Study Title: A pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy for insomnia disorder to sleep hygiene in primary care

Internal Reference Number / Short title: Health professional Administered Brief Insomnia Therapy (HABIT) trial

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Chief Investigator Signature:	

Conflict of Interest statement: Colin Espie 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. This study is in no way connected to Big Health Ltd. All other investigators report no potential conflicts of interest.

Confidentiality Statement

This document contains confidential information that must not be disclosed to anyone other than the Sponsor, the Investigator Team, HRA, host organisation, and members of the Research Ethics Committee, unless authorised to do so.

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1. SYNOPSIS

Study Title	A pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy (SRT) for insomnia disorder to sleep hygiene (SH) in primary care
Internal ref. no. / short title	**H**ealth professional **A**dministered **B**rief **I**nsomnia **T**herapy (HABIT) trial
Study Design	Parallel, open-label, randomised-controlled trial
Study Participants	Adults (≥ 18yrs) meeting criteria for Insomnia Disorder
Planned Sample Size	up to 672 patients 30 nurses, GPs and Practice Managers for interviews
Planned Study Period	42 months

Objectives	**Outcome Measures**
Primary Objective: To compare the effect of SRT+SH versus SH on insomnia severity	Self-rated insomnia severity using the insomnia severity index (ISI) questionnaire
Secondary Objectives: To compare the effect of SRT+SH versus SH on health-related quality of life (HRQoL)	Self-rated HRQoL using the SF-36 questionnaire (Total Score, Mental component summary [MCS] score and Physical component summary [PCS] score)
To compare the effect of SRT+SH versus SH on subjective sleep	Subjective sleep recorded over 7 nights using the consensus sleep diary (CSD) (sleep-onset latency [SOL]; wake-time after sleep onset [WASO]; sleep efficiency [SE]; total sleep time [TST]; sleep quality [SQ])
To compare the effect of SRT+SH versus SH on objective estimates of sleep	Actigraphy-recorded sleep over 7 nights (SOL; WASO; SE; TST)
To compare the effect of SRT+SH versus SH on 1) patient-generated quality of life; 2) depressive symptoms; 3) work productivity; 4) hypnotic medication use; 5) use of other prescribed sleep-promoting medications; and 6) pre-sleep arousal and sleep effort	Self-rated quality of life using the Glasgow Sleep Impact Index [GSII Ranks 1,2,3] Self-rated depressive symptom severity using the Patient Health Questionnaire (PHQ-9) Self-rated work productivity and activity impairment questionnaire (WPAI) Use of prescribed hypnotics (quantified from 7-day diary) Use of other prescribed sleep-promoting medications (e.g., sedative antidepressants, anti-histamines, antipsychotics, melatonin) (quantified from 7 day diary)

	Pre-sleep arousal scale (PSAS) and Glasgow sleep effort scale (GSES)
To compare the incremental cost-effectiveness of SRT+SH over SH, from both NHS and societal perspectives	Trial records (time and number of nurse-led appointments), practice records (medications), Client Service Receipt Inventory (self-reported service use, medications), Insomnia Severity Index, WPAI, EQ-5D-3L (QALY)
To undertake a process evaluation to understand intervention delivery, fidelity and acceptability.	Semi-structured interviews with 1) trial participants; 2) nurses; 3) GPs and 4) practice managers. Number of appointments attended/received by participant; fidelity appraisal of recorded consultations; and adherence to prescribed sleep window (from sleep diary).
To compare the number of specified adverse events between the groups	Questionnaire

2. ABBREVIATIONS

BDI	Becks Depression Inventory
CBT	Cognitive Behavioural Therapy
CI	Chief Investigator
CRF	Case Report Form
CSD	Consensus Sleep Diary
CTRG	Clinical Trials & Research Governance, University of Oxford
DMC	Data Monitoring Committee
EMA	Early morning awakenings
EQ-5D-3L	EuroQol Heath Status Questionnaire
GCP	Good Clinical Practice
GMC	General Medical Council
GP	General Practitioner
GSES	Glasgow Sleep Effort Scale
GSII	Glasgow Sleep Impact Index
HRA	Health Research Authority
HTA	Health Technology Assessment
HRQoL	Health-Related Quality of Life
IAPT	Improving Access to Psychological Therapies

ICF	Informed Consent Form
ID	Insomnia Disorder
ISI	Insomnia Severity Index
MCS	Mental component summary
MEQr	Morningness-Eveningness Questionnaire reduced version
NHS	National Health Service
NMC	Nursing and Midwifery Council
NRES	National Research Ethics Service
PHQ-9	Patient Health Questionnaire
PCS	Physical component summary
PC-CTU	Primary Care-Clinical Trials Unit
PIS	Participant Information Sheet
PSAS	Pre-sleep arousal scale
PSQI	Pittsburgh Sleep Quality Index
QALY	Quality-Adjusted Life Years
R&D	NHS Trust R&D Department
REC	Research Ethics Committee
SAP	Statistical Analysis Plan
SCI	Sleep Condition Indicator
SE	Sleep Efficiency
SF-36	Short-Form 36 Questionnaire
SH	Sleep Hygiene
SOL	Sleep Onset Latency
SOP	Standard Operating Procedure
SRT	Sleep Restriction Therapy
TAU	Treatment As Usual
TIB	Time in bed
TMG	Trial Management Group
TSC	Trial steering committee
TST	Total Sleep Time
WASO	Wake-time after sleep onset
WPAI	Work Productivity and Activity Impairment questionnaire

3. BACKGROUND AND RATIONALE

Insomnia disorder (ID) is characterised by persistent problems with sleep initiation and/or maintenance, resulting in significant impairment to quality of life (QoL; 1-3). ID is the most common sleep disorder and second most prevalent mental health complaint in Europe, affecting 10-12% of the adult population (4,5). Historically viewed as a symptom of a so-called 'primary illness', ID is now recognised as 1) a disabling, non-remitting condition in its own right (1); and 2) a causal factor in the evolution and maintenance of physical and mental ill-health, particularly depression and cardiometabolic disease (6). Moreover, recent prospective data suggest that persistent insomnia is a robust risk factor for all-cause mortality, after adjustment for potential confounding factors (7). Although UK data are limited, extrapolation from per person cost data calculated in Canada (8) suggest that direct and indirect costs of insomnia are likely to exceed £14 billion per year. Associated costs reflect increased healthcare usage, absenteeism, reduced productivity ('presenteeism') and accidents (9;10).

This expensive and burdensome condition is treatable but access to evidence-based intervention (Cognitive Behavioural Therapy; CBT) is almost non-existent. In the absence of available treatment, GPs are limited to administering sleep hygiene guidelines, hypnotics, and (off-label) sedative antidepressants (11;12); yet none of these are evidence based for persistent insomnia (NICE) and hypnotics have well-defined side-effects (5). UK healthcare requires a scalable and cost-effective model to address unmet need. Barriers to wide-scale adoption of CBT for insomnia in the NHS - and worldwide - relate to limited training, expertise and funding. A major development in the insomnia field, therefore, has been the dismantling of multicomponent CBT into focussed, condensed treatment sessions (13), and the training of non-experts to deliver such therapies (14-16). Sleep Restriction Therapy (SRT) has emerged as one of the primary active ingredients within multi-component CBT and because of its focus on behaviour change, coupled with structured and prescriptive delivery, it is ideally suited for primary care delivery. SRT involves restricting and standardizing a patient's time in bed with the aim of increasing homoeostatic sleep pressure, over-riding cognitive and physiological arousal, and strengthening circadian control of sleep. Tailored prescription of bed and rise-times over several weeks leads to reduced sleep variability and improved sleep consolidation and quality.

