PROJECT TITLE

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

[Short Title: Health professional Administered Brief Insomnia Therapy (HABIT)]

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DETAILED PROJECT DESCRIPTION

SUMMARY OF RESEARCH

Background: Insomnia disorder is a common, persistent and impairing health problem affecting approximately 10% of the UK population. Multicomponent cognitive behavioural therapy (CBT) is the treatment of choice for insomnia but access is severely limited in primary care settings. Instead, patients are treated with sleep-promoting hypnotics, off-label sedative antidepressants or sleep hygiene guidelines. None of these approaches have been shown to improve insomnia in the long-term, and pharmacotherapy is characterised by issues of tolerance, addiction and acute and long-term side-effects. Systematic review evidence shows that a single component of CBT for insomnia, called Sleep Restriction Therapy (SRT), effectively treats insomnia under efficacy conditions. Recent pilot work from overseas suggests that a simplified version of SRT can be delivered in primary care, leading to improvements in insomnia severity and fatigue. While previous studies in UK primary care show multicomponent CBT to be effective when delivered by nurses or counsellors, there has been no large-scale evaluation of the clinical and cost-effectiveness of a brief and scalable behavioural intervention.

Aim: To test whether nurse-delivered SRT for insomnia disorder in primary care is both clinically- and cost-effective.

Design: Multicentre pragmatic individual randomised parallel group clinical trial of SRT+sleep hygiene (+TAU) versus sleep hygiene (+TAU), with a 6-month internal pilot phase. Stop/Go criteria will be based on feasibility of recruitment, treatment fidelity and contamination. Participants will be randomised (1:1) to SRT+SH or SH using a web-based randomisation programme, carried out by Oxford Primary Care Clinical Trials Unit (PC-CTU), with minimisation algorithm to ensure use of hypnotic medication at baseline, age, sex, site, and baseline insomnia severity are balanced across the two trial arms.

Setting: Participants will be recruited through general practices in Thames Valley, Lincolnshire, and Greater Manchester.

Target population: Adults (≥18 yrs) who meet DSM-5 criteria for insomnia disorder.

Health Technology Assessed: SRT involves restricting and standardising a patient's time in bed with the aim of increasing sleep pressure, overriding cognitive and physiological arousal, and strengthening circadian control of sleep. The net result is improved sleep consolidation and sleep quality.

Outcomes: The primary outcome will be self-reported insomnia severity (ISI) at 6 months. Secondary outcomes include sleep parameters (collected via one week of sleep diary and actigraphy), health-related quality of life (SF-36), patient-generated quality of life (GSII), health status (EQ-5D), depression (PHQ-9), work productivity (WPAI) and hypnotic use. Primary and secondary outcomes will be collected at baseline, 3, 6, and 12 months. A within-trial economic evaluation alongside the RCT will estimate the incremental cost-effectiveness of SRT+SH (+TAU) over SH (+TAU) only, from both NHS and societal perspectives. A process evaluation will be undertaken to explain trial results and understand intervention delivery, fidelity and acceptability.

Sample size: We will recruit 294 participants in each group (588 in total). This sample size has 90% power to detect a minimum effect size difference of 0.3, accounting for 20% attrition. Data analysis: Analysis will be intention-to-treat and follow the CONSORT statement. We will use a mixed-effect model for the analysis of the primary outcome. A full detailed analysis plan will be prepared prior to recruitment.

Timetable: Total duration=42 months. M1-M6=trial set-up; M7-M24=recruit 33 participants per month in total (11 per centre), inclusive of a 6 month internal pilot; M25-M36=Follow-up; M37-M42=analysis, write-up, trial close-out.

Team: We have assembled a multidisciplinary team, comprising world-leading expertise in sleep medicine, CBT/SRT, primary care, clinical trials methodology, statistics, qualitative scholarship, health economics and strong NIHR track record. Our team has a proven track record of both training nurses to deliver sleep therapies in primary care and executing large, multi-centre, clinical trials.

