Study Title: Targeting insomnia to treat depression: An explanatory randomised controlled trial of sleep restriction therapy

Internal Reference Number / Short title: Randomised Evaluation of Sleep Treatment to Ease Depression (RESTED)

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Disclosures

CAE is co-founder of and shareholder in Big Health Ltd., a company which specialises in the digital delivery of cognitive behavioural therapy for sleep improvement (the Sleepio programme), outside the present project. All other authors declare no competing interests.

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Protocol Date and Version No: insert

Protocol signature page

The undersigned has read and understood the trial protocol detailed above and agrees to conduct the trial in compliance with the protocol.

Principal Investigator (Please print name)	**Signature**	**Site name or ID number**	**Date**

Following any amendments to the protocol, this page must be updated with the new protocol version number and date and re-signed by the site PI.

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1. KEY CONTACTS

Table 1: Table of key contacts

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2. LAY SUMMARY

WHY IS THIS RESEARCH IMPORTANT?

Depression is a very common and impairing condition. Current treatments include antidepressant medication and psychological therapy. Both can be effective, but more than one-third of people do not benefit from these treatments. There are reasons to think that poor sleep is an important contributor to depression, and that if sleep could be improved, depression would improve too.

WHAT DO WE WANT TO FIND OUT?

Previous research has shown that we can improve sleep quality using a behavioural treatment called 'sleep restriction therapy'. This treatment involves reviewing the patient's current sleep pattern and supporting them to follow a new, personalised sleep schedule. We want to find out whether using this treatment to improve sleep will also improve depression and, if so, how it works.

HOW WILL WE DO THIS?

We plan to recruit patients from general practice who experience symptoms of both sleep disruption (insomnia) and depression. We will identify people in two main ways. GPs will search medical records and send out study invitations. They will also make patients aware of the study during consultations. Patients who are interested in taking part in the study will be asked to complete two short questionnaires and a phone interview with a member of the research team to determine if the study is suitable for them. Eligible participants will be allocated at random, by a computer, to one of two groups. One group will receive the behavioural sleep treatment alongside any existing treatment they are receiving for depression or sleep. This will involve meeting with a nurse each week for 6 weeks and following a personalised daily sleep schedule. The treatment aims to reduce awakenings during the night and encourage a more regular sleep pattern. The second group will not receive a specific treatment as part of the study but will continue to receive any existing treatment for depression or sleep. All participants will complete assessments at baseline (before the random allocation of treatment), and at 1 month, 2 months and 6 months. This will help us to determine whether the treatment has worked. We will measure symptoms of depression using a questionnaire and ask participants to complete computerised tasks that assess responses to emotional words and images. We will measure sleep quality using questionnaires, daily sleep diaries and actigraphy (a watch-like device that measures movement and therefore can indicate when one is asleep or awake). We will also collect information on medication prescriptions and any other treatments participants may access during the study. Importantly, at all stages of the study, five members of the public with experience of poor sleep and depression will act as advisors to the research team. This will ensure that our research takes into account the needs and views of patients, and that our findings can be translated to the NHS in a meaningful way. At the end of the study, we will send all participants a summary of the findings, publish our results in scientific journals, and work with the university's media office and the Mental Health Foundation to share our work with the broader public.

WHAT MIGHT BE THE IMPACT OF OUR RESEARCH?

Our study will provide clear evidence on whether improving sleep quality improves depression. Our research may lead to new ways of treating depression in the future and provide important knowledge on how sleep and mental health are connected.

3. SYNOPSIS

Table 2: Study synopsis

Study Title	Targeting insomnia to treat depression: An explanatory randomised controlled trial of sleep restriction therapy		
Internal ref. no. / short title	**R**andomised **E**valuation of **S**leep **T**reatment to **E**ase **D**epression **(RESTED)**		
Study registration	ISRCTN:73764282		
Sponsor	University of Oxford Research Governance, Ethics & Assurance Team (RGEA) University of Oxford, Boundary Brook House, Churchill Drive, Headington, Oxford OX3 7GB		
Funder	National Institute for Health and Care Research – Efficacy and Mechanism Evaluation Programme (NIHR:EME)		
Study Design	Individually randomised, parallel group, randomised controlled trial (RCT)		
Study Participants	Adults aged ≥18 years with insomnia and major depression		
Sample Size	250 patients [135 SRT(+TAU); 115 standalone TAU]		
Planned Study Period	Total length of project: 30 months		
Planned Recruitment period	1st December 2022 – 31st March 2024		
	Objectives	Outcome Measures	Timepoint(s)
Primary	To compare the effect of SRT+TAU versus TAU on depression severity at follow-up	Self-reported depression severity via the Patient Health Questionnaire-9 (PHQ-9)	26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on depression severity at mid and post-treatment	Self-reported depression severity via the Patient Health Questionnaire-9 (PHQ-9)	4- and 8-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on insomnia severity at mid-treatment, post-treatment, and follow-up	Self-reported insomnia severity via the Insomnia Severity Index (ISI)	4-, 8- and 26weeks post-randomisation.

Secondary	*Mediation hypothesis:* To examine if insomnia improvement mid-treatment (week 4) mediates the treatment effect on depression	Self-reported insomnia severity via the Insomnia Severity Index (ISI)	Mediation analysis will be ISI at week 4 as mediator of PHQ-9 at 26 weeks post-randomisation

	severity at follow-up (week 26)		
Secondary	To compare the effect of SRT+TAU versus TAU on actigraphy-estimated sleep and rest-activity pattern (measured over 1 week) at post-treatment and follow-up	Sleep onset latency (SOL); Wake After Sleep Onset (WASO); Sleep Efficiency (SE); Total Sleep Time (TST); Relative Amplitude (RA); Interdaily Stability (IS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on emotional processing bias at post-treatment and follow-up	Oxford Emotional Test Battery: Facial Expression Recognition Task (FERT); Emotional Categorisation Task (ECAT); Emotional Recall Task (EREC)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on positive and negative affect at post-treatment and follow-up.	Positive and Negative Affect Schedule (PANAS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on repetitive negative thinking at post-treatment and follow-up	Perseverative Thinking Questionnaire (PTQ)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on behavioural activation at mid-treatment, posttreatment and follow-up	Behavioural Activation for Depression Scale (BADS)	4-, 8- and 26weeks post-randomisation
Secondary	Mediation hypothesis: To examine if reduction in insomnia at mid-treatment (week 4), drives increased behavioural activation at the end of treatment (week 8), which in turn mediates the treatment effect on depression at follow-up (week 26)	ISI, BADS, PHQ-9	4-,8-, and 26weeks post-randomisation

Secondary	To compare the effect of SRT+TAU versus TAU on self-reported sleep and daily activation (over 1 week)	Consensus Sleep Diary (CSD) -Sleep diary parameters: Sleep onset latency (SOL); Wake-time After Sleep Onset (WASO); Sleep Efficiency (SE); Total Sleep Time (TST); Sleep Quality (SQ); Time in Bed (TIB);	8- and 26-weeks post-randomisation
		Time to bed (TTB); Time out of Bed (TOB) -Level of daily activation computed from evening component of sleep diary	
Secondary	To compare the effect of SRT+TAU versus TAU on psychological well-being	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on cognitive complaints	British Columbia Cognitive Complaints Inventory (BC-CCI)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on pre-defined adverse events	Suicidal ideation (PHQ9 item) and accidents (bespoke questionnaire)	4, 8 and 26-weeks post-randomisation
Tertiary	To compare the effect of SRT+TAU versus TAU on daytime activity levels and light exposure (1 week)	Gross and threshold levels of activity and light exposure quantified from actigraphy and measures of their phase	8- and 26-weeks post-randomisation
Intervention(s) **SRT + TAU**	6-session behavioural sleep intervention SRT(+TAU), delivered by trial nurses		
Comparator **TAU**	Participants randomised to TAU will continue to access treatments for depression (or insomnia). There will be no restriction on usual care in either trial arm.		

4. ABBREVIATIONS

Table 3: Table of abbreviations

AE	Adverse event
AR	Adverse reaction
BADS-SF	Behavioural Activation for Depression Scale (Short form)
BC-CCI	British Columbia Cognitive Complaints Inventory
BDI	Beck Depression Inventory
CACE	Compiler Average Causal Effect
CI	Chief Investigator
CSRI	Client Service Receipt Inventory
CRF	Case Report Form
CSD	Consensus Sleep Diary
DMC	Data Monitoring Committee
DMP	Data Management Plan
ECAT	Emotional Categorisation Task
EMEM	Emotion
FERT	Facial Expression Recognition Task
GCP	Good Clinical Practice
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
IRB	Independent Review Board
IS	Interdaily Stability
ISI	Insomnia Severity Index
NIHR:EME	National Institute for Health and Care Research: Efficacy and Mechanism Evaluation Programme
NHS	National Health Service
PANAS	Positive and Negative Affect Schedule

PC-CTU	Primary Care Clinical Trials Unit
PHQ-9	Patient Health Questionnaire-9
PSQI	Pittsburgh Sleep Quality Index
RCT	Randomised Controlled Trial
PTQ	Perseverative Thinking Questionnaire
PI	Principal Investigator
PIS	Patient Information Sheet
R&D	NHS Trust R&D Department
RA	Relative Amplitude
REC	Research Ethics Committee
RGEA	Research Governance, Ethics and Assurance team
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SCID-5	Structured Clinical Interview for DSM-5
SDV	Source Data Verification
SE	Sleep Efficiency
SISQ	Single-Item Screening Question [for substance use]
SOL	Sleep Onset Latency
SOP	Standard Operating Procedure
SRT	Sleep Restriction Therapy
SUSAR	Suspected Unexpected Serious Adverse Reactions
TAU	Treatment As Usual
TIB	Time in bed
TIDieR	Template for Intervention Description and Replication checklist
TMF	Trial Master File

TSC	Trial Steering Committee
TST	Total Sleep Time
WASO	Wake After Sleep Onset
WEMWBS	Warwick-Edinburgh Mental Wellbeing Scale

5. BACKGROUND AND RATIONALE

Depression is one of the leading causes of disability worldwide. It has a 12-month prevalence of approximately 6% and causes substantial impairment to the individual and society – costing over £11 billion in lost workdays alone. The majority of people with depression in the UK are managed in primary care, typically with antidepressant medication or through referral to psychological therapy (e.g., the Improving Access to Psychological Therapies [IAPT] programme). Effect sizes for antidepressants and psychotherapy are in the small-to-medium range (1, 2); and the former are associated with increasingly recognised side-effects (3). More than one third of patients do not respond to existing depression treatments and clinical outcomes have not improved over the last three decades (4). Patients prefer psychological approaches, but access – while improving – continues to be limited relative to high disorder prevalence (5). Innovation with respect to novel treatment targets, delivery methods, and optimisation of outcomes is clearly required in the depression field.