We conducted a systematic review to assess the efficacy of single-component SRT, finding medium-to-large effects for sleep continuity parameters (17). Since then, SRT has been trialled in the primary care context, via GP delivery (over two sessions), to a highly selected group of insomnia patients, free from comorbidity or medication use (18). Compared to sleep hygiene, SRT significantly reduced insomnia severity at 6 months (Cohen's d=.54). While an important first study, a pragmatic trial in NHS settings, testing a scalable model of treatment delivery with a representative sample of people with insomnia, is clearly required. We have developed a brief SRT protocol, based upon 1) our extensive research using multicomponent CBT (14-16) and 2) systematic examination of the patient experience of SRT (19). We aim to test whether brief SRT alongside sleep hygiene advice, delivered by primary care nurses, is both clinically and cost-effective, relative to sleep hygiene advice on its own. We have chosen practice nurses, instead of GPs, based on previous successful trial experience with this professional group (15) and with cost-effectiveness and scalability in mind. Practice nurses are increasingly involved in chronic disease management (where sleep disturbance is a common comorbidity) and, in particular, the delivery of brief behavioural interventions in primary care (20). While previous studies in UK primary care show multicomponent CBT to be effective when delivered by nurses (14,15), counsellors (21), or through self-help CBT booklets (22), *there has been no large-scale evaluation of the clinical and cost-effectiveness of a brief and scalable behavioural intervention.*

The objectives of the study are as follows:

1) To establish whether nurse-delivered sleep restriction therapy (+sleep hygiene) for insomnia disorder in primary care is clinically effective compared to sleep hygiene alone. Both groups will continue to receive treatment as usual without restriction.
2) To establish whether nurse-delivered sleep restriction therapy (+sleep hygiene) for insomnia disorder in primary care is cost-effective compared to sleep hygiene, from NHS and societal perspectives.
3) To undertake a process evaluation to understand intervention delivery, fidelity and acceptability.

4. OBJECTIVES AND OUTCOME MEASURES

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure (if applicable)**
Primary Objective: To compare the effect of SRT+SH versus SH on insomnia severity	Self-rated insomnia severity using the insomnia severity index (ISI) questionnaire	Baseline, 3, 6 and 12 months post-randomisation. Primary outcome is at 6 months.
Secondary Objectives: To compare the effect of SRT+SH versus SH on health-related quality of life (HRQoL)	Self-rated HRQoL using the SF-36 questionnaire (Total Score, Mental component summary [MCS] score and Physical component summary [PCS] score)	Baseline, 3, 6 and 12 months post-randomisation.
To compare the effect of SRT+SH versus SH on subjective sleep	Subjective sleep recorded over 7 nights using the consensus sleep diary (CSD) (sleep-onset latency [SOL]; wake-time after sleep onset [WASO]; sleep efficiency [SE]; total sleep time [TST]; sleep quality [SQ])	Baseline, 6 and 12 months post-randomisation.
To compare the effect of SRT+SH versus SH on objective estimates of sleep	Actigraphy-recorded sleep over 7 nights (SOL; WASO; SE; TST)	Baseline, 6 and 12 months post-randomisation.
To compare the effect of SRT+SH versus SH on 1) patient-generated quality of life; 2) depressive symptoms; 3) work productivity; 4) hypnotic medication use; 5) use of other prescribed sleep-promoting	Self-rated quality of life using the Glasgow Sleep Impact Index [GSII Ranks 1,2,3]	Baseline, 3, 6 and 12 months post-randomisation. Medication use will be quantified from diaries at baseline,

medications; and 6) pre-sleep arousal and sleep effort	Self-rated depressive symptoms severity using the Patient Health Questionnaire (PHQ-9) Self-rated work productivity and activity impairment questionnaire (WPAI) Use of prescribed hypnotics (quantified from 7-day diary) Use of other prescribed sleep-promoting medications (e.g., sedative antidepressants, anti-histamines, antipsychotics, melatonin) (quantified from 7 day diary) Pre-sleep arousal scale (PSAS) and Glasgow sleep effort scale (GSES)	6 and 12 months post-randomisation.
To compare the incremental cost-effectiveness of SRT+SH over SH, from both NHS and societal perspectives	Trial records (time and number of nurse-led appointments), practice records* (medications), Client Service Receipt Inventory (self-reported service use, medications), Insomnia Severity Index, WPAI, EQ-5D-3L (QALY)	Baseline, 3, 6 and 12 months post-randomisation. *baseline and 12 months only
To undertake a process evaluation to explain trial results and understand intervention delivery, fidelity and acceptability.	Semi-structured interviews with 1) trial participants; 2) nurses; 3) GPs and 4) practice managers. Number of appointments attended/received by participants; fidelity appraisal of recorded consultations; and adherence to prescribed sleep window (from sleep diary)	Throughout the trial.
To compare the number of specified adverse events between the groups	Questionnaire	Baseline, 3, 6, and 12 months.
Tertiary objectives: *Moderator analysis:* Test whether objective short sleep duration at baseline (< 6hrs vs. ≥ 6hrs) moderates the effect of SRT on clinical outcomes (at 6 months)	Actigraphy, ISI, GSII, SF-36	Baseline and 6 months.

Mediator analysis: Test whether group difference on the ISI (6 months) is mediated by change in pre-sleep arousal (PSAS) and sleep effort (GSES) assessed at month 3 Test whether SRT adherence mediates degree of clinical change (ISI) from baseline to 3 months, and from baseline to 6 months.	ISI, Pre-Sleep Arousal Scale (PSAS), Glasgow Sleep Effort Scale (GSES) Sleep diary during intervention phase, ISI	Baseline, 3 and 6 months.

5. STUDY DESIGN

The study will utilise a pragmatic, multicentre, individual, randomised, parallel group, clinical trial design within primary care (see Appendix A). There will be a 6-month internal pilot phase, after which "Stop-Go" criteria will be used to evaluate feasibility of recruitment, treatment fidelity, and contamination (see Section 7.10). Participants will be identified from GP records. We will aim to recruit up to 672 participants across approximately 24 general practices (aiming for 8 in Thames Valley, Manchester and Lincoln, respectively). On completion of baseline assessments participants will be randomised to SRT+SH or SH booklet. SRT treatment will involve 4 sessions (two face-to-face; two over the phone) with a trained practice nurse over a four-week period. Those in the SH group will receive a printed sleep hygiene guide detailing lifestyle and environmental variables that help or hinder sleep. Consistent with the requirements of a pragmatic trial, there will be no restrictions upon usual care for both groups. Usual care for insomnia is likely to be general sleep advice, hypnotics or sedative antidepressants. In this way, the trial represents a comparison of SRT+SH (+treatment as usual [TAU]) vs. SH (+TAU). Outcomes will be assessed at baseline, 3, 6 and 12 months post-randomisation. The primary outcome will be the between group difference in self-rated insomnia severity, using the insomnia severity index (ISI), at 6 months. Patient participation in the study will last one year from randomisation to final follow-up.