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; 6-8). ID is the most common sleep disorder and second most prevalent mental health complaint in Europe, affecting 10-12% of the adult population (9,10). 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 (6); and 2) a causal factor in the evolution and maintenance of physical and mental ill-health, particularly depression and cardiometabolic disease (11). Moreover, recent prospective data suggest that persistent insomnia is a robust risk factor for all-cause mortality, after adjustment for potential confounding factors (12). Although UK data are limited, extrapolation from per person cost data calculated in Canada (13), 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 (14,15).

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 (2;23); yet none of these are evidence based for persistent insomnia (NICE) and hypnotics have well-defined side-effects. 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 (31), and the training of non-sleep experts to deliver such therapies (17-19). 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. We conducted a systematic review to assess the efficacy of single-component SRT, finding medium-to-large effects for sleep continuity parameters (1). 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 (42). 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 (17-19) and 2) systematic examination of the patient experience of SRT (32). Responding to the commissioned call, we aim to test whether brief SRT, delivered by primary care nurses, is both clinically and cost-effective, relative to sleep hygiene advice. We have chosen practice nurses, instead of GPs, based on previous successful trial experience with this professional group (18) 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 (16). While previous studies in UK primary care show multicomponent CBT to be effective when delivered by nurses (17,18), counsellors (61), or through

self-help CBT booklets (62), *there has been no large-scale evaluation of the clinical and cost-effectiveness of a brief and scalable behavioural intervention.*

EVIDENCE EXPLAINING WHY THIS RESEARCH IS NEEDED NOW:

There is a clear discord between clinical science and clinical practice in the treatment of insomnia. NICE and prominent organisations in the United States (American College of Physicians; 22) endorse CBT as the first-line treatment for chronic insomnia, yet access continues to be limited. One recent study found that GPs in the UK had limited awareness of CBT as a potential management option for insomnia, and were unlikely to apply such techniques themselves (2). As a consequence, benzodiazepines – indicated for short-term use only – are commonly prescribed beyond indication (23,24), and sedative antidepressants are used off-label (2). The only non-pharmacological option available to patients is sleep hygiene advice, but this is rarely standardised beyond verbal guidance from the GP; is considered ineffective by GPs (2); and has no evidence base for sleep improvement (5). UK data show the prevalence of insomnia is increasing (25); a trend paralleled by increased hypnotic prescriptions (NHS Prescription Services). The situation is compounded by mounting evidence that sleeping pill use is associated with adverse health risks, including falls in the elderly (for whom insomnia is most prevalent), dementia, cancer and early mortality [26-29]. Thus, people with insomnia in primary care are not just failing to receive evidence-based, NICE recommended treatment; patient safety is potentially at risk through pharmacological alternatives.

To address the gulf between evidence and practice several innovations have taken place in the insomnia field. These include the development and evaluation of brief therapies, and training of non-sleep experts to deliver treatment. We have been at the international forefront of these innovations through our training of nurses and focus on components of CBT, specifically Sleep Restriction Therapy. The NHS is now in a position to take advantage of these developments through the systematic evaluation of nurse-delivered SRT in primary care. Such work is timely and important because 1) the detrimental health consequences of untreated insomnia are increasingly apparent; 2) insomnia is costly to the NHS and broader society; 3) insomnia prevalence is increasing; 4) existing treatment pathways are not evidence-based and may be harmful; 5) GPs are frustrated by lack of evidence-based alternatives to medication; and 6) brief psychological therapies for insomnia, grounded in behavioural medicine and sleep science, are ready for evaluation and translation into primary care.

AIMS AND OBJECTIVES:

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 relative to sleep hygiene. 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 relative to sleep hygiene, from NHS and societal perspectives.
3) To undertake a process evaluation to explain trial results and understand intervention delivery, fidelity and acceptability.