Clinical science and laboratory manipulations suggest a key role for sleep in the expression of psychiatric symptoms. The most common sleep disorder is insomnia disorder, defined as chronic problems with sleep initiation or maintenance leading to impaired daytime function and reduced quality of life (6). Insomnia characterises more than 85% of patients with depression (7) and features as one of the key symptoms listed in diagnostic nosologies. Experimental disruption of sleep in good sleepers decreases positive affect, increases negative affect, and impairs emotion regulation (8). Moreover, prospective studies show that insomnia is associated with the future onset of depression (9), while poor sleep quality on a given night predicts increased severity of next-day suicidal thoughts in those with depression (10). Clinical trial evidence also demonstrates that 1) pre-treatment insomnia severity is associated with blunted response to depression intervention, and 2) insomnia is one of the most common residual symptoms after "successful" depression treatment; the presence of which is associated with future relapse back into depression (11). Effectively managing insomnia in the context of depression could directly ameliorate depressive symptoms, help improve engagement with and outcomes from ongoing depression treatment and reduce risk of future relapse. This latter point is important because depression is increasingly viewed as a relapsing-remitting condition with approximately 50% of patients experiencing relapse after their initial episode (12).

Sleep Restriction Therapy (SRT) is a key part of multicomponent CBT for insomnia, which is the recommended treatment modality for insomnia disorder. SRT involves both restricting and regularising time in bed in order to reduce wakefulness during the night and consolidate sleep. It counters behaviours that perpetuate insomnia, specifically time-in-bed extension, variability in sleep-wake timing, and daytime napping. Weekly adjustment of prescribed time-in-bed helps to establish a robust sleep-wake pattern, improve sleep quality, reduce pre-sleep cognitive arousal, and ameliorate sleep-related daytime dysfunction.

The current trial proposes to rigorously test for the first time if a brief, six-session, standalone SRT treatment programme can treat depression through insomnia reduction. We will randomise participants with insomnia and depression to 6-session SRT (plus treatment as usual [TAU]) or TAU. The primary hypothesis is that SRT + TAU compared with TAU will lead to a reduction in depressive symptoms at 26 weeks follow-up. We will test whether reduction in insomnia at mid-treatment (week 4) mediates

reduction in depression at 26 weeks follow-up. This trial will also investigate the mechanistic pathways that may explain the effect of insomnia reduction (through SRT) on depressive symptoms. We hypothesise that, at post-treatment (week 8), SRT will lead to 1) consolidation of objectively estimated sleep; 2) enhanced stability and amplitude of circadian rest-activity rhythms; 3) reduced negative emotion processing bias; 4) increased positive affect/reduced negative affect; 5) reduced repetitive negative thinking and 6) increased behavioural activation. We will examine whether change in these putative mechanisms subsequently mediate depression outcome at week 26. We will also test a serial mediation hypothesis that reduction in insomnia at mid-treatment (week 4) predicts increased behavioural activation at post-treatment (week 8), which in turn mediates depression outcome at follow-up (week 26).

6. OBJECTIVES AND OUTCOME MEASURES

Table 4: Summary of study objectives and outcome measures

	Objectives	Outcome Measures	Timepoint(s)
Primary	To compare the effect of SRT+TAU versus TAU on depression severity at follow-up	Self-reported depression severity via the Patient Health Questionnaire-9 (PHQ-9)	26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on depression severity at mid and post-treatment	Self-reported depression severity via the Patient Health Questionnaire-9 (PHQ-9)	4- and 8-weeks post randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on insomnia severity at mid-treatment, post-treatment, and follow-up	Self-reported insomnia severity via the Insomnia Severity Index (ISI)	4-, 8- and 26weeks post-randomisation.
Secondary	Mediation hypothesis: To examine if insomnia improvement mid-treatment (week 4) mediates the treatment effect on depression severity at follow-up (week 26)	Self-reported insomnia severity via the Insomnia Severity Index (ISI)	Mediation analysis will be ISI at week 4 as mediator of PHQ-9 at 26 weeks post-randomisation

Secondary	To compare the effect of SRT+TAU versus TAU on actigraphy-estimated sleep and rest-activity pattern (measured over 1 week) at post-treatment and follow-up	Sleep onset latency (SOL); Wake After Sleep Onset (WASO); Sleep Efficiency (SE); Total Sleep Time (TST); Relative Amplitude (RA); Interdaily Stability (IS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on emotional processing bias at post-treatment and follow-up	Oxford Emotional Test Battery: Facial Expression Recognition Task (FERT); Emotional Categorisation Task (ECAT); Emotional Recall Task (EREC)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on positive and negative affect at post-treatment and follow-up.	Positive and Negative Affect Schedule (PANAS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on repetitive negative thinking at post-treatment and follow-up	Perseverative Thinking Questionnaire (PTQ)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on behavioural activation at mid-treatment, post-treatment and follow-up	Behavioural Activation for Depression Scale (BADS)	4-, 8- and 26weeks post-randomisation
Secondary	Mediation hypothesis: To examine if reduction in insomnia at mid-treatment (week 4), drives increased behavioural activation at the end of treatment (week 8), which in turn mediates the treatment effect on depression at follow-up (week 26)	ISI, BADS, PHQ-9	4-,8-, and 26weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on self-reported sleep and	Consensus Sleep Diary (CSD) -Sleep diary parameters:	8- and 26-weeks post-randomisation

	daily activation (over 1 week)	Sleep onset latency (SOL); Wake-time After Sleep Onset (WASO); Sleep Efficiency (SE); Total Sleep Time (TST); Sleep Quality (SQ); Time in Bed (TIB); Time to bed (TTB); Time out of Bed (TOB) -Level of daily activation computed from evening component of sleep diary	
Secondary	To compare the effect of SRT+TAU versus TAU on psychological well-being	Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on cognitive complaints	British Columbia Cognitive Complaints Inventory (BC-CCI)	8- and 26-weeks post-randomisation
Secondary	To compare the effect of SRT+TAU versus TAU on pre-defined adverse events	Suicidal ideation (PHQ9 item) and accidents (bespoke questionnaire)	4, 8 and 26-weeks post-randomisation
Tertiary	To compare the effect of SRT+TAU versus TAU on daytime activity levels and light exposure (1 week)	Gross and threshold levels of activity and light exposure quantified from actigraphy and measures of their phase	8- and 26-weeks post-randomisation

7. STUDY DESIGN

The study will utilise an individual, randomised, parallel group, clinical trial design within primary care. There will be a 4-month internal pilot phase, after which "Stop-Go" criteria will be used to evaluate feasibility of recruitment and treatment fidelity (see Section 9.11). Participants will be identified from general practice (GP) records. We will aim to recruit up to 250 participants. On completion of baseline assessments participants will be randomised to SRT+TAU or TAU alone. SRT treatment will involve six weekly sessions with a trained research nurse. TAU may include existing treatment regimen for depression (and insomnia). There will be no restriction upon usual care for either group. Usual care for depression is likely to be antidepressant medication and/or referral to psychological therapy services. Usual care for insomnia is likely to be no treatment, general sleep advice, hypnotics or sedative antidepressants. We will record usual care during the trial. Outcomes will be assessed at baseline, 4-, 8- and 26-weeks post randomisation. The window of opportunity for participants to complete assessments at each time-point will be as follows: 4 weeks (+14 days), 8 weeks (+28 days), 26 weeks (+28 days). The primary outcome will be the between group difference in self-rated depression severity, using the PHQ-9 questionnaire at 26 weeks. Patient participation in the study will last six months from randomisation to last participant data capture.

8. PARTICIPANT IDENTIFICATION

8.1. Study Participants

Participants aged 18 years and above who meet criteria for major depressive disorder and insomnia disorder will be recruited from general practice. Practice records will be searched for people with a history of low mood/depression or treatment for depression. Individuals who are interested in the study will undergo eligibility appraisal, involving screening questionnaire completion and structured clinical interview, to determine whether full study inclusion and exclusion criteria are met.