6. PARTICIPANT IDENTIFICATION

6.1. Study Participants

Participants, aged 18 years and above, who meet criteria for insomnia disorder will be recruited from general practice. Since insomnia is not commonly coded within practice records we will initially search records for broad sleep-related terms, sleep-related medications and associated conditions in order to identify those most *likely* to be eligible (see section 7.1). Individuals who are interested in the study will undergo eligibility appraisal, involving questionnaire completion and structured checklist review, to determine whether full study inclusion and exclusion criteria are met.

6.2. Study Inclusion Criteria

- Participant is willing and able to give informed consent for participation in the study.
- Screen positive for insomnia symptoms on the Sleep Condition Indicator (SCI) questionnaire and meet criteria for insomnia disorder according to DSM-5 (American Psychiatric Association)
- Sleep efficiency < 85% over the past month
- Age ≥18 years
- Able to attend appointments during baseline and 4-week intervention (both face-to-face at the practice and over the phone) and adhere to study procedures
- The participant's practice is participating in the trial

6.3. Exclusion Criteria

Exclusions will be limited to conditions contraindicated for SRT or factors that would preclude implementation of SRT instructions (see below).

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

- Pregnant/pregnancy planning in the next 6 months
- Additional sleep disorder diagnosis (e.g., restless legs syndrome, obstructive sleep apnoea, narcolepsy) OR screen "positive" on screening.
- Dementia/Mild Cognitive Impairment (MCI)
- Epilepsy
- Psychosis (schizophrenia, bipolar disorder)
- 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.
- Life expectancy of <2 years
- Another person in the household already participates in this trial

7. STUDY PROCEDURES

7.1. Practice and Patient Recruitment

All practices within the study regions (defined according to proximity with research centres) will be approached by the study team and the NIHR Clinical Research Network (CRN). They will be provided with a research information sheet for practices outlining the nature of the study and nurse/GP commitment.

To identify potential participants, practice lists will be searched for relevant sleep-related terms (e.g., insomnia, sleep disturbance; associated conditions [depression, anxiety] and medications [hypnotics, sedative anti-depressants, melatonin]), applying exclusionary diagnoses [e.g., dementia, epilepsy, psychosis]. We will also identify potential participants through a) direct face-to-face GP referral (participants will be provided with an information sheet and contact details for the research team) and b) placement of poster adverts in practices (containing study contact details). Once identified and prior to invitation, practices will have the opportunity to screen the search list of potential participants to check that those identified are medically appropriate to participate in the trial. Practice screen will *not* be mandatory before initial contact, since our screening process will identify those for whom the trial and

intervention are not suitable. Our broad search approach will result in a large number of participant invitations. 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 participant information sheet the main exclusions and ask participants to complete a questionnaire to determine eligibility.

Identified participants will be sent a letter inviting them to take part alongside the participant information sheet (PIS) from their practice, a consent-to-be-contacted form, and a brief questionnaire to confirm insomnia inclusion (23). 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 inclusion criteria, a researcher will subsequently call the participant to go through the remaining eligibility questionnaire

b) contacting the study team directly so that eligibility can be assessed (i.e. go through the screening questionnaire over the phone)

c) going to a study website and completing the eligibility questionnaire online;

We will ask practices to send reminder letters (maximum of 2 reminder letters) to those identified from initial searches of practice lists, and repeat searches during the course of the trial to identify new participants for whom the study may be suitable. In addition to letter invitation we will also engage potential participants through: 1) direct email and text messaging from practices; 2) placement of poster adverts in local pharmacies; 3) posting study adverts on the internet (e.g., Facebook, practice websites, twitter), in newspaper/print and broadcast media; and 4) placement of brief study information on printed prescriptions. To limit the possibility that participants are overwhelmed with direct study invitations we will endeavour to invite participants on a maximum of three occasions (this can include a combination of letter and text/email but will not exceed three direct contacts in total).

For those who remain eligible after screening a baseline visit will be scheduled. At the baseline visit the participant will provide written informed consent and be asked to complete baseline measures prior to randomisation.

7.2. Screening and Eligibility Assessment

Screening and eligibility will be assessed at screening:

1. Identified participants will complete the Sleep Condition Indicator (SCI; 23), supplemented by a question on work pattern to assess for shift work. Contact details will also be requested. To progress to the next phase, participants are required to report the absence of shift work (defined as night, early morning, evening or rotating shift-work), and meet putative criteria for insomnia disorder (i.e. scoring ≤2 on item 1 (sleep latency) *or* item 2 (wakefulness during the night) + scoring ≤2 on item 3 (frequency of disturbance) + scoring ≤1 on item 4 (sleep quality) + scoring ≤2 on daytime functioning items 5 *or* 6 + scoring ≤2 on item 8 (chronicity of problem).

2. For those meeting the above criteria a structured checklist will then be administered, over the phone (by research team) or online, to further ascertain study eligibility. Here, participants will confirm that they meet the eligibility criteria, that is have 1) difficulty falling asleep and/or maintaining sleep (Y/N for issue with SOL/WASO/EMA); 2) experience daytime impairment as a consequence of poor sleep; 3) have adequate opportunity to obtain sleep (disturbance not due to children, caring responsibilities or environmental noise); and 4) have a sleep efficiency of <85% (*PSQI items 1+3 [difference score=TIB]/PSQI item 4 [TST]*100*). They will also confirm that they are a) not pregnant/planning pregnancy in the next 6 months; b) do not have a diagnosis of, or being treated for, dementia, psychosis/bipolar disorder, epilepsy, sleep apnoea, narcolepsy, restless legs syndrome;; c) not currently receiving cancer treatment; d) will not

undergo major surgery during next 2 months; e) are not currently engaged in psychological treatment for insomnia or online treatment programme for insomnia; f) do not currently have suicidal ideation with intent (have to score ≤1 on item 9, BDI; 24); g) have not attempted suicide in the past 2 months; and h) do not have life expectancy <2 yrs. They will be screened for additional sleep disorders using the brief sleep disorders screen (25), and required to screen 'negative' for the following comorbid sleep disorders: narcolepsy, sleep apnoea, restless legs syndrome, parasomnia, and circadian rhythm sleep-wake disorder.

Should participants meet all eligibility criteria then the researcher will arrange to meet with them for the baseline visit (within 8 weeks of eligibility assessment) where they will complete baseline questionnaires and be provided with a sleep diary and actigraph watch to wear for the next 7 days.

7.3. Informed Consent

The participant information sheet will be received in the initial mail out or referral from the GP. The consent form details the nature of the study; what it will involve for the participant; the implications and constraints of the protocol; the known side effects and any risks involved in taking part. It will be clearly stated that the participant is free to withdraw from the study at any time for any reason without prejudice to future care, without affecting their legal rights, and with no obligation to give the reason for withdrawal.

The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their GP or other independent parties to decide whether they will participate in the study. Written informed consent will then be obtained by means of participant dated signature and dated signature of the person who presented and obtained the informed consent. The person who obtains consent must be GCP 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.