RESEARCH PLAN

HEALTH TECHNOLOGIES BEING ASSESSED

<u>Intervention structure and content – Sleep Restriction Therapy (SRT)</u>

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:

1. The first session will be a 30 minute face-to-face session with the nurse. Here, the rationale for SRT will be introduced, alongside a review of 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 (4). 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 (32).

2. One week later the nurse will speak to the patient over the phone (10 mins) to review progress. Based on review, and according to a structured algorithm (34), nurses will advise upon titration of the sleep schedule for the following seven days.
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. 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.

All treatment materials will be further reviewed by our PPI representatives although they are already in accessible plain English having been used successfully in our previous trials and in direct-to-public self-help books (63,34). For participants randomised to SRT (+sleep hygiene leaflet), there will be no limitation regarding other interventions as part of treatment as usual.

The intervention is based on our extensive research on the development, evaluation, implementation and mechanistic appraisal of CBT and SRT in diverse populations, using a range of professionals to deliver treatment (17-19,32-36,40). Four brief nurse sessions over 4 weeks is the preferred treatment schedule because 1) patient implementation and adherence is most challenging during this acute period (32,33,65); 2) studies in the US of brief insomnia interventions delivered by nurses over 4 sessions have shown to be effective (31); and 3) 4 sessions has been shown to be the optimal dose in dose-response studies (66). The brief and structured nature of SRT, focussing on sleep behaviour change over 4 weeks renders it highly suitable for deployment in primary care by practice nurses.

Training

Co-applicants Kyle, Espie and Siriwardena 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 (4 hours) workshop, consisting of informational delivery and structured review and discussion of example clinical vignettes. To further ensure treatment fidelity and demonstrate competence, nurses will also be asked to complete an online training module (30 minutes). All nurses will be trained to adhere to a SRT 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).

Supervision/peer group

Supervision will be supported by suitably qualified members of the research team and will consist of monthly online 'drop-in' supervision sessions. Sessions will be conducted using Webex, an online conference software package used to deliver our Oxford Online Programme in Sleep Medicine to health professionals. This will permit a drop-in session for nurses involved in the trial, to discuss cases and share experiences with other nurses involved in the trial.

Our structured approach to training and supervision, incorporating online components, has the potential to be highly scalable across UK primary care.

Treatment fidelity

We will ensure that treatment fidelity is embedded in all aspects of our trial (study design, training, delivery, receipt, and enactment), consistent with the fidelity framework put forward by the National Institutes of Health (NIH) behaviour change consortium (67). Several features of our approach will enhance treatment fidelity. For example, we have led the CBT and SRT field in defining and reporting on key therapeutic parameters (34). Emphasizing these throughout nurse training, delivery and supervision will be fundamental to fidelity enhancement. We will train nurses to adhere to a structured

manual and ask them 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. *Fidelity monitoring*: Consistent with best practice and expert recommendations (67), we will record all nurse-delivered SRT sessions using a digital voice recorder, provided both participants and nurses agree to be recorded. A random sample of sessions from each nurse will be independently rated against a structured list of key elements to be covered, defined a priori. We have experience of successfully employing these approaches to fidelity monitoring in primary care trials (18,68). We will make adherence to treatment a stop-go criterion for trial progression (see below).

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 (2,23). 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 (2). Due to our primary recruitment method (see below), the majority of patients will have consulted their practice for sleep disturbance, but some may not have (7,69). 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 treatment arm will be provided with the same standardised sleep hygiene information in the form of a leaflet. This leaflet has been developed by us and used in previous studies as a control condition (4). The content of sleep hygiene is based on recognised advice (3), 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.

DESIGN AND THEORETICAL/CONCEPTUAL FRAMEWORK

The study will utilise a multicentre, individual, pragmatic, randomised, parallel group, clinical trial design within primary care. We will incorporate an internal pilot phase over the first 6 months of recruitment with pre-specified 'stop-go' criteria.