8.2. Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the trial.
- Aged 18 years or above.
- Screen positive for depressive symptoms on the PHQ-9 (≥10) and meet criteria for major depressive disorder, assessed via the Structured Clinical Interview for DSM-5 (SCID-5)
- Screen positive for insomnia symptoms on the sleep condition indicator and meet criteria for insomnia disorder
- Self-reported sleep efficiency <85% over the past month, assessed via the Pittsburgh Sleep Quality Index (PSQI)
- Able to attend appointments for assessments and treatment and adhere to study procedures
- The participant's GP surgery is participating in the trial

8.3. Exclusion Criteria

The participant may not enter the trial if ANY of the following apply:

- Female participant who is pregnant or planning pregnancy during the course of the trial.
- Additional sleep disorder diagnosis OR "positive" on screening questionnaire (e.g., OSA, RLS)
- Dementia or mild cognitive impairment (MCI)
- Alcohol or substance-use dependent
- Epilepsy
- Psychosis (schizophrenia, bipolar disorder)
- Currently or recently received in-patient psychiatric treatment within the past 2 months
- Current suicidal ideation with intent OR attempted suicide within past 2 months
- Currently receiving cancer treatment OR planned major surgery during treatment phase
- Night, evening, early morning or rotating shift work
- Currently receiving psychological treatment for insomnia from a health professional or taking part in an online treatment programme for insomnia
- Previously received sleep restriction therapy from a health professional
- Life expectancy of <1 year
- Another person in the household already participates in this trial
- Currently taking part in another clinical trial which could affect outcomes in RESTED
- Recruiting clinician deems not suitable for the trial

9. PROTOCOL PROCEDURES

9.1. Recruitment

GP practices will be used to recruit trial participants. As well as recruiting participants through routine consultations, practices will search their databases according to the eligibility criteria, and telephone, write via letter, email or text potentially eligible individuals to invite them to take part in the trial. Posters will be placed in the GP practice and/or associated pharmacy.

Letter invitation: Participants who receive a letter will be provided with a participant pack containing a letter inviting them to take part alongside the participant information sheet (PIS), a consent-to-be-contacted form, and a brief questionnaire to confirm insomnia and depression inclusion and the absence of shift work (see section 9.2). To ensure we engage with people for whom the study may be both relevant and suitable, we will make clear in both the invitation letter and the participant information sheet the main exclusions and ask participants to complete a questionnaire to determine eligibility. The invitation letter will outline the different methods that participants can respond with, which include:

a) Returning the consent-to-be-contacted form and questionnaire measure in a (provided) stamp-addressed envelope. For those who would like to be contacted and meet insomnia/depression/shift work criteria, a researcher will subsequently call the participant to go through the remainder of the eligibility questionnaire;

b) Contacting the study team directly so that eligibility can be assessed (i.e. a researcher will go through the screening questionnaire with the participant over the phone or via MS Teams, whichever is preferred by participant);

c) Going to a study website and completing the full eligibility questionnaire online (a URL link for which will be included in the invitation letter);

Text/Email invitation: Participants who receive a text or an email will receive a link to the screening

form. They will be able to complete the screening form directly on their mobile telephone. They will also receive a link which will take them to the study website where they can download the participant information sheet and also find contact details for the trial team including the study email address and telephone number, so that they can contact the trial team to be assessed if they do not wish to complete the screening form online, or so that they can ask questions about the trial.

- Reminders will be sent by the practice to those identified from initial searches of their practice lists and repeat searches may be run during the trial to identify new participants for whom the study may be suitable. Practices will be asked to ensure that participants who ask not to be contacted are not sent repeat letters. In addition to practice letter or text message invitation, we will also engage potential participants through: 1) placement of poster adverts in local pharmacies; 2) posting study adverts on the internet (e.g., Facebook, practice websites, twitter), in newspaper/print and broadcast media; 3) placement of brief study information on printed prescriptions; 4) Engaging with local businesses and charities to ask them to display posters or promote the trial on their websites and on social media accounts; 5) Engaging with local businesses and charities to ask them to display posters or promote the trial on their websites and on social media accounts; and 6) Running a stand outside practices, or placing an unmanned stand within practices with flyers and posters explaining about the trial
-

. To limit the possibility that participants are overwhelmed with direct study invitations we will endeavour to invite participants a maximum of three times (this can include a combination of letter and text/email but will not exceed three direct contacts in total inclusive of the original invitation letter).

9.2. Screening and Eligibility Assessment

The screening and eligibility assessment will involve two stages:

Stage 1: Identified potential participants will be invited to complete a screening questionnaire to appraise key inclusion/exclusion criteria. The screening questionnaire will be presented to potential participants via their preferred method of communication, or a hybrid of preferred methods as outlined in Section 9.1. Potential participants will be asked to consent to completing the screening questionnaire, which at the end will ask participants (if eligible) to provide identifying information (full name, email address, phone number, name of GP surgery) in order to schedule stage 2. We will also ask participants how they found out about the trial for more effective monitoring of trial recruitment strategies. This information will be reviewed by the trial management group (TMG) regularly during the trial to inform and guide recruitment approaches.

The screening questionnaire comprises the following items and measures to assess key inclusion/exclusion criteria at stage 1, which are shown in Table 5, below:

Table 5: Inclusion/exclusion criteria at stage 1 of screening

Inclusion Criterion	**Assessed by**
GP Practice	List of GP practices open to study
Age	Reported age
Depressive symptoms	PHQ9 (>=10)
Insomnia symptoms	SCI
Sleep efficiency <85%	PSQI items 1+3 [difference score=TIB]/PSQI item 4 [TST]*100
Exclusion Criterion	
Pregnant/pregnancy planning, diagnosis of sleep disorder, dementia or MCI, epilepsy, schizophrenia or bipolar disorder, currently or recently received in-patient psychiatric treatment, cancer treatment or planned major surgery during treatment phase, life expectancy <1 year, currently receiving psychological treatment for insomnia or online treatment programme, previously received sleep restriction therapy,	Yes/No response
Shift work	Bespoke questionnaire item

Stage 2: For those meeting the above criteria a brief interview will be arranged with a trained member of the research team. The interview will take place over the phone, online, or in-person at the participating GP surgery, to further ascertain study eligibility. We will also ask whether the participant has access to a computer or tablet and an internet connection at home for operational purposes.

The interview at stage 2 will appraise the following inclusion/exclusion criteria, which are shown in table 6, below:

Table 6: Inclusion/exclusion criteria at stage 2 of screening

Inclusion Criterion	**Assessed by**
Major depressive episode	SCID-5 (13)
Insomnia disorder	Bespoke questions mapping onto DSM-5 diagnostic criteria
Exclusion Criterion	
Recent history of suicide attempt and current suicidal ideation and intent	C-SSRS (14)
Substance use dependence over the past 12 months	SISQ (15) and SCID-5 (13)
Alcohol dependence	AUDIT (16) (>=14 Female/>=16 Male) and clinical judgement
Additional sleep disorder symptoms	Sleep Disorders Screen administered as semi-structured interview (40)
Taking part in additional clinical trial	Bespoke item
Another member of household taking part	Yes/No

A baseline visit will be scheduled for all potential participants meeting all eligibility criteria (within 4 weeks of eligibility assessment) where they will complete baseline questionnaires, tasks from the Oxford Emotional Test Battery, and be provided with a sleep diary and actigraph watch to wear for the next 7 days.

Rescreening: If it is not possible to arrange a participant baseline within 4 weeks of the clinical interview section of the eligibility assessment, participants will be rescreened to ensure they are still eligible before the baseline assessment takes place. Rescreening may either take place prior to or at the baseline visit, whichever is more convenient for the participant. Re-screening for stage 1 will also take place if the time between stage 1 and stage 2 is more than 8 weeks.

9.3. Informed Consent

The participant will receive the PIS detailing no less than: the exact nature of the trial; and the known side effects and risks involved in taking part. It will be clear that the participant is free to withdraw from the trial at any time, without the need to provide a reason and in knowledge of the fact that withdrawing from the trial will not affect their future care from their healthcare provider. Adequate time will be given to the participant to consider the information and to ask any questions about the trial before deciding whether to participate. Written or remote informed consent will then be obtained by means of a conversation between the participant and researcher at the baseline visit by means of participant dated signature and dated signature of the person who presented and obtained the informed consent, or in the case of remote informed consent, dated signature of the person who witnessed and obtained the informed consent. Written informed consent or informed e-consent will be obtained in instances where the participant and the person obtaining consent are meeting face-to-face; informed e-consent will be obtained in instances where this meeting is not conducted face-to-face (i.e. remotely). The type of consent form used will be at the discretion of whether the participant chooses an in-person meeting or online meeting for the baseline visit. The person who obtains consent will be qualified and experienced and be authorised to do so by the chief investigator (CI). A copy of the signed informed consent will be given to the participant; a copy will be retained in the medical notes and the third copy in the investigator site file. Where a paper consent form is used, the participant must personally sign and date the latest approved version of the Informed Consent Form (ICF) or the researcher must sign and date the latest approved version of remote ICF before any study specific procedures are performed. Where electronic consent is used, the participant will complete the electronic consent form themselves, and a copy will be emailed to the participant.

9.4. Randomisation

Following baseline assessments, participants will be eligible for randomisation. Eligible participants will be randomised to SRT+TAU (135 participants) or TAU (115 participants) using a secure, validated and compliant web-based randomisation system (Sortiton), with a non-deterministic minimisation algorithm to ensure practice, use of antidepressant medication (yes/no), current receipt of psychological therapy for depression (yes/no), age (18-65yrs vs. >65yrs), sex (male/female/other), baseline insomnia severity (ISI score: <22 vs. 22-28) and depression severity (PHQ-9 score: <19 vs. 19-27) are balanced across the two groups. Individual randomisation is appropriate because the risk of control group contamination is very low: treatment will be delivered by trained research nurses who will be independent from the practice and will only interact with participants in the experimental arm.

9.5. Blinding and codebreaking

The study is an open label trial. The participants and nurses will know the treatment allocation due to the design of the study. Treatment providers (i.e. nurses delivering SRT) will not be involved in the collection of trial outcomes. Outcomes (questionnaires, actigraphy, computer tasks) will be self-completed, limiting the possibility of observer/interviewer bias. Communication from the research team to participants, post-randomisation, will be limited to collection of outcome assessments and not therapeutic procedures. Should participants want to complete questionnaire outcomes over the phone, we will ensure that the researcher is blind to group allocation. Actigraphy data will be scored by a researcher who will be blind to group allocation.