7.4. Baseline Assessments

Once eligibility is confirmed, a member of the research team will meet with the participant at baseline. Here 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 informed consent. The baseline meeting will take place at a location most convenient for the participant and may include, for example, general practice, participant home or university site. 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 will be used and data will be entered to the online version.

The researcher will confirm eligibility, collect basic demographic data and ask participants to complete self-report questionnaires (related to sleep and functioning; see Table 1 below). Data on healthcare resource use (hospital appointments, in-patients stays etc.) will be measured with a self-reported version of the Client Service Receipt Inventory (CSRI; 26) and through extraction of key information from practice records, while adverse events (e.g., accidents and falls) will be collected through a bespoke questionnaire. Information on prescription medication use and comorbidities will be extracted from practice records (notes review) by the researcher; this may or may not occur in the presence of the participant depending on where the baseline visit takes place (i.e. if at home the researcher will visit the practice separately). Participants will be provided with an actigraph watch (a device which measures movement to infer sleep/wake periods) 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 daily sleep diary (CSD; 27) for seven days to capture nightly subjective sleep and sleep medication use. 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 SH or SRT+SH. The SH group will receive a booklet providing information on good sleep practices, while the SRT+SH group will, in addition, meet with the trained practice nurse on four occasions over a four 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 a paper form.

Table 1: Data collection at baseline visit

1.	*Demographic Information*	Post code*, sex, age, marital status, level of education, ethnicity, self-reported height and weight (BMI), alcohol intake, smoking status
2.	*Self-report questionnaires (sleep and daytime functioning)*	*Insomnia Severity Index* (ISI; 28), insomnia duration and help-seeking (bespoke questions), *Short-Form 36* (SF-36; 29), *Glasgow Sleep Impact Index* (GSII; 3), *Patient Health Questionnaire* (PHQ-9; 30), *Work Productivity and Activity Impairment* questionnaire (WPAI; 31), *EuroQol* (EQ-5D-3L; 32), *Pre-sleep Arousal Scale* (PSAS; 33), *Glasgow Sleep Effort Scale* (GSES; 34), *Morningness-Eveningness Questionnaire reduced version* (MEQr; 35)
3.	*Subjective sleep and nightly use of sleep-promoting medication (prospective)*	Sleep diary (CSD) completed daily for 1 week – providing information on sleep timing, continuity and quality, and nightly use of sleep-promoting medication
4.	*Objective estimates of sleep (prospective)*	Actigraph watch (MotionWatch 8, CamNTech Ltd.) worn for 1 week – providing information on objective estimates of sleep timing and continuity.
5.	*Resource use data*	Client Service Receipt Inventory (CSRI; 26), medical records extraction (medications and comorbidities)
6.	*Comorbidities and adverse events*	Comorbidities (medical records), accidents [e.g., driving, work-related], falls and near misses while driving (questionnaire)
*will be converted to an index of multiple deprivation rank and the demographic variables will be presented by group at baseline for descriptive purposes only.		

7.5. Randomisation, blinding and code-breaking

Once participants have completed baseline assessments they will be eligible for randomisation. Sleep diaries must be returned, and be at least partially completed (i.e. have at least four days of data), to be eligible for randomisation. Participants will be randomised (1:1) to SRT+SH or SH using a validated web-based randomisation programme (Sortition), with a non-deterministic minimisation algorithm to ensure site, use of prescribed sleep promoting medication (yes/no), age (18-65 yrs vs. > 65yrs), sex, baseline insomnia severity (ISI score <22 vs. 22-28) and depression symptom severity (PHQ-9 score <10 vs. 10-27) are balanced across the two groups. Appropriate study members at each site will have access to the web-based randomisation software to complete randomisation.

This is an open-label study and therefore both participants and nurses will be aware of allocation. The PIS will inform participants that the study compares two different sleep intervention programmes but will not reveal the study hypothesis. Treatment providers (nurses) will not be involved in the collection of trial outcomes. Outcomes (questionnaires, diaries and actigraphy) are self-completed, remotely, by

participants. Due to impracticalities associated with blinding of the research team, combined with minimal risk of bias due to use of self-report outcome measures, researchers at each site will be aware of treatment allocation. Communication from the research team to participants, post-randomisation, will be limited to collection of outcome assessments and not therapeutic procedures. The statisticians will remain blind to allocation.

7.6. Subsequent Visits

Both groups will have follow-up assessments at 3, 6 and 12 months post-randomisation (see Table 2 for data collection). A member of the research team will notify participants (through e.g., call, text, email or letter) that a questionnaire pack will be sent to them forthwith, either electronically or through the post. This pack will contain self-report questionnaire measures, sleep diary, actigraph watch and envelope for return depending on the time point. Depending on participant preference, and to optimise retention, questionnaire outcome measures can be completed using paper, electronically through web-based survey, or over the phone through interview with the research team. Practice records will be accessed at 12 months to extract information on medications throughout the trial. On completion of questionnaire measures and 7-day diary/actigraphy, assessments will be returned to the research team (using postal mail or direct collection methods). Should participants not respond or return questionnaires we will follow-up with reminders (which can include emails, text messages, and phone calls). In addition, we will send a reminder letter from the practice at 6 months to all participants who do not respond to optimise completion of primary outcome data. We will also send participants newsletters during the trial to retain participant engagement.

To gauge potential contamination, participants in the control arm who endorse receipt of sleep treatment from their practice nurse (item from the CSRI) will receive a phone call from the research team to determine whether participants have received SRT through their practice.

Table 2: Data collection at *3, 6 and 12 months*

1.	Self-report questionnaires (sleep and functioning)	*Insomnia Severity Index* (ISI), *Short-Form 36* (SF-36), *Glasgow Sleep Impact Index* (GSII), *Patient Health Questionnaire* (PHQ-9), *Work Productivity and Activity Impairment* questionnaire (WPAI), *EuroQol* (EQ-5D-3L), *Pre-sleep Arousal Scale* (PSAS), *Glasgow Sleep Effort Scale* (GSES), *Morningness-Eveningness Questionnaire reduced version* (MEQr)
2.	Subjective sleep and nightly hypnotic use (prospective)***	Sleep diary (CSD) completed daily for 1 week – providing information on sleep timing, continuity and quality, and nightly use of sleep-promoting medication. Sleep diary data collected during treatment (SRT+SH group only; returned after completion of 4-week intervention)
3.	Objective estimates of sleep (prospective)***	Actigraph watch (MotionWatch 8, CamNtech Ltd.) worn for 1 week – providing information on objective estimates of sleep timing and continuity.
4.	Resource use data	Client Service Receipt Inventory (CSRI), medical records extraction[#] (medications), contamination check** in control group (brief phone interview for those scoring positive on CSRI)

5.	Treatment satisfaction*	Satisfaction with treatment received on a 5-point scale, condensed into three categories to aid interpretation (satisfied, neutral, or dissatisfied)
6.	Adverse events	accidents [driving, work-related], falls and near misses while driving (questionnaire)

*collected at 3 months only; **3 and 6 months only; *** 6 and 12 months only;

7.7. Process evaluation

As recommended for trials of complex interventions, we will conduct a process evaluation in line with MRC guidance.