TARGET POPULATION

The target population is adults aged 18 and over reporting persistent insomnia disorder.

INCLUSION CRITERIA

- Meet criteria for insomnia disorder according to DSM-5 (American Psychiatric Association)
- Age ≥18 yrs
- Able to attend appointments (face-to-face and over the phone)

EXCLUSION CRITERIA

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

- Pregnancy/pregnancy planning in the next 6 months
- Additional sleep disorder (Restless Legs Syndrome, Obstructive Sleep Apnoea, Narcolepsy, Parasomnia)
- Dementia
- Epilepsy
- Psychosis (Schizophrenia, Bipolar Disorder)
- Substance use disorder
- Suicidal ideation with intent

- Currently receiving cancer treatment or planned major surgery during trial phase
- night, evening or rotating shift-work
- trans-meridian travel planned for during the baseline or 4 week treatment phase

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). 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 sleep restriction therapy (SRT) appointments they will recommend that the participant seek additional support from their GP. We will record such information. We will draw up a trial specific standard operational procedure for all these purposes, to be included as part of the ethical submission and review procedure.

SETTING/CONTEXT

Treatment will be delivered by general practice nurses in their respective practices across Thames Valley, Lincolnshire and Greater Manchester. Participants will be recruited through their general practice. The multicentre design spreads the burden of recruitment and enables rapid response should we recruit below target. It also enhances trial external validity, given we will be recruiting across different regions of England with different socioeconomic profiles.

SAMPLING

SAMPLE SIZE

The trial aims to recruit a minimum of 588 participants over 18 months. To detect an average difference of 1.35 points (standard deviation=4.50) on the ISI at 6 months between 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 (42). Accounting for 20% attrition - estimated from our previous work in primary care (18) and meta-analytic data (43) - the total sample size required becomes 588 (i.e. 294 per group).

Most CBT evaluations show large effects on the ISI (38,39,43) 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 (42) 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 (70;75)] on the SF-36 (HRQoL), *our important secondary outcome*, at 90% power and 5% level of significance.

PARTICIPANT SELECTION

We will recruit 588 participants across 24 general practices (8 for Thames Valley, Manchester and Lincolnshire, respectively). Our approach to identifying potential participants will involve 1) searching practice lists for relevant sleep-related terms (including associated conditions and medications); 2) GP referral; and 3) poster adverts displayed in practice waiting areas. We have successfully used these methods in previous studies (17,18). Once identified, and after GP review of study suitability, participants will be sent a study information sheet, consent form, and two brief questionnaires, to confirm insomnia inclusion (71) and screen for potential exclusion variables. Participants will subsequently return the signed consent form and questionnaire measures. Those who appear eligible at this stage will undergo a brief phone call with the research team to further check for eligibility. Those

who remain eligible will be asked to complete baseline measures (see below) and subsequently be randomised to SRT+SH (+TAU) or SH (+TAU).

Based on prevalence criteria we anticipate that approximately 10% of patients per practice will be potentially eligible for the study, reflecting >700 people per average practice size. Preliminary practice searches with broad sleep-related terms using the FARSITE system (Greater Manchester CRN) identified 152,725 adults (18%) from a population total of 853,903. Taking into account our search method resolution, combined with listed exclusions, we conservatively estimate that 5% of patients per practice will be both reachable and eligible against our full inclusion/exclusion criteria. Assuming study uptake of 20% means that at least 70 people per practice will be identifiable, eligible and interested in taking part. An 18-month recruitment period means we need to recruit ~33 participants per month (across 24 practices). To achieve our recruitment target each practice will recruit 1-2 patients per month (25 in total) over an 18-month recruitment period. We consider this number to be eminently achievable and have already secured interest from 12 practices in the Thames Valley region alone. Importantly, adopting an individual patient randomised trial design - versus a cluster design - ensures that we can readily recruit additional practices should we recruit below our target *n*.