9.6. Description of study intervention(s), comparators and study procedures (clinical)

9.6.1. Description of study intervention (SRT+TAU)

Participants randomised to the intervention arm will be offered nurse-delivered insomnia therapy in the form of sleep restriction therapy (SRT), a manualised behavioural intervention (see Appendix D for detailed description of the intervention included as a TIDieR checklist (Template for Intervention Description and Replication [ref]). SRT will be in addition to TAU. SRT will be delivered by trained nurses over six brief weekly sessions and participants in the intervention arm will receive a booklet at the first session. The six sessions will comprise three in-person sessions (1/3/5) and three remote sessions (2/4/6), although all sessions could be delivered remotely if needed (e.g., due to participant preference, scheduling difficulties, COVID restrictions, or room availability at practice).

Nurses will complete an "intervention checklist" at the end of each session, to 'sign off' coverage of key treatment ingredients and indicate start/end times to ensure standardisation of dose. To enable fidelity assessment, SRT sessions will be audio recorded, if participants provide informed consent at baseline. A sample of these will then be rated by a member of the research team.

To permit quantification of patient adherence to SRT guidance, sleep diaries completed during the intervention phase will be returned to the research team.

Nurse training of SRT and supervision: Suitably experienced members of the team will deliver manualised training to research nurses, covering sleep and insomnia, depression, the interaction between sleep and depression, and SRT. The team has an extensive track record of delivering SRT training in the context of trial evaluation but also to a range of health professionals through educational programmes (e.g., Oxford Online Programme in Sleep Medicine, Doctorate in Clinical Psychology), workshops, books and CPD events. Training will involve a 2-day workshop consisting of informational delivery and structured review and discussion of example clinical vignettes. All nurses will be trained to adhere to a manual and will be provided with a list of FAQs to enable troubleshooting of potential issues that may arise during patient consultations.

9.6.2. Description of comparator(s)

Participants randomised to the control group will receive TAU only. It is anticipated that participants receiving TAU will have been prescribed antidepressant medication(s) by their GP and/or have been referred to local IAPT or other psychological therapy services. Usual care for insomnia is likely to be general sleep advice, hypnotics, or sedative antidepressants. We will record TAU in both trial arms.

9.7. Baseline Assessments

The researcher will answer any questions that participants may have, remind them that that they are free to withdraw from the study at any point and obtain written or remote informed consent (depending on whether baseline is in person or remotely). The baseline meeting will take place at a location most convenient for the participant and may include, for example, general practice or participant home. If in-person meeting is not possible the research team can hold the baseline appointment remotely over Teams and collect remote informed consent. An electronic case report form (e-CRF) will be used to record information for each participant. Should the researcher be unable to access the e-CRF on the computer, a paper copy of the CRF may be used and data entered by researcher into the trial database at the earliest convenience.

The researcher will collect basic demographic data, medication/comorbidity data, and ask participants to complete self-report questionnaires (related to sleep, depressive symptoms, and functioning; see Table 7 below) and computerised tasks that examine emotional processing bias [Facial Expression Recognition Task (FERT; 17), Emotional Categorisation Task (ECAT; 17), and Emotional Recall Task (EREC; 17) from the Oxford Emotional Test Battery].

Briefly, the Oxford Emotional Test Battery is a computerised assessment of cognitive-emotional processing, which has shown sensitivity to depression and its pharmacological and behavioural treatment. The following 3 tasks will be administered (see appendix E for examples):

- *FERT:* faces with six different basic emotions (happiness, fear, anger, disgust, sadness, surprise) are displayed on a screen and participants are asked to identify the emotion in each face as quickly and accurately as possible by selecting a corresponding button. The task takes approximately 15 minutes to complete (5 minutes per block). The primary FERT outcomes are accuracy for sad and happy facial expressions, defined as the percentage of accurately identified faces for each emotion (Number of correct responses for each emotion)/(Number of faces of each emotion).
- *ECAT:* the ECAT assesses speed to respond to positive and negative self-referent personality descriptors. Participants are asked whether they would 'like' or 'dislike' to be referred to as each characteristic. The task takes approximately 5 minutes to complete. Mean reaction time for correct responses for positive and negative words will be considered as the main outcomes for this task. THE ECAT also serves as the stimulus set for the subsequent free recall (see EREC below).
- *EREC:* Participants are asked to write down (type) as many of the words previously presented in the emotional categorisation task (ECAT), in a 2-minute interval. The recall of emotional words gives a measure of bias for both positive and negative words. The main outcome measures are number of positive and negative self-referent words correctly recalled.

Participants will be provided with an actigraph watch (a device which measures movement to infer sleep/wake periods and environmental light exposure) and instructions on its use. The researcher will review instructions with the participant to ensure they are clear on its use and ask them to wear the watch for the next seven days. Concurrently, participants will record a modified daily sleep diary (CSD; 25) for seven days to capture nightly subjective sleep and daytime activation. On completion, participants will return the diary and watch through either 1) recorded-delivery postage; 2) direct delivery to the researcher's office or local practice; or 3) arrange for the researcher to collect directly from the participant.

On return of sleep diary and actigraph watch, participants will be randomised by a member of the research team to either SRT+TAU or standalone TAU. The SRT+TAU group will meet with the trained nurse on six occasions over approximately an eight-week period to receive guidance on the rationale and implementation of SRT (see *Interventions* below).

Questionnaires will be collected electronically unless the server is unavailable or a participant requests to complete the questionnaire in paper form. Tasks will be completed on a study laptop if held in person, or completed online using the participant's device (e.g., laptop, desktop, or tablet) if the visit is completed remotely.

Table 7: Data collection at baseline visit

1.	*Demographic and clinical information*	Post code*, sex, age, marital status, level of education, ethnicity, self-reported height and weight (BMI), number of episodes of depression, age of onset of first depression episode, antidepressant treatment (type/dose) and duration, psychological therapy for depression, insomnia duration, insomnia treatment, medical conditions (records)
2.	*Self-report questionnaires (assessing depression, insomnia, level of activation, affect, repetitive thinking, wellbeing, cognitive complaints)*	*Patient Health Questionnaire-9 (PHQ-9;* 18*), Insomnia Severity Index* (ISI; 19), *Behavioural Activation Scale for Depression – Short Form* (BADS-SF; 20), *Positive and Negative Affect Schedule (PANAS;* 21*), Perseverative Thinking Questionnaire (PTQ;* 22*), Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS;* 23*); British Columbia Cognitive Complaints Inventory (BC-CCI;* 24*)*
3.	*Oxford Emotional Test Battery*	*FERT; ECAT; EREC*
4.	*Subjective sleep and daytime activation*	Adapted sleep diary (CSD; 25) completed daily for 1 week – providing information on sleep timing, continuity, and quality, and daytime activation (4 items from the BADS-SF [20])
5.	*Objective estimates of sleep*	Actigraph watch (MotionWatch 8, CamNTech Ltd.) worn for 1 week – providing information on objective estimates of sleep timing and continuity, daytime activity and light exposure
6.	*Adverse events*	Adverse effects [pre-defined as accidents, falls, and near misses while driving, and suicidal ideation (item 9 from PHQ9)]
*Will be converted to an index of multiple deprivation score and the demographic variables will be presented by group at baseline for descriptive purposes only.		

9.8. Subsequent Assessments

Following the baseline assessment, participants will have follow-up assessments at 4-, 8-, and 26-weeks post-randomisation. The window of opportunity for participants to complete assessments at each timepoint will be as follows: 4 weeks (+14 days), 8 weeks (+28 days), 26 weeks (+28 days). For each follow-up, a member of the research team will notify participants (through e.g., call, text, email or letter) that their assessment is due (see Table 8 for breakdown of outcomes collected at each time-point).

Depending on participant preference (which will be ascertained at baseline), and to optimise retention, questionnaire outcome measures can be completed electronically through web-based survey (participants will be sent the link to access), over the phone with the research team, or using a paper version. Should participants want to complete questionnaire outcomes over the phone, we will ensure that the researcher is blind to group allocation. A sleep diary and actigraph watch will be posted to all participants (at 8 weeks and 26 weeks) along with a pre-paid return envelope for sending back to research team. Computer tasks (i.e. FERT, ECAT, and EREC) at 8 and 26 weeks can be completed remotely by the participant at home, over the internet (using the e-Pro system). If the participant does not have access to their own device or prefers

to complete the tasks in person with the researcher present, they may complete the task with a researcher at a convenient location (e.g. GP practice, home).

A description of the primary and secondary outcomes for the trial are listed below. Table 8 details what outcomes are assessed at the follow-up assessment points.

Primary clinical outcome: The primary outcome is self-reported depression severity at 26 weeks post-randomisation measured with the PHQ-9. The PHQ-9 is a nine-item (0-27 score) measure of depressive symptoms that is widely used in primary care mental health and is sensitive to change (26). A cut-off score ≥10 shows good sensitivity and specificity for major depression, while a >20% reduction in score is suggested to be the minimal clinically important difference (27). The PHQ-9 will also be completed by participants at mid-treatment (i.e. 4-weeks post-randomisation) and post-treatment (8-weeks post-randomisation).