The aim of the process evaluation is to explore how nurse administered SRT provided in the primary care setting functions as part of this trial, by examining implementation, mechanisms of impact, and contextual factors.

This will be complementary to the outcomes evaluation, helping to understand the trial results through exploration of:

(i) how intervention training is delivered to practice nurses and its acceptability to them,

(ii) how the intervention is administered by practice nurses and whether intervention fidelity is maintained (i.e. delivered as intended) in terms of the content, just to those patients in the intervention group or more widely (i.e. contamination), how this is applied and whether there are any modifications, and

(iii) the patient's response to the intervention, how they interact with it, what they do as a result and any unexpected consequences; and

(iv) any contextual factors within practices and the wider health service environment that affect intervention implementation during the trial, increasing understanding of barriers and facilitators to intervention effectiveness during the trial and providing insights into how this might enable or prevent further implementation and spread thereafter, should the intervention be shown to be effective and cost-effective.

Qualitative data collection: Semi-structured interviews will be conducted by the research team with a sample of practice nurses (n=15), patients (n=15) and practice managers or GPs (n=15) across the three study sites with approximately two-thirds during the pilot phase and one-third during the main trial. These will be in-depth semi-structured *telephone*, *Skype* or *face-to-face* interviews (at a convenient location for the participant) lasting 30-60 minutes using separate interview schedules for each group. Consent process and interviews will be digitally audio recorded and transcribed verbatim. Professionals will be asked about their working role in relation to delivering the SRT intervention. Patient interviews will take place after completion of the intervention phase.

Patient consent for the qualitative sub-study will be sought at the time of consent for the main trial. Consent forms will be returned to the University of Lincoln or University of Oxford directly after consent has been taken. At the end of the trial consent forms will be collated and archived at the University of Oxford. Practice staff (GPs/Nurses/Practice Managers) will be provided with a specific participant information sheet and informed consent form (electronically and/or via postal mail) for the qualitative sub-study. Written informed consent will be obtained for those who meet with the researcher in person, while for those opting to complete the interview by telephone or Skype, consent will be obtained over the phone by a trained member of the research team. A copy of the consent form will be given to the

participant if doing a face-to-face interview. For remote interviews a copy will be sent to them after the interview (to their place of work as appropriate).

Quantitative data collection: We will collect data about the number of nurses trained, their demographics (age, gender, education level) 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 for sleep diaries during intervention; and intervention adherence (number of nights per week participant adheres [within 15 mins] to prescribed bed and rise-time).

Fidelity: All in-person nurse-delivered SRT sessions will be recorded with a dictaphone device. A sample of sessions from each nurse will be fidelity appraised by a member of the research team against a structured checklist, for coverage of key therapeutic elements.

Control group contamination: All participants will complete the Client Service Receipt Inventory which asks about access to sleep treatments in the previous three months. For participants in the control group, who endorse receiving sleep treatment from their practice nurse, a follow-up phone call will be arranged with a member of the research team to determine if SRT was delivered.

The process evaluation will begin during the 6-month internal pilot phase and continue into the main trial employing a mixed methods design, involving collection and integration of both qualitative and quantitative data.

7.8. Discontinuation/Withdrawal of Participants from Study

Some participants may want to withdraw from treatment and we will endeavour to keep them in follow-up to avoid biasing the trial. We will explain the value of their data in giving a true reflection of the impact of the treatment on outcomes. However, we will also be clear that each participant has the right to withdraw from the trial at any time. Participants will receive the Patient Information Sheet prior to eligibility assessment, which will detail how to withdraw and who to contact should they no longer wish to participate in the treatment or in follow-up. If the participant wishes to withdraw from follow-up, we will use their data up to the point that they withdrew unless they explicitly say otherwise. No patients will be replaced if they are discontinued or withdraw.

Participants will only be withdrawn from the trial by the research team should treatment be deemed unsafe or for ineligibility.

The reason for withdrawal will be recorded in the e-CRF.

Definition of End of Study: The end of study is the final data capture of the last participant's notes review.

7.9. Internal pilot phase and Stop-Go Criteria

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 below) will be assessed by the Trial Steering Committee (TSC) at 6 months in relation to recruitment, treatment fidelity, and control group contamination. We aim to recruit 196 participants within six months of the first participant being randomised.

Recruitment - Stop/Go [against target of 196 by the end of month 6]

Recruitment Criteria (% of Target n)	***Proposed Action***
>80%	progress to main trial phase
70-80%	progress to main trial phase, implementing strategies (e.g., recruitment of additional practices and nurses)
50-69%	Urgent measures required, discuss with TSC and HTA
<50%	Consider stopping trial, discuss with TSC and HTA

Treatment Fidelity – Stop/Go [appraisal of sample of recorded nurse-patient consultations]

Treatment Fidelity Criteria (On average…)	***Proposed Action***
>70% of SRT elements are covered during sampled sessions	progress to main trial phase
60-69% of SRT elements are covered during sampled sessions	progress to main trial phase, implementing strategies (e.g., retrain certain nurses)
<60% of SRT elements are covered during sampled sessions	Consider stopping trial, discuss with TSC and HTA

Contamination – Stop/Go [based on questionnaire response and follow-up phone call with control group]

Contamination criteria	***Proposed Action***
≤5% of control participants receive SRT through their practice	Progress to main trial
6-15% of control participants receive SRT through their practice	Progress to main trial phase, consider implementing strategies (e.g., drop specific practices if disproportionately affected) and conduct review of sample size and statistical methods to ascertain need for adjustment. Suggestions will be fully considered with the DMC/TSC before implementation.
>15% of control participants receive SRT through their practice	Consider stopping trial, discuss with TSC and HTA

8. INTERVENTIONS

8.1. Sleep Restriction Therapy (SRT)

Participants in the intervention arm will be offered nurse-delivered insomnia therapy in the form of sleep restriction therapy (SRT), a manualised behavioural intervention. Therapy will be delivered by trained practice nurses over four brief, weekly sessions [total contact time = ~ 1hr 5 mins]:

1. Week 1: The first session will be a 30-minute face-to-face session with the nurse at the local practice. Here, the nurse will work through power-points slides with the participant to introduce the rationale for SRT alongside a review of (baseline) sleep diaries, selection of prescribed bed and

rise-times (for the following seven nights), management of daytime sleepiness, and discussion of barriers/facilitators to implementation. Participants will also be provided with a booklet to read in their own time, which includes information on theory underlying SRT and a list of sleep hygiene guidelines (36). In addition, this booklet will outline strategies to support adherence, presented in the form of direct patient quotes generated from our previous mixed-methods research (19). Participants will be provided with diaries and sleep efficiency calculation grids for the next four weeks to support implementation of SRT instructions and permit weekly review of progress.

2. Week 2: One week later the nurse will speak to the patient over the phone (10 mins) to review progress. Based on this review, and according to a structured algorithm (37), nurses will advise upon titration of the sleep schedule for the following seven days.

3. Week 3: Session three will follow the same structure as session two, but will be face-to-face with the practice nurse (15 minutes), and both sessions will emphasise overcoming any barriers to implementation.