RANDOMISATION

Participants will be randomised (1:1) to SRT+SH (+TAU) or SH (+TAU) using a web-based randomisation programme, carried out by Oxford Primary Care Clinical trials Unit (PC-CTU), with a non-deterministic minimisation algorithm to ensure site, use of hypnotic medication (yes/no), age (18-65 yrs vs. > 65yrs), sex, and baseline insomnia severity (ISI score <21 vs. 22-28) are balanced across the two groups.

DATA COLLECTION

Outcomes will be assessed at baseline, 3,6 and 12 months post-randomisation. The primary outcome and important secondary outcomes will be measured with self-reported questionnaires (see below), returned via postal mail to the research team. Actigraphy watches will provide objective estimates of sleep. Actigraphic data will be scored by an experienced sleep researcher blind to group allocation. Consistent with NIHR recommendations we will also seek patient consent to access GP records for up to 5 years post-trial completion to enable analysis of longer-term health outcomes associated with insomnia treatment.

To facilitate outcome completion and participant retention across both trial arms we:

1. have costed in participant payment for outcome collection across the four time-points (£5; £10; £10; £15).
2. will provide stamped-addressed envelopes to facilitate return of measures and send several reminders.
3. will record email and mobile phone numbers, as additional means of contact, to permit supplementary prompts.
4. have included travel provision in order to facilitate collection of measures directly from participants' homes, should this be necessary.

<u>Primary outcomes</u>

The primary end-point will be the 7-item Insomnia Severity Index (72), a commonly used measure of *global insomnia severity*, measured at 6 months from baseline. The ISI is a recommended outcome measure in insomnia trials (45) and is the preferred tool because it 1) captures both night-time and daytime features of insomnia; and 2) has established criteria to determine treatment response and remission (73).

<u>Secondary outcomes</u>

- *Health-Related Quality of Life* will be assessed with the Short Form-36 (74) Health Survey (mental health and physical health component scores) which is a recommended outcome measure in insomnia trials (45), with sensitivity to CBT and SRT (e.g. 18,31,32,75).
- *Sleep-related quality of life* will be assessed with the Glasgow Sleep Impact Index (GSII; 8), a patient-generated tool. This measure asks patients to generate, in their own words, important

areas of their life affected by sleep, which are subsequently ranked and rated. Patient ranks and corresponding ratings can then be assessed at the group level over time. The GSII shows sensitivity to SRT in preliminary studies (8,32).

- *Sleep parameters* will be assessed for one week. Subjective sleep will be recorded with the consensus sleep diary (76) while actigraphy, a small wrist-watch device (Motionwatch8 CamNtech) that assesses movement to index sleep-wake, will be used to estimate objective sleep. Key sleep parameters derived from these measures include: sleep onset latency, wake-time after sleep-onset, sleep efficiency, total sleep time.
- *Depressive symptoms* will be measured with the Patient Health Questionnaire (PHQ-9; 77)
- *Work productivity* from those who are in employment will be measured with the Work Productivity and Activity Questionnaire (78), which has documented sensitivity to CBT for insomnia (60). This metric also permits modelling of societal costs associated with insomnia and its treatment.
- *Health Status* will be measured with the EQ-5D incorporating sleep bolt-on (79,80) permitting quantification of quality-adjusted life years (QALYs); the preferred metric by NICE.
- *Hypnotic medication use* will be quantified from GP records. Medications prescribed for sleep-promoting purposes (e.g., sedative antidepressants, antihistamines, melatonin) will also be recorded.

Process measures

We will assess adherence to SRT through sleep diaries and the sleep restriction adherence scale (36). We will also assess for treatment-related daytime symptom exacerbation through a purposely-developed measure by our group (32).