Secondary mechanistic outcomes:

- Objective estimates of sleep and circadian rest-activity rhythms: measured using actigraphy (Motionwatch 8, Camntech Ltd.) over 7 days to derive estimates of sleep continuity, as well as non-parametric circadian rhythm metrics of relative amplitude (RA) and interdaily stability (IS) of rest-activity.
- Emotional processing bias: Facial Expression Recognition Task [FERT] for the perception of social cues and the Emotional Categorisation Task [ECAT] and Emotional Recall Task [EREC] for memory of affective word stimuli [from the Oxford Emotional Test Battery (17, 28)] (See appendix E for examples)
- Positive and negative affect: Positive and Negative Affect Schedule (PANAS; one-week version; (21))
- Repetitive negative thinking: Perseverative Thinking Questionnaire (PTQ; 22)
- Behavioural activation: Behavioural activation for depression scale-Short

Form (BADS-SF; 20)

Secondary clinical outcomes:

- Insomnia severity assessed with the insomnia severity index (ISI; 19)
- Self-reported sleep and daytime activity assessed prospectively: consensus sleep diary (CSD; 25)
- Psychological well-being: Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS (23))
- Cognitive complaints: British Columbia Cognitive Complaints Inventory (BC-CCI (24))

- Secondary safety outcomes:
- Adverse events: Falls, accidents (road-traffic and work-related), near-miss driving incidents, and falling asleep while driving; and suicidal ideation (item 9 from the PHQ9).

Tertiary (exploratory) outcome:

- Daytime activity levels and patterning of light exposure: derived from wrist-worn actigraphy

Table 8: Data collection at *4-, 8-, and 26- weeks post-intervention*

Collection time-point	***Measure***
4-weeks (+14-day window) post-randomisation	• Questionnaires: PHQ-9; ISI; BADS-SF; adverse events
8-weeks (+28-day window) post-randomisation	• Questionnaires: PHQ-9; ISI; PANAS; PTQ; BADS-SF; WEMWBS; BC-CCI; adverse event questionnaire • Computerised tasks: FERT; ECAT; EREC • Sleep and daytime activity diary (CSD) • Actigraphy (7 days)

9.9. Trial Process Evaluation

Quantitative data collection in relation to nurses and treatment sessions: We will collect data about the number of nurses trained and the number of participants treated per nurse; number of SRT appointments attended per participant (face-to-face and/or telephone) and duration of appointments (mins); prescribed sleep window times for each intervention week for each participant; completion rate of sleep diaries during intervention; and intervention adherence (number of nights per week participant adheres [within 15 mins] to prescribed bed and rise-time).

9.10. Early Discontinuation/Withdrawal of Participants

Each participant has the right to withdraw from the trial at any time, without the need to provide a reason and in knowledge of the fact that withdrawing from the trial will not affect their future care from their healthcare provider. However, de-identified data that have already been collected and incorporated in the study database will be included in the analysis (and any personally identifiable data will be destroyed). In addition, the Investigator may discontinue a participant from the trial (or intervention) at any time if the Investigator considers it necessary for any reason including, but not limited to:

- Ineligibility (either arising during the trial or retrospectively)
- For safety reasons, rendering participation in the trial or intervention inappropriate

In the event of an investigator withdrawal, the reason will be recorded on the eCRF.

A participant may wish to discontinue their treatment and/or withdraw from follow-up data collection. If a participant wishes to discontinue their treatment, the study team will contact the participant and ask if they are still willing to participate in the collection of follow-up data. Participants that continue to participate in follow-up data collection will not be considered a withdrawal. If a participant wishes to

withdraw from follow-up data collection, data collected up to the point of withdrawal will still be used, as detailed in the PIS.

The reason for withdrawal, if provided, will be recorded on the eCRF.

No participants will be replaced if they are discontinued or withdraw.

9.11. Internal Pilot Phase and Stop-Go Criteria

We will incorporate a four-month internal pilot phase to test trial procedures and determine trial progression against measurable "stop-go" criteria in consultation with the Trial Steering Committee (TSC) and NIHR. Trial progress in relation to recruitment and retention will be monitored monthly by the Trial Management Group (TMG). If progress is below target, remedial strategies will be implemented (e.g., recruitment of additional practices and trained nurses).

Pre-specified stop/go criteria (see Tables 9 and 10 below) will be assessed by the Trial Steering Committee (TSC) in relation to recruitment (at the end of month 4) and treatment session fidelity (at the end of month 8). We aim to recruit 63 participants within four months of the first participant being randomised.

Table 9: "Stop-Go" Recruitment Criteria

Recruitment Criteria (% of target n=63 at month 4)	Number of participants recruited	Proposed Action
100%	63	Progress to main trial phase
50-99%	32-62	Discuss progress with TSC and NIHR:EME and implement strategies (e.g., recruitment of additional practices and/or nurses)
<50%	<32	Consider stopping trial, discuss with TSC and NIHR:EME

Table 10: "Stop-Go" Treatment Fidelity Criteria

Treatment Fidelity Criteria (available complete session recordings assessed at month 8)	Proposed Action
≥70% of SRT elements are covered	Progress to main trial phase
60-69% of SRT elements are covered	Discuss with TSC and NIHR:EME, implement strategies (e.g., nurse re-training, additional nurses)
<60% of SRT elements are covered	Consider stopping trial, discuss with TSC and NIHR:EME

9.12. Definition of End of Study

The end of the study will be the last data capture of last participant.

10. SAFETY REPORTING

10.1. Serious Adverse Event Definition

A serious adverse event (SAE) is any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- Consists of a congenital anomaly or birth defect.

All participants, and the research nurses facilitating SRT, will be prompted to self-report SAEs. Along with self-reporting of SAEs, we will also ask participants about unplanned hospitalisations (as opposed to elective procedures or planned admissions for treatment) as part of the assessments at 4, 8, and 26 weeks, and follow-up participants who report being hospitalised.

We will record planned hospital admissions at baseline and when they occur, these will not be counted as SAEs. SAEs will be assessed for severity, seriousness, and relatedness to study procedures by a medically qualified member of the team. SAEs will be reported and followed up from date of randomisation until either the date of trial withdrawal or 26-week follow-up completion, whichever is earlier. Any SAEs that are continuing at trial withdrawal or 26-week follow-up completion will be marked as “Continuing” at the end of the study.

Other adverse events that require medical intervention may also be considered a serious adverse event when, based upon appropriate medical judgement, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

NOTE: The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

10.2. Reporting Procedures for Serious Adverse Events

A serious adverse event (SAE) occurring to a participant will be reported to the REC that gave a favourable opinion of the study where in the opinion of the Chief Investigator the event was ‘related’ (resulted from administration of any of the research procedures) and ‘unexpected’ in relation to those procedures. Reports of related and unexpected SAEs should be submitted within 15 working days of the Chief Investigator becoming aware of the event, using the HRA report of serious adverse event form (see HRA website). Any SAEs that are continuing at trial withdrawal or 26-week follow-up completion will be marked as “Continuing” at the end of the study.

10.3. Other Adverse Events

We will record incidences of falls, accidents (road-traffic accidents and work-related injuries), near miss driving incidents, and falling asleep while driving alongside outcomes at baseline, 4-, 8-, and 26-weeks post-randomisation. We will also assess proportion of each group showing an increase in suicidal ideation using item 9 from the PHQ9. As above, these outcomes will be assessed at baseline, 4-, 8-, and 26-weeks post-randomisation.

11. STATISTICS AND ANALYSIS

11.1. Statistical Analysis Plan (SAP)

Analyses will be described in detail in a Statistical Analysis Plan (SAP). All analyses will be conducted in accordance with PC-CTU SOPs. Our main planned analyses are summarised below.

11.2. Description of the Statistical Methods

In accordance with CONSORT guidelines, we will record and report participant flow. Descriptive statistics of recruitment, drop-out, and completeness of interventions will be provided. The primary analysis will be according to randomised treatment assignment and will include all randomised participants for whom data are available, as defined by protocol eligibility. Baseline variables will be presented by randomised group using frequencies (with percentages) for binary and categorical variables and means (and standard deviations) or medians (with lower and upper quartiles) for continuous variables. There will be no tests of statistical significance nor confidence intervals for differences between groups on any baseline variables. The results from the trial will be presented as comparative summary statistics (difference in proportions or means) with 95% confidence intervals. All tests will be done at a 5% two-sided significance level. The study results will be reported in accordance with the CONSORT 2010 statements and a full detailed statistical analysis plan will be prepared before recruitment starts.

The primary comparison is the mean difference in the primary outcome (PHQ-9 score) at 26 weeks for all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received or compliance of intervention. A multi-level model will be fitted to the data with PHQ-9 score at 4-, 8- and 26-weeks post-randomisation, adjusting for minimisation factors and baseline score. Practice and participant will be included as random effect and an interaction term for the treatment by time interaction will allow the treatment effect to differ at each time point. “Therapist effect” (i.e. effect from the intervention being delivered by the same nurse) will also be considered in the model. A similar approach will be used for secondary (mechanistic) outcomes. Numbers of participants who experienced serious adverse events will be compared in the safety population using Chi-square or Fisher’s exact test. Pre-specified subgroup analyses of the primary outcome will be explored by baseline depression severity, insomnia severity, and antidepressant medication use at baseline.

Causal mediation analysis with bootstrap confidence intervals will be carried out to estimate the indirect effect of treatment on depression at 26 weeks via insomnia (ISI) at 4 weeks. We will use measures collected at all time-points to estimate the direct and indirect effects in the presence of missing data and accounting for measurement error (29). This approach uses structural equation modelling to estimate the “true” value of the mediator accounting for measurement error using a latent variable by assuming the variance of the measurement error is constant across all time points. All measures of the mediator will be included in the

model, but the 4-week measure will be used as the main mediator of interest. The model will also adjust for baseline values of mediator and outcome to account for possible confounding. Full information maximum likelihood will be used to estimate the model, as this is valid under a missing at random (MAR) assumption; that is, missingness is dependent only on variables included in the analysis model. If there are non-identifiability issues, then the indirect effect will be estimated using an approach similar to Baron and Kenny but will follow the adaptation in Freeman et al. (30) which makes use of linear mixed effects models. This is valid under a MAR assumption but does not account for measurement error in the mediator. We will use the same approach to examine whether change in mechanistic outcomes (at 8 weeks) mediates change in depressive symptoms (at 26 weeks).