4. Week 4: The final treatment session will be delivered over the phone and involve a similar 'review and titrate' structure (10 minutes), combined with suggestions for ongoing implementation and the management of residual or recurrent insomnia symptoms.

Should there be scheduling difficulties between nurses and participants, making attendance at face-to-face appointments not possible, then sessions can take place over the phone.

We will ask nurses to 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, all SRT in-person sessions will be recorded – if participants agree – using a dictaphone device. As part of the site agreement with the practice, the nurse will agree for these to be recorded. A sample of these will then be rated by a member of the research team.

To permit quantification of patient adherence to SRT instructions, sleep diaries completed during the 4 week intervention phase will be returned to the research team.

Nurse training and supervision: Suitably experienced members of the team will deliver manualised training to practice nurses, covering basic sleep-wake regulation, development and maintenance of persistent insomnia, principles of SRT, and the application of 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 one half-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, consistent with the training approach adopted by the Department of Health for their training of brief psychological interventions as part of the improving access to psychological therapies programme (IAPT). Nurses will be provided with a list of FAQs to enable trouble-shooting of potential issues that may arise during patient consultations. In addition, nurses will be able to access a study-specific website where they can access treatment-related resources and post questions on a discussion forum.

Our principal focus is on training practice nurses to deliver SRT in primary care, however should we encounter scheduling or staffing issues we will train other suitably qualified staff (e.g., CRN nurses to support the study in a peripatetic manner).

8.2. Sleep Hygiene (SH)

Usual care in relation to persistent insomnia is likely to involve a mixture of sleep hygiene advice, repeat hypnotic prescription, and use of sedative antidepressants or antihistamines (11,12). For those aged 55+, melatonin may also be prescribed for insomnia, consistent with NICE guidelines. Evidence shows that access to, and awareness of CBT for insomnia in primary care is very limited (11).

Because NICE recommends that individuals with persistent insomnia should receive sleep hygiene education it is likely that some of our participants have been exposed to such information in the past. Therefore, to avoid bias, all participants in both the control arm and intervention arm will be provided with the same standardised sleep hygiene information in the form of a booklet. The content of sleep hygiene is based on recognised advice (38), comprising behavioural guidance in relation to lifestyle factors and environmental factors associated with sleep and sleeplessness. It will cover the importance of limiting caffeine, nicotine, and alcohol and of carefully managing diet and exercise (lifestyle), as well as limiting noise and light, managing room temperature and body temperature, and improving air quality and bed comfort (environment).

Consistent with the requirements of a pragmatic trial, there will be no restrictions upon usual care for both groups. In this way, the trial represents a comparison of SRT+SH (+TAU) vs. SH (+TAU), permitting clear judgment to be made regarding the relative clinical utility of SRT in routine clinical practice.

9. SAFETY REPORTING

9.1. Definition of Serious Adverse Events

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.

Other ‘important medical events’ may also be considered serious if they jeopardise the participant or require an intervention to prevent one of the above consequences.

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.

9.2. Reporting Procedures for Serious Adverse Events

We will record planned hospital admissions at baseline and when they occur, these will not be counted as serious adverse events.
The likelihood of serious adverse events occurring due to treatment is low since neither CBT-I/SRT nor sleep hygiene education have been reported to cause them.

Therapists and patients will be prompted to self-report serious adverse events. Along with self-reporting of SAEs, we will also use responses on the CSRI questionnaire, which includes questions on hospitalisations, to follow-up participants who endorse being hospitalised.

SAEs will be reported after date of randomisation until either the date of trial withdrawal or 6-month follow-up completion, whichever is earlier.

Recorded serious adverse events will be reported to the REC who gave a favourable opinion of the study where, in the opinion of an appropriately medically qualified PI, 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 serious adverse events will be submitted within 15 working days of the study team becoming aware of the event, using the HRA report of serious adverse event form.

9.3 Adverse effects

Because implementation of SRT may be associated with increased sleepiness we will also record incidences and severity of falls, accidents (including road-traffic accidents and work-related injuries) and near miss driving incidents alongside outcomes at baseline, 3, 6, and 12 months post-randomisation and report these by randomised group.

10. STATISTICS AND ANALYSIS

10.1. Description of Statistical Methods

Analyses will be described in detail in a Statistical Analysis Plan (SAP) drafted by a Trial Statistician and signed off by the CI and Lead/Senior Statistician. All analyses will be conducted in accordance with Oxford Primary Care CTU SOPs. Our main planned analyses are summarised below.

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 on an intention-to-treat basis. That is, after randomisation, participants will be analysed according to their allocated treatment group irrespective of what treatment they actually receive. 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. There will be no planned interim analysis for efficacy or futility.

10.2. The Number of Participants

To detect a difference of 1.35 points (standard deviation=4.5) between the group means of SRT+SH and SH, with a power of 90% at 5% level of significance (2-sided), 235 participants would be required in each treatment group. The standard deviation was chosen based on the results from the primary care evaluation of SRT conducted by Falloon and colleagues (18). Accounting for 20%, 25% and 30% attrition, the total number of participants required to recruit would be 588 (294 per group), 628 (314 per group), and 672 (336 per group), respectively.

Most CBT evaluations show large effects on the ISI (39) but these studies are predominantly outside of the UK, have small samples, are tightly controlled and recruit participants from the community, free from comorbidity or medication. Given that our study is a pragmatic trial, across multiple NHS sites, with a varied group of insomnia patients (representing clinical reality), we would anticipate a lower effect size for the ISI. Falloon and colleagues (18) recruited a highly selected group of patients and delivered treatment via one research GP, observing an effect size of 0.54 at 6 months on the ISI. Thus, powering the study for a moderate standardised effect size of 0.3 is conservative, clinically important, and appropriate given our design features. The sample size will also allow us to detect an average difference of 2.7 points [standard deviation=9.0; Abell et al (40;41)] on the SF-36 (HRQoL), *our important secondary outcome*, at 90% power and 5% level of significance.

For the interviews we aim to recruit 15 participants, consistent with our previous experience of framework analysis (42) and guidelines recommending that a minimum of 12 interviews are needed to achieve theoretical data saturation (43).

10.3. Analyses

A three-level mixed effect linear model based on an unstructured covariance matrix will be fitted to the primary outcome data (ISI at 6 months), utilising 3, 6 and 12-month time-points. Practice and participant will be included as random effects. Fixed effects will include randomised group, baseline ISI score, stratification variables, time and a time by randomised group interaction term to allow estimation of treatment effect at each time point.

Missing data will be reported with reasons given where available and the missing data pattern will be explored. We will explore the mechanism of missing data, though the mixed effects model does implicitly account for data missing at random. Standard residual diagnostics will be assessed for the appropriateness of the model and if assumptions are violated we will consider alternative non-parametric approaches for the main analysis. Continuous secondary outcomes will be analysed using the same method. Secondary outcomes that are binary (e.g. zero hypnotic use over 7 days) or count variables (e.g. number of nights hypnotic-free over 7 nights) will be analysed using generalised linear mixed effects models with appropriate link function. We will undertake pre-specified subgroup analysis of the primary outcome by short sleep duration at baseline [(< 6 hours vs ≥ 6 hours]). Mediation analyses will be conducted using the approach of Baron and Kenny (44) but will follow the adaptation in Freeman et al (45) which makes use of linear mixed effects models. This will allow us to determine the extent to which the 3-month arousal outcomes (PSAS, GSES) mediate the 6-month ISI outcome. All models will include the baseline assessments of the mediator and ISI as covariates.