Process evaluation

As recommended for trials of complex interventions, we will conduct a process evaluation in line with MRC guidance (81). A sample of 15-20 patients receiving the intervention, purposively sampled to capture a broad range of treatment adherence, and 15-20 nurses delivering the intervention will be asked to take part in semi-structured interviews (telephone or face-to-face), designed to probe experiences of SRT alongside usual care, focusing on acceptability, feasibility, contextual factors and perceived impact/benefits. To inform and guide these interviews we will review, in advance, recorded nurse-patient consultations, providing context for individualised discussion of SRT delivery and implementation. Patients will be interviewed within 4 weeks of treatment completion and again between 3 and 6 months post-randomisation. We will also assess for contamination in the control group during the six month pilot through a brief telephone interview (see below). Data collection will begin during the internal pilot phase, with preliminary findings feeding back to inform, where appropriate, the continuation of trial procedures.

We will also conduct qualitative interviews with other key stakeholders, specifically GPs (n=5-10) and practice managers (n=5-10), focusing on contextual factors affecting implementation and outcomes. Interviews will begin during the pilot phase and continue into the main trial. Data will be managed by Nvivo 10 software and a Framework approach (82) will be utilised for analysis. The process evaluation will be conducted by experienced researchers based in Manchester and Lincoln, under the direction of co-applicants Bower and Siriwardena. We have extensive experience of process evaluations and qualitative research applied to the primary care management of insomnia (30,83,84).

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%	Stop Trial

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	Stop Trial

Contamination – Stop/Go [based on brief phone interview 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	Stop trial

DATA ANALYSIS

Statistical analysis

Analyses will be described in detail in a statistical analysis plan drafted by the Trial Statisticians and signed off by the CI and TSC. 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 all participant flow. Descriptive statistics of recruitment, drop-out, and completeness of interventions will be provided. The main efficacy analysis will be via intention-to-treat including all participants, with no planned interim analysis for efficacy or futility. Baseline characteristics will be presented by randomised group without formal statistical tests. We will test the primary hypothesis for between-group change in the primary outcome (ISI) at 6 months using three-level linear mixed effects model which models the response at 3,6, and 12 months, with baseline outcome measure and treatment assignment as fixed effects. Stratification variables will be included as fixed effects in the model, and practice and repeated measurements from the same participant will be accounted for by means of random effects. The linear mixed effects model will account for missing data assuming data are missing-at-random (MAR). Standard residual diagnostics will be assessed for the appropriateness of the model. Secondary outcomes will be analysed using an analogous method. Analysis of all treatment effects will be undertaken after follow-up (12 month) assessments are completed.

Economic analysis

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.

We will quantify participants' engagement with SRT from clinical records and summarise resource commitment from nurses and trainers in relation to therapy delivery. We will collect data on health care usage through GP records (primary care consultations and medication use) and the Client Service Receipt Inventory. Published sources (specifically 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: 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+sleep, which includes the sleep bolt-on, at baseline, 3, 6 and 12 months, and calculating the area under the curve.

The EQ-5D+sleep will be used to obtain utilities for both the original EQ-5D-3L, using the Dolan value set (85) and the EQ-5D+sleep using the Yang value set (80). The bolt-on itself has an insignificant effect on utility, based on valuations in the general population, but it has been suggested that public perceptions of sleep disturbance may differ from patient experiences in important ways. Using the bolt-on, we will explore 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.

DISSEMINATION AND PROJECT OUTPUTS

Outputs and engagement

We will publish our primary findings (on clinical and cost-effectiveness of SRT) in high-impact, peer-reviewed journals. There will be further important journal outputs in relation to process evaluation and secondary, exploratory moderator analyses. We will send trial participants a summary of study outcomes and present our findings at national (e.g. British Sleep Society, Society for Academic Primary Care), international (e.g. Sleep, North American Primary Care Research Group) and practitioner (e.g. RCGP) conferences.