11.3. Sample Size Determination

We have powered our trial based on a minimum between-group standardised effect size difference (SMD) of 0.50, reflecting approximately a 3-point difference between arms (pooled SD=6) on the primary outcome, PHQ-9. There is preliminary evidence of large effect size differences following sleep treatment in depression, but these studies have mainly been pilot RCTs, recruiting very small sample sizes (31-33). Our medium effect size estimate is informed by 1) our meta-analysis of SRT on depressive symptoms; 2) our previous studies investigating the effects of CBT for insomnia on PHQ-9 scores in community-recruited participants (34, 35); 3) the minimum effect size that we would consider clinically important; and 4) a realistic treatment effect on depressive symptoms when adding a targeted sleep treatment to ongoing TAU for depression.

Assuming a SMD of 0.50 with power set at 90%, significance level at 5%, and accounting for up to 20% attrition (36, 37), a sample size of 250 participants (135 in the SRT group and 115 in the control group) is required to detect effects on the primary depression outcome at 26 weeks. The sample size also accounts for the “therapist effect”, assuming an intraclass correlation coefficient of 0.01 and a cluster size of 40. In terms of the mediation hypothesis, this sample size will have more than 90% power to detect a small-to-medium effect for the indirect path through insomnia severity (standardised coefficients for A and B paths = 0.3, giving an indirect effect of 0.09). This sample size will also enable detection of medium effect sizes for our mechanistic outcomes, which we consider plausible based on studies showing medium-to-large effects on our selected measures following either depression treatment or sleep treatment (e.g. SMD=0.60 for actigraphy-defined sleep efficiency (38); SMD=0.62 for PTQ (39); SMD=1.02 for FERT(17)).

11.4. Analysis populations

The primary analysis population will be all randomised participants, as defined by protocol eligibility criteria, regardless of what intervention they actually received, compliance of intervention, or completion of outcome. We will also perform exploratory Compiler Average Causal Effect (CACE) analysis to assess the effects of minimum treatment compliance (defined as attending at least 3 treatment sessions) and full treatment compliance (attending all 6 treatment sessions) on the primary outcome.

The safety population will consist of participants who engaged to some extent (defined as attending at least one session of SRT), according to the treatment they actually received (as-treated).

11.5. Decision points

N/A.

11.6. Stopping rules

There will be no stopping guidance for efficacy. Guidance on stopping the trial for safety concerns will be described in the DMC charter.

11.7. The Level of Statistical Significance

All statistical tests will be done at a 5% two-sided significance level.

11.8. Procedure for Accounting for Missing, Unused, and Spurious Data.

Primary analyses will be performed using mixed effect models which account for missing data. The missing data pattern will be explored, and assumptions tested in pre-defined sensitivity analyses (e.g. adjusting for baseline predictors of outcome completion, pattern mixture model, multiple imputation).

11.9. Procedures for Reporting any Deviation(s) from the Original Statistical Plan

Any deviation from the SAP will be detailed in the final analysis report.

12. DATA MANAGEMENT

The data management aspects of the study are summarised here with details fully described in the Data Management Plan.

12.1. Source Data

Source documents are where data are first recorded. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

CRF entries will be considered source data if the CRF is the site of the original recording (e.g. there is no other written or electronic record of data). All documents will be stored safely in confidential conditions according to Nuffield Department of Primary Care and Health Sciences Information Governance policies and UK GDPR. On all study-specific documents, other than the signed consent, the participant will be referred to by the study participant number/code, not by name.

12.2. Access to Data

Direct access will be granted to authorised representatives from the Sponsor and host institution for monitoring and/or audit of the study to ensure compliance with regulations.

Should participants request access to their actigraphy data, a standardised report on their baseline data will be provided. This report will show their rest-activity pattern and a description of what the watch records.

12.3. Data Recording and Record Keeping

The trial is being run as part of the portfolio of trials in the PC-CTU. The data management will be run in accordance with the Trials Unit SOPs, which are fully compliant with Good Clinical Practice (GCP). A study specific Data Management Plan (DMP) will be developed for the RESTED trial outlining in detail the procedures that will be put in place to ensure that high quality data are produced for statistical analysis. Data will be de-identified at the first instance and any data issues within trial team will be communicated using unique trial specific ID number. For postcode data collected at baseline, once it has been converted to an index of multiple deprivation quintile rank, it will be removed from the study documentation to maintain participant confidentiality.

The Oxford Emotional Test Battery data will be captured using software developed by a company called P1vital Products Ltd. Participants will sign up to create an account which only they will be able to access. Data management by P1vital will comply to GCP standards, and contractual agreements will be made between P1vital which will dictate the frequency and quality of data provided to the trial team from P1vital's database. P1vital will be a data processor along with the Primary Care Clinical Trials Unit.

All data will be directly entered into electronic Case Report Forms (eCRFs) using the REDCap database, with the exception of the Oxford Emotional Test Battery data, which will be collected in E-pro, P1vital's electronic database. Any participant identifiable information, with the exception of postcode, age and ethnicity, will be held in a separate database to the clinical database. The information stored in the PII database will not be shared. Paper versions will be provided but should only be used if access to the online CRF is not possible. In this case the original copy of the CRFs will be returned to the study team and a copy will be held at the research site. All paper CRFs will be date stamped upon receipt. A full pre-entry review and electronic data validation for all data entered into the clinical database will be provided by study specific programmed checks. A separate database within REDCAp will be used to securely store all identifiable patient information required to contact patients and permit follow up. Access to this information will be strictly on a need-to-know basis and databases will be password protected on a secure server.

On completion of the trial and data cleaning, the study documentation will be transferred to a secure, GCP compliant archiving facility, where they will be held for 5 years. Participants' identifiable information will be destroyed at the end of the trial. Prior to any interim/hard database lock, the Data Manager and the Trial Statistician will undertake a dataset review as specified in DMP.

13. QUALITY ASSURANCE PROCEDURES

The study may be monitored, or audited in accordance with the current approved protocol, GCP, relevant regulations and PC-CTU Standard Operating Procedures (SOP).

13.1. Risk assessment and monitoring

A risk assessment and monitoring plan will be prepared before the study opens and will be reviewed as necessary over the course of the study to reflect significant changes to the protocol or outcomes of monitoring activities. Monitoring will be performed by the PC-CTU Quality Assurance Manager or delegate. The level of monitoring required will be informed by the risk assessment.

13.2. Study Committees

The composition, roles and responsibilities of committees are detailed in their respective charters, their basic functions are as follows:

Trial Management Group (TMG) - will be responsible for the day-to-day running of the trial, including monitoring all aspects of the trial and ensuring that the protocol is being adhered to. It will include Co-Investigators and will meet monthly once recruitment commences.

Data Monitoring Committee (DMC) The role of the DMC will be to review the data to safeguard the interests of trial participants, assess the safety and efficacy of the interventions during the trial, to ensure continued trial integrity, scientific value, and ethical treatment of study subjects and monitor the overall conduct of the clinical trial. Composition, roles and responsibilities, and frequency of meetings of the DMC are detailed in the DMC charter.

Trial Steering Committee (TSC) - will ensure the rights, safety, and wellbeing of the trial participants. They will respond to concerns/recommendations from the DMC and make recommendations to the funder about how the trial is operating, any ethical or safety issues and any data being produced from other relevant studies that might impact the trial. Composition, and roles and responsibilities of the TSC are detailed in the TSC charter. The TSC advises the TMG about the conduct of the trial. Frequency of meeting will be agreed with the TSC and specified in the TSC charter.

14. PROTOCOL DEVIATIONS

A study related deviation is a departure from the ethically approved study protocol or other study document or process (e.g. consent process or administration of study intervention) or from Good Clinical Practice (GCP) or any applicable regulatory requirements. Any deviations from the protocol will be documented in a protocol deviation form and filed in the trial master file. Where required, sites will be asked to provide details of corrective and preventative actions.

The investigator is not allowed to deviate from the protocol except in the case of an urgent safety measure to protect clinical trial participants from any immediate hazard to their health and safety, in which case such deviations shall be documented and reported to PC-CTU **as soon as possible**.

A PC-CTU SOP is in place describing the procedure for identifying non-compliances, escalation to the central team and assessment of whether a non-compliance /deviation may be a potential Serious Breach.

15. SERIOUS BREACHES

A “serious breach” is a breach of the protocol or of the conditions or principles of Good Clinical Practice which is likely to affect to a significant degree –

(a) The safety or physical or mental integrity of the trial subjects; or

(b) The scientific value of the research.

Investigators must notify the trial team **within 1 working day** if a serious breach is suspected. In the event that a serious breach is suspected the Sponsor must be contacted within 1 working day. In collaboration with the C.I., the serious breach will be reviewed by the Sponsor and, if appropriate, the Sponsor will report it to the approving REC committee and the relevant NHS host organisation within seven calendar days.

16. ETHICAL AND REGULATORY CONSIDERATIONS

16.1. Declaration of Helsinki

The Investigator will ensure that this study is conducted in accordance with the principles of the Declaration of Helsinki.

16.2. Guidelines for Good Clinical Practice

The Investigator will ensure that this study is conducted in accordance with relevant regulations and with Good Clinical Practice.

16.3. Approvals

Following Sponsor approval, the protocol, informed consent form, participant information sheet and any proposed advertising material, and any other participant-facing literature will be submitted to an appropriate Research Ethics Committee (REC), and HRA (where required) and host institutions for written approval.