A complier-average causal effect (CACE) analysis of the primary outcome will be carried out to determine the impact of the treatment effect when accounting for non-compliance of the allocated intervention (i.e. SRT session attendance). CACE is a measure of the causal effect of an intervention on the participants who received it as intended by the original group allocation. We will also explore the effect of level of adherence to prescribed bed and rise-times (captured by sleep diaries) on the primary outcome in those who received SRT.

<u>Economic analysis</u>

A within-trial economic evaluation alongside the RCT will estimate the incremental cost-effectiveness of SRT+SH over SH, from both NHS and societal perspectives. In our economic analyses we will adopt the UK NHS and personal social services perspective, consistent with the NICE reference case. Additional analyses will examine costs from a societal perspective, quantifying productivity losses in relation to absenteeism and presenteeism.

From clinical records we will quantify participants' attendance at SRT sessions and summarise resource commitment from nurses and trainers in relation to therapy delivery. We will collect data on health care usage through GP records (medication use) and a self-reported version of the Client Service Receipt Inventory. The Personal Social Services Research Unit Costs of Health and Social Care and NHS Reference Costs will be used to apply national average unit costs to service utilisation and construct a cost profile per patient. Productivity will be quantified from the WPAI, a measure which is sensitive to CBT treatment of insomnia and costed using the human capital approach.

Analysis of the ISI (assessed at baseline, 3, 6 and 12 months) will indicate the incremental cost per unit change in self-reported insomnia severity. As recommended by NICE, cost-utility analysis will examine incremental QALYs. This will be achieved through collecting data on health status using the EQ-5D-3L at baseline, 3, 6 and 12 months, and calculating the area under the curve. We will add a sleep dimension (46) to the standard EQ-5D-3L allowing us to examine, in exploratory analysis, the relationship between sleep bolt-on scores and other measures of insomnia severity, to identify possible disparities between general population and (insomnia) patient perceptions of health status in relation to sleep.

Process evaluation analysis

We will use a Framework approach to data analysis supported by QSR NVivo (version 10), with the framework based on the main areas of implementation, mechanisms of impact, and contextual factors together with the more detailed issues that arise from these. Analysis will begin as soon as earlier interviews are transcribed, and interview schedules will be applied flexibly so that qualitative data are collected iteratively allowing themes that are identified in earlier interviews to be explored in later ones. We will analyse and report qualitative process data prior to knowing trial outcomes to avoid biased interpretation. Analysis of quantitative data will primarily be descriptive; this is intended to describe whether we have sampled across a range of patients and practitioners as far as is practicable. Quantitative and qualitative data will be integrated allowing qualitative to complement quantitative findings, and quantitative data to test hypotheses generated by qualitative data.

The findings of the process evaluation during the pilot study will be used to improve the delivery of intervention as intended, where this is possible without altering the intervention itself.

11. DATA MANAGEMENT

11.1. Source Data

Source documents are where data are first recorded, and from which participants' CRF data are obtained. These include, but are not limited to, primary care and hospital records (from which medical history and previous and concurrent medication may be summarised into the CRF), diaries, 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. On all trial-specific documents, other than the signed consent, the participant will be referred to by the trial participant number/code, not by name.

11.2. 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.

11.3. 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 HABIT 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 anonymised at the first instance possible and anonymity will be maintained where required, the details of which will be outlined in the SAP and the DMP. For postcode data collected at baseline, once it has been converted to an index of multiple deprivation rank, it will be removed from the study documentation to maintain anonymity.

A unique trial specific number and/or code in any database will identify the participants. All data will be directly entered into electronic Case Report Forms (eCRFs). 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 CRFs (electronic or paper) 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. All paper data will be locked in secure cabinets and only the researchers will have access to the files. A separate database 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 database lock, the Data Manager and the Trial Statistician will undertake a dataset review.

12. QUALITY ASSURANCE PROCEDURES

The trial will be conducted in accordance with the current approved protocol, GCP, relevant regulations and standard operating procedures.

Regular monitoring will be performed according to GCP by the quality assurance manager and trial manager as documented in the risk assessment. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the monitors will verify that the clinical trial is conducted and data are generated, documented and reported in compliance with the protocol, GCP and the applicable regulatory requirements.

An independent Trial Steering Committee (TSC) will provide oversight of all matters relating to participant safety and data quality. The TSC will include at least one independent clinician, an independent statistician and a participant representative. The TSC will be asked to review the trial protocol and will provide expert advice to the Trial Management Group (TMG) on the trial progress.

A data monitoring and ethics committee (DMEC) will be convened for this study.

13. ETHICAL AND REGULATORY CONSIDERATIONS

13.1. Declaration of Helsinki

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

13.2. Guidelines for Good Clinical Practice

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

13.3. Approvals

The protocol, informed consent form, participant information sheet and any proposed advertising material will be submitted to an appropriate Research Ethics Committee (REC), and HRA for written approval.

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

13.4. 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 and Sponsor. In addition, an End of Study notification and final report will be submitted to the same parties.

13.5. Participant Confidentiality

The study staff will ensure that the participants' anonymity is maintained. The participants will be identified only by a participant ID number on all study documents and any electronic database, with the exception of the CRF, where participant initials may be added. All documents will be stored securely and only accessible by study staff and authorised personnel. The study will comply with the Data Protection Act and General Data Protection Regulation (GDPR) 2018, which requires data to be anonymised as soon as it is practical to do so.

13.6. Expenses and Benefits

Participants in both arms may benefit from an improved understanding of their insomnia and experience improved sleep/ reduction in insomnia symptoms. It is hypothesised that these benefits will be greater in the SRT arm.

All participants will be reimbursed for each completed assessment [vouchers = £5 at baseline, £10 at 3 months, £15 at 6 months and £10 at 12 months]

Qualitative sub-study: Participants (SRT arm only) will receive a voucher for participation in interviews as part of the process evaluation (£10 voucher). Practice staff will be reimbursed for their time according to standardised hourly rates.

All participants who are interested in receiving a summary of the study findings will also be sent a copy of this at the end of the study.

13.7. Other Ethical Considerations

Potential for undiagnosed depression in sample

Given the 'real-world' context of our trial, and the high comorbidity of insomnia and depression, we will not exclude people with depressive symptoms, or those being treated for depression at baseline (only

those showing evidence of suicidal ideation with intent). Should we identify participants with current suicidal ideation with intent during screening we will provide them with standardised information on where to seek support. Because we will recruit from medical records it is likely that many participants will have been reviewed for depression by their GP. To ensure parity across trial arms, as well as appropriate clinical governance, we will make clear during screening and post-randomisation that if a participant is in any way concerned about their mental health they should consult with their GP directly. Indeed, all documentation and communication will make it clear that participation, in either arm of the study, will in no way affect usual care. Should practice nurses become aware of mental distress during SRT appointments they will recommend that the participant seek additional support from their GP. We will record such information in the e-CRF. 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).

