was measured using 20 items in which participants were asked to rate the way that

they feel at the present moment (e.g. *"I feel calm", "I am presently worrying over possible misfortunes"*). Each item was assessed on a scale ranging from not at all, to very much so. Higher scores are indicative of greater state anxiety. *Trait* anxiety was measured using 20 items in which participants were asked rate the extent to which they generally feel (e.g., *"I make decisions easily", "I worry too much over something that really doesn't matter"*), on a scale ranging from not at all, to very much so. Higher scores are indicative of greater trait anxiety. The STAI has been shown to be a reliable and valid measure of anxiety symptoms [22].

Mood and Feelings Questionnaire (MFQ) [23] – Depressed mood was measured using the 13-item MFQ. Participants rated the way that they had felt or acted during the past two weeks (e.g. *"I felt miserable and unhappy"*, *"I found it hard to think properly or concentrate"*) on a 3-point scale (not true, sometimes, true). A higher score is indicative of a higher depressed mood over the last 2 weeks. This has been shown to be a valid measure of depressed mood [24].

ADHD – This bespoke measure examined symptoms of attention deficit hyperactivity disorder (ADHD) according to DSM-5 criteria [25]. Participants were asked about 18 symptoms of ADHD according to DSM-5 criteria. Each item is responded as either a yes or no answer. A higher score is indicative of greater ADHD symptomatology. This is a valid and reliable measure of ADHD symptoms, and has been previously used to in young adults to assess ADHD symptomatology in the context of sleep quality [26].

Specific Psychotic Experiences Questionnaire (SPEQ) [27] – The SPEQ measures 6 facets of psychotic experiences. For this study, sub-scales relating to paranoia [28], hallucinations [29],

and cognitive disorganisation [30] were used. These sub-scales were selected based upon prior work showing that these 3 aspects of psychotic experiences are most strongly associated with sleep disturbances in a community sample [31]. As space for questionnaire measures was limited, the 5-highest loading items from each of the 3 sub-scales were selected for inclusion [27]. The paranoia and hallucinations sub-scales were scored on a scale ranging from not at all, to daily, whilst items on the cognitive disorganisation subscale were scored as either yes or no. On all scales, a higher score reflected greater frequency of psychotic experiences. The scale has been shown to have good reliability and validity [27].

Positive Mental Health Scale (PMH) [32] – Positive mental health was assessed using the 9-item PMH. The scale assesses positive aspects of health and life experiences (e.g. *"I am often carefree and in good spirits"*, and *"I am in good physical and emotional condition"*). Each item was answered on a 4-point scale ranging from do not agree to agree. An overall mean score is derived, with a higher score indicating greater positive mental health. The reliability and validity of the measure has been shown to be good [32].

Perceived Stress Scale (PSS) [33] – This 10-item scale was used to measure stress. Participants rated the extent to which they had felt and thought in a certain way over the past month (e.g. *"How often have you felt confident about your ability to handle your personal problems"*), on a scale ranging from never to very often. All items are summed to create an overall score with higher scores indicating a greater level of perceived stress over the past month. A review of articles assessing the psychometric properties of the PSS found the measure to be a reliable and valid measure of life stress [34].

List of Threatening Experiences (LTE) [35,36] – Participants were asked to indicate whether they had experienced any threatening life events from a list of 24. Example events include: *"Been in hospital with a serious illness or injury"*, *"Death of a child or spouse"*, and *"Been sacked from a job"*. For each event, participants were asked to indicate whether they had experienced it recently, answering either yes or no. Scores are summed to create an overall exposure to threatening life events score, with a higher score indicating exposure to a greater number of different threatening events. The LTE has been shown to have high reliability and be a valid measure of exposure to potentially threatening experiences [37].

Lifestyle measures

Sleeping arrangements – Participants were asked 2 questions relating to their sleeping arrangements. They were: 1 – *"During the past month, who usually sleeps in the same room as you"*, and 2: *"During the past month, who usually sleeps in the same bed as you"*. Responses options for both items were: nobody, partner, baby/child, other. These items have been used previous work examining sleep in a healthy sample [38].

Alcohol intake [39] – This was assessed by four items: 1 – *"Do you drink?"* (scored as either yes or no), 2 – *"When you have an alcoholic drink, how many drinks do you have?"* (scale ranged from 1 to 8 or more, with one alcoholic drink being ½ pint of beer or lager/one glass of wine/one glass of spirits/one alcopop), 3 – *"How often do you have an alcoholic drink?"* (scale ranged from once or twice a year to almost every day), and 4 – *"During the last 30 days, how many times did you have five or more alcoholic drinks on the same occasion"* (scale included: four or

more times, three times, twice, once, I have not had five or more drinks on the same occasion in the past month, I have never had five or more drinks on the same occasion). Using items 2 – 4, average alcohol intake in terms of units of alcohol consumed per week can be calculated.

Caffeine intake [40]– The number of caffeinated drinks consumed per day for the last month was assessed. The drinks included were freshly brewed coffee (one shot espresso = one cup), instant coffee, caffeinated tea, and caffeinated soft drinks. The number of each drink type consumed ranged from 0, to 8 or more. The number of each drink type consumed is then recoded to reflect the amount of caffeine present in each type of drink, in order to calculate a score of total caffeine intake.

Smoking behaviour [39] – Three items were used to assess smoking behaviour: 1 – *"Do you smoke?"* (scored as yes, no, or used to but have given up), 2 – *"How often do you smoke cigarettes?"* (scale ranging from every day to once a month), and 3 – *"On the days that I do smoke, I smoke ... cigarettes"* (response options are: 1-5, 6-10, 11-15, 15-20, more than 20). The latter two questions are then used to calculate the number of cigarettes smoked per week.

Vaping behaviour – A bespoke measure of electronic (e) cigarette usage was used based on items from previous studies of e-cigarette usage [41–43]. Usage is assessed using 6 items: 1 – *"Do you use an electronic cigarette (e-cigarette)?"* (scored as either yes or no), 2 – *"How many days have you used an e-cigarette in the past two weeks?"*, 3 – *"Each time you use the e-cigarette, how many puffs do you inhale?"*, 4 – *"What strength of e-cigarette liquid do you use?"* (options are: 0 mg/l, 6 mg/ml, 12 mg/ml, 16mg/ml, 18 mg/ml, 26 mg/ml, other, don't know), 5 – *"How*

many cartridges/refills do you use per day?", and 6 – *"How long does a refill/cartridge typically last (hours)?"*.

Treatment acceptability

Treatment Acceptability Questionnaire (TAQ) [44] – The TAQ is a 6-item measure assessing the treatment acceptability of psychological treatments for adult populations. Participants in the digital CBT-I group are asked the degree to which they find the treatment acceptable, ethical, effective, and likelihood of negative side effects on a 7-point scale, with a lower number indicating lower treatment acceptability. They are also asked two questions specifically about the nature of the therapist, regarding how knowledgeable and trustworthy participants judge them to be. These items are answered using the same 7-point scale, and were adapted for use with a virtual CBT-I therapist used in this study. The measure has been shown to be reliable and valid [44].

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