The Investigator/delegate will submit and, where necessary, obtain approval from the above parties for all substantial amendments to the original approved documents.

16.4. Other Ethical Considerations

Potential to identify participants with a risk of suicide or acute mental distress

We will make clear in participant-facing documents that, if a participant is in any way concerned about their health, they should consult with their GP directly. The PIS will also make it clear that study participation, in either arm of the study, will in no way affect usual care. Participants in both arms will be able to access/continue to access support relevant to their mental health (which may include e.g., antidepressant medication, psychology referral).

Suicidal ideation with intent or recent suicide attempt are part of the study exclusion criteria and will be assessed at the eligibility phase via structured clinical interview. Should we identify participants with current suicidal ideation with intent (or acute mental distress) we will provide them with standardised information on where to seek support and inform the participant's GP practice so that appropriate follow-up can take place. Study consent will require participants to agree to the research team contacting their practice if there is concern about their health at any point during the study.

16.5. Reporting

The CI shall submit once a year throughout the study, or on request, an Annual Progress report to the REC Committee, HRA (where required) host organisation, Sponsor and funder (where required). In addition, an End of Study notification and final report will be submitted to the same parties.

16.6. Transparency in Research

Prior to the recruitment of the first participant, the trial will be registered on the ISRCTN registry. The trial information will be kept up to date during the trial, and the CI or their delegate will upload results to all those public registries within 12 months of the end of the trial date, as specified on the end of trial declaration.

16.7. Participant Confidentiality

The study will comply with the UK General Data Protection Regulation (UK GDPR) and Data Protection Act 2018, which require data to be de-identified as soon as it is practical to do so. The processing of the personal data of participants will be minimised by making use of a unique participant study number only on all study documents and any electronic database(s). All documents will be stored securely and only accessible by study staff and authorised personnel. The study staff will safeguard the privacy of participants' personal data.

16.8. Expenses and Benefits

Participants randomised to the SRT+TAU intervention arm may benefit from an improved understanding of their insomnia and experience improved sleep/ reduction in insomnia symptoms.

All participants will be reimbursed for their time and effort after each completed assessment [vouchers = £15 at baseline; £10 at week 4; £15 post-treatment at week 8; and £20 at week 26]

Reasonable travel expenses for any visits additional to normal care will be reimbursed on production of receipts, or a mileage allowance provided as appropriate.

17. FINANCE AND INSURANCE

17.1. Funding

Research funding is provided by the National Institute for Health and Care Research: Efficacy and Mechanism Evaluation (NIHR:EME) Programme [PI: Dr Simon Kyle].

This project (NIHR131789) is funded by the Efficacy and Mechanism Evaluation (EME) Programme, an MRC and NIHR partnership. The views expressed in this publication are those of the author(s) and not necessarily those of the MRC, NIHR or the Department of Health and Social Care."

17.2. Insurance

The University has a specialist insurance policy in place which would operate in the event of any participant suffering harm as a result of their involvement in the research (Newline Underwriting Management Ltd, at Lloyd's of London). NHS indemnity operates in respect of the clinical treatment that is provided.

17.3. Contractual arrangements

Appropriate contractual arrangements will be put in place with all third parties.

18. PUBLICATION POLICY

The Investigators will be involved in reviewing drafts of the manuscripts, abstracts, press releases and any other publications arising from the study. Authors will acknowledge that the study was funded by NIHR:EME. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged. DEVELOPMENT OF A NEW PRODUCT/ PROCESS OR THE GENERATION OF INTELLECTUAL PROPERTY

Ownership of IP generated by employees of the University vests in the University. The University will ensure appropriate arrangements are in place as regards any new IP arising from the trial.

19. ARCHIVING

Archiving will be done according to PC-CTU SOP and trial specific working instructions. Research documents with personal information, such as consent forms, will be held securely at the University of Oxford's archiving facility according to the PC-CTU Archiving SOP.

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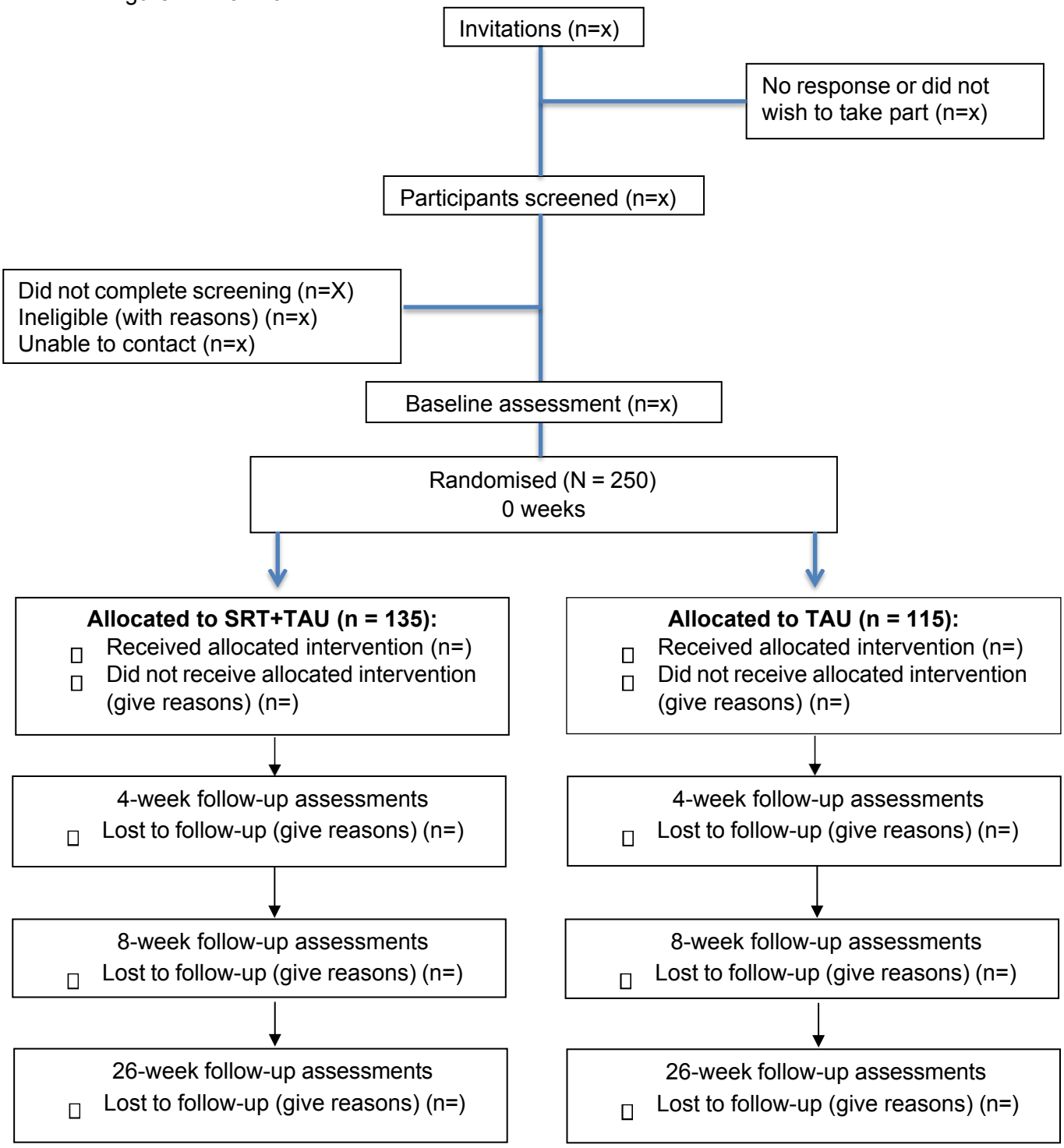
1.

22. APPENDIX A: STUDY FLOW CHART

Figure 2: Trial Flow.



SRT=Sleep Restriction Therapy; TAU=Treatment as Usual

23. APPENDIX B: SCHEDULE OF STUDY PROCEDURES

Table 11: Schedule of Events

Procedures	**Visits**					
	Screening	**Baseline**	**Week 0**	**Week 4**	**Week 8**	**Week 26**
Informed Consent to Screen	**x**					
Eligibility Assessment	**x**					
Informed Consent to Study		**x**				
Demographics/Clinical data		**x**				
Randomisation			**x**			
Treatment arm			**X (six SRT sessions over 6 week period or TAU)**			
Questionnaires						
PHQ-9	**x**	**x**		**x**	**x**	**x**
SCI	**x**					
ISI		**x**		**x**	**x**	**x**
BC-CCI		**x**			**x**	**x**
PANAS		**x**			**x**	**x**
PTQ		**x**			**x**	**x**
WEMWBS		**x**			**x**	**x**
BADS-SF		**x**		**x**	**x**	**x**
Emotional Test Battery						
ECAT		**x**			**x**	**x**
EREC		**x**			**x**	**x**
FERT		**x**			**x**	**x**
Sleep Estimates / Circadian RAR						
Actigraphy (1 week)		**x**			**x**	**x**

CSD + BADS items (1 week)		**x**			**x**	**x**
Other						
Adverse events		**x**		**x**	**x**	**x**
Record of treatments for depression and insomnia		**x**				**x**

24. APPENDIX C: AMENDMENT HISTORY

Table 12: Table of Amendments

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	3.0	03 April 2023	Simon Kyle, Ly-Mee Yu, Charles Vicary	Update to sample size and allocation ratio as a result of need to account for therapist effect. Update to Stop/Go criteria at the request of the funder. Minor wording changes throughout the document for clarity, consistency and ease of reading.
2	4.0		Charles Vicary	Update to eligibility assessments and recruitment strategies; minor wording changes throughout the document for clarity