Potential to discover poor professional practice among practice staff

Nurse intervention recordings will be appraised for fidelity and should topics be covered that are beyond the scope of SRT, or SRT is not appropriately implemented, the nurse will be asked to undergo intervention re-training.

We do not expect any evidence to emerge from interviews (with practice staff) of malpractice. However we will follow the guidance provided by the General Medical Council (GMC) and Nursing and Midwifery Council (NMC) recommendations: https://www.rcn.org.uk/get-help/rcn-advice/fitness-to-practise-concerns#How%20to%20raise%20concerns

14. FINANCE AND INSURANCE

14.1. Funding

Research funding is provided by the National Institute for Health Research Health Technology Assessment Programme.

14.2. 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.

15. 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-HTA. Authorship will be determined in accordance with the ICMJE guidelines and other contributors will be acknowledged.

Ownership of IP generated by employees of the University vests in the University. The protection and exploitation of any new IP is managed by the University's technology transfer office, Oxford University Innovations.

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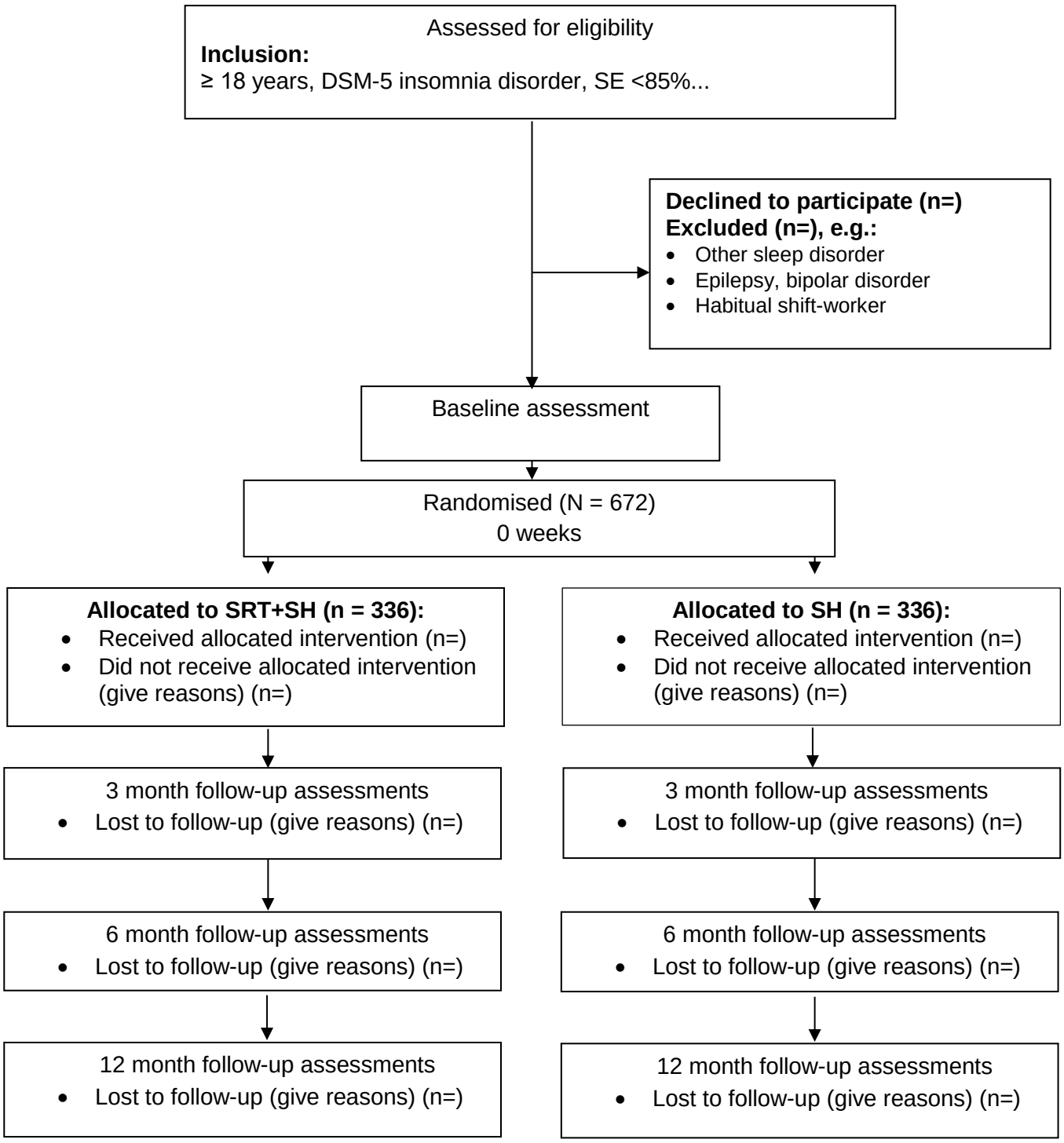
17. APPENDIX A: STUDY FLOW CHART

Figure 1: Trial Flow.



SH=Sleep Hygiene; SRT=Sleep Restriction Therapy.

APPENDIX B: SCHEDULE OF KEY STUDY PROCEDURES

Procedures							
	Pre-study						**Ongoing or during treatment**
	Screening	**Baseline**	**Randomisation**	**3mths F-up**	**6 mths F-up**	**12 mths F-up**	
Eligibility assessment	X						
Informed consent		X					
Demographics		X					
Questionnaires*		X		X	X	X	
Satisfaction with treatment				X			
CSRI		X		X	X	X	
Medical record extraction		X				X	
Sleep diary (7 days)		X			X	X	X (during 4 week treatment in SRT group)
Actigraphy (7 days)		X			X	X	
Randomisation			X				
Adverse event assessments (SAEs; accidents and falls)		X		X	X	X	X
Contamination check (based on CSRI response for control group)				X	X		
Qualitative interviews							X

*ISI, SF-36, GSII, PHQ-9, WPAI, EQ-5D-3L, PSAS, GSES, MEQr

18. APPENDIX C: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Author(s) of changes	Details of Changes made
1	Version 2.0.	11.07.2018	Simon Kyle Emma Ogburn	• Removal of travel exclusion • Addition of current engagement with online insomnia treatment as exclusion criterion • Addition of control group contamination at 6 months • Wording clarification, correction of typographic errors and updating to comply with GDPR
2	Version 3.0	30.10.2018	Simon Kyle Joy Rahman	• Addition of methods to advertise trial to potential participants • Addition of other suitably qualified staff (e.g., CRN nurses) to deliver sleep intervention • Wording clarification, correction of typographic errors
3	Version 4.0	29.07.2019	Nargis Begum Simon Kyle	• Wording clarification of MCI as an exclusion criterion • Additional methods for participant contact by research team • Clarification of SAE Reporting timeline • Wording clarification, correction of typographic errors
4	Version 5.0	20.12.2019	Simon Kyle Ly-Mee Yu Nargis Begum	• Total sample size increased from 588 to 672 allow for higher than expected attrition • Addition to inclusion criteria for clarification • Addition to exclusion criteria to limit trial entry to 1 per household to minimise risk of contamination • Addition to send actigraphy data in lay-terms at participants request • Removal of comorbidities collection at 12-months

				• Wording clarification, correction of typographic errors