25. APPENDIX D: TIDieR Checklist for Intervention Description and Replication

Name of intervention	Sleep Restriction Therapy (SRT) for Insomnia Disorder
Why	Insomnia is assumed to be maintained, in part, by excessive amounts of time in bed and irregular sleep-wake schedules, which serve to fragment sleep. Time in bed awake further contributes to insomnia because the bed/bedroom environment may become associated with wakefulness over time; subsequently acting as a trigger for arousal and sleep fragmentation. SRT aims to: 1) restrict time in bed [to enhance sleep efficiency]; 2) regularise the timing of the sleep-wake cycle; and 3) recondition the bed-sleep association.
What: Materials	*Materials for patients*: patients will be provided with a folder at the beginning of the intervention. This folder contains: a copy of the slides used during session 1; worksheets to complete during sessions 1-6; sleep diaries and sleep efficiency grids to enable recording of sleep efficiency each day during the 6week intervention period; and a booklet which contains enhanced information on the background and implementation of SRT, including quotes from patients who have previously underwent SRT *Materials for nurses*: nurses will be provided with a training folder (as part of a 2-day training session), which contains background information on sleep and insomnia, depression, the interaction between sleep and depression, and SRT. The folder also contains a list of frequently asked questions in relation to trouble-shooting and specific patient scenarios that may arise, with standardised guidance on how to navigate. Nurses will be provided with access to recorded videos that give an overview of insomnia, depression, and SRT implementation. Nurses will be provided with a power-point slide set to work through with each patient during session 1. They will also work through a structured checklist (completed online) for each session to guide content and structure and enable recording of session attendance and duration.

What: Procedures	In session 1 the nurse will work through Power-Point slides with the participant to introduce the rationale for SRT alongside a review of sleep diaries, selection of bed and rise-times (for the following seven nights), management of daytime sleepiness (including implications for driving), and discussion of barriers/facilitators to implementation. Participants will be provided with paper or electronic diaries and sleep efficiency calculation grids to support implementation of SRT instructions and permit weekly review of progress. Sessions 2-6 will be brief sessions to review progress, trouble-shoot any difficulties and advise upon titration of the sleep schedule.
Who provided	Research nurses from clinical research networks will be trained to deliver SRT.
How provided	Intervention is delivered one-to-one, involving both face-to-face (sessions 1, 3, 5) and remote sessions (sessions 2, 4 and 6) via web-conferencing software or phone call. Sessions can be provided fully remotely based on participant preference, scheduling issues, or other related restrictions that may impact face-to-face appointments.
Where	The face-to-face sessions will take place in a consultation room within general practice.
When and how much	Intervention will be delivered over six sessions. Duration and format of sessions is as follows: • session 1 (in-person, ~45 minutes) • session 2 (remote, ~15 minutes)
	• session 3 (in-person, ~30 minutes) • session 4 (remote, ~15 minutes) • session 5 (in-person, ~30 minutes) • session 6 (remote, ~15 minutes)

<table>
<tr>
<td>Tailoring</td>
<td>The treatment will be tailored to each individual's sleep pattern but follows standardised instructions for setting and titrating time in bed (TIB):
<table>
<tr><th>Criterion</th><th>SRT</th></tr>
<tr><td>Calculation of prescribed time in bed (TIB)</td><td>Based on average total sleep time (TST) from 7-day sleep diary. Minimum TIB = 5 hrs.</td></tr>
<tr><td>Rise time selection</td><td>Time that aligns with working schedule and can be adhered to 7 days a week</td></tr>
<tr><td>Bedtime selection</td><td>Typically delayed in order to equal the prescribed TIB.</td></tr>
<tr><td>Weekly adjustments to TIB based on average sleep efficiency for 7 days (SE) (sessions 26)</td><td>a) SE ≥ 85% increase TIB by 15 minutes
b) SE = 80-84% no change to TIB
c) SE ≤ 79% decrease TIB by 15 minutes

Adjustments (advancing or delaying) are typically made to the prescribed bedtime.</td></tr>
<tr><td>Napping</td><td>Recommendation to eliminate all napping</td></tr>
</table>
Nurses will be encouraged to adapt the TIB prescription in the following circumstances: patient is struggling to adhere or cannot tolerate the restriction; patient is excessively sleepy; or change in health precludes full implementation. In these circumstances nurses will be encouraged to agree a revised time in bed (increasing in 15 minute blocks) until the patient is content.

On completion of nurse sessions, participants are encouraged to continue self implementing SRT on their own according to the standardised rules. Participants are provided with sleep diaries and grids to enable self implementation at home. Once daytime functioning has improved and sleep efficiency remains high – and no further sleep is obtained with additional TIB – the participant is considered to have reached their optimal sleep schedule.</td>
</tr>
<tr>
<td>How well</td>
<td>Sessions are audio-recorded (if consent is provided) and independently appraised for fidelity by a Clinical Psychologist experienced in cognitive behavioural therapy for insomnia. Nurses will follow and 'sign-off' a checklist at the end of each session in order to capture duration of session and adherence to treatment instructions.</td>
</tr>
</table>

26. APPENDIX E: Examples of the FERT and ECAT Measures

Facial Expression Recognition Task (FERT)
via P1vital Products Ltd. ePRO system

Example task instructions shown to participant

Faces will be presented in the centre of the screen and they will appear for about half a second only.

For each face you need to decide whether the emotional expression on the face is:

ANGER, DISGUST, FEAR, HAPPY, NEUTRAL, SAD, SURPRISE

Respond by clicking the correspondingly labelled button using a mouse or by using your touchscreen (if you are completing the task on a touchscreen device).

Remember: Please respond as quickly and accurately as possible.

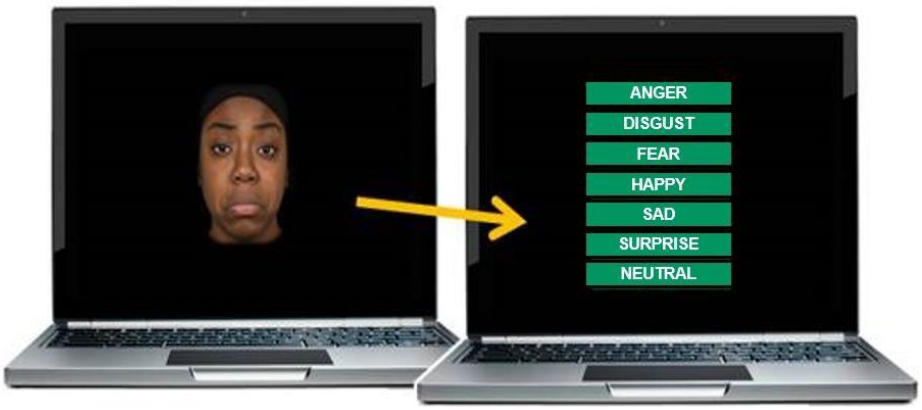
You must select just one button for every face and the next face will not be presented until you have responded to the current one.

General advice. The faces appear quickly, and sometimes it might be difficult to judge their expression. Do the best you can, responding as quickly and as accurately as possible. Focus on the faces whilst they briefly appear, and remember that your initial response is often the best one (rather than over-thinking it). Where necessary, make your best guess. Finally, do not feel concerned if you think you are making some mistakes - this is normal.

When you are ready to continue, please select the CONTINUE button below.

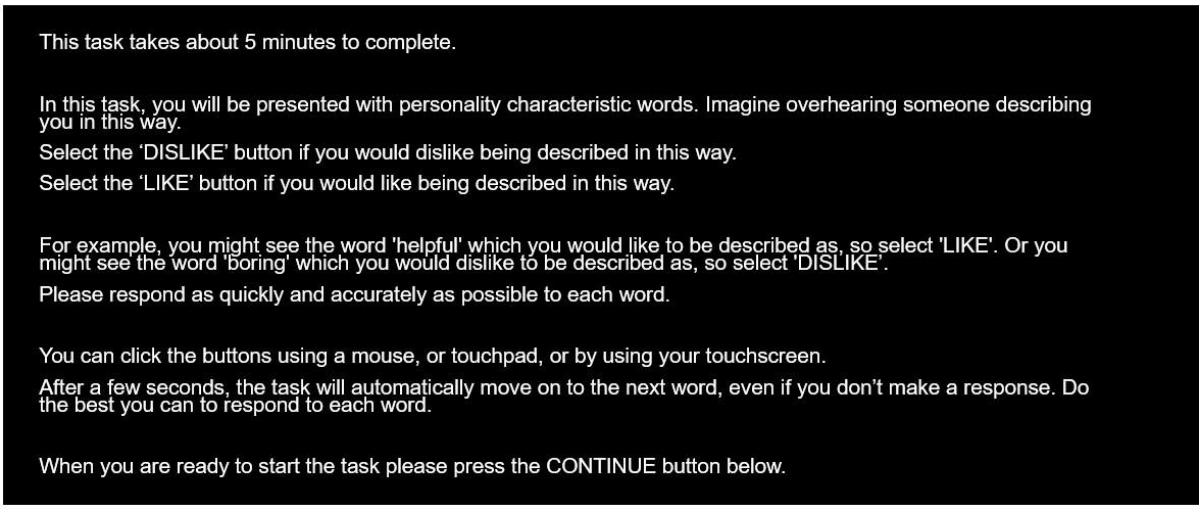
Facial Expression Recognition Task (FERT)
via P1vital Products Ltd. ePRO system

Example facial expression stimulus and choices



Emotional Categorisation Task (ECAT)
via P1vital Products Ltd. ePRO system

Example task instructions shown to participant



Emotional Categorisation Task (ECAT)
via P1vital Products Ltd. ePRO system

Example stimuli shown to participant