The Sleep and Circadian Neuroscience Institute (SCNi) at Oxford has an international reputation in public engagement and we will work with our Wellcome Trust-funded public engagement officer to maximise reach of our findings. Co-applicant Espie frequently features on media outlets, appearing on prime time programmes to provide expert opinion on sleep issues (e.g. ITV News Tonight, BBC TV & Radio). He recently co-authored a report by the *Royal Society of Public Health* on the importance of sleep [https://www.rsph.org.uk/our-work/policy/championing-the-publics-health/sleep.html] and collaborated with the *Mental Health Foundation* in 2011 to raise awareness of the importance of sleep through the publication "Sleep Matters", which generated 300 related media articles. Such opportunities will provide additional means to disseminate key study findings to the general public.

Impact on NHS

Should our trial reveal SRT to be effective, we will make our manual and therapy materials available to the NHS forthwith. We are also committed to, and have extensive experience in, training of NHS staff through a range of training platforms. One scalable method is through our Oxford Online Programme in Sleep Medicine (directed by co-applicants Kyle and Espie; https://www.ndcn.ox.ac.uk/study/continuing-professional-development/the-oxford-online-programme-in-sleep-medicine). This innovative programme currently delivers training in sleep medicine (MSc, PgDip, CPD modules) to healthcare professionals from various backgrounds, in over

10 countries around the world. SRT is already part of the curriculum. We consider it highly feasible to support training and supervision of practice nurses across the NHS via this method. Indeed such an approach to sleep education and therapy training could also be extended to other primary care staff, including practice-based mental health therapists and clinical pharmacists, consistent with the five year plan for General Practice put forward by NHS England in 2016 [*General Practice, Forward View*; https://www.england.nhs.uk/gp/gpfv/].

At this time, given the fundamental importance of sleep to all aspects of health, not just mental or physical illness, we see practice nurses as the ideal inter-disciplinary professional group to incorporate sleep management into their clinical responsibilities. We believe that the introduction of nurse-delivered SRT to the NHS has the potential to fundamentally alter primary care management of insomnia, and by extension increase implementation of NICE guidance.

PLAN OF INVESTIGATION AND TIMETABLE

See Table 1 below.

Work package 1:
-3 to 0 Months= identify practices and begin preparation for ethical approval

Months 1-6= Trial set-up [Milestones: recruit team; secure ethics and governance approval; set-up trial procedures and committees (TST, DMEC); confirm practices and complete nurse training]

Work package 2:
Months 7-12= Internal pilot [Milestones: recruit 33 participants per month in total (11 per centre) + appraise trial progress against Stop/Go criteria to determine progression]

Months 13-24= Continue recruitment [Milestones: recruit 33 participants per month (11 per centre); cessation of recruitment (n=588) by M24]

Work package 3:
Months 25-36= Follow-up [Milestones: complete full follow-up data collection]

Work package 4:
Months 37-42= Trial close-out [Milestones: data cleaning; statistical and economic analysis; write-up, journal submission, HTA final report]

Work Packages		Year 1 (Months)		Year 2 (Months)		Year 3 (Months)		Year 4 (Months)	
	-3-0	0-6	7-12	13-18	19-24	25-31	32-36	37-42	
WP1: Trial Set-up									
WP1a: Finalisation of protocol									
WP1b: Ethics application									
WP1c: Identification of practices									
WP1d: Recruit team									
WP1e: Set up procedures and committees									
WP1f: Nurse training									
MS1: Finalise trial set-up		MS1							
MS2: Ethical approvals in place		MS2							
WP2: Internal Pilot & Trial Recruitment									
WP2a: Recruitment (~ 33 per month)									
WP2b: Appraise trial progress (stop/go criteria)									
MS3: Determine trial progression (internal pilot)			MS3						
MS4: Cessation of recruitment (n=588)					MS4				
WP3: Trial Follow-up									
WP3a: Collect follow-up data									
MS5: Complete follow-up data collection							MS5		
WP4: Trial Close-out									
WP4a: Data cleaning									
WP4b: Statistical and economic analysis									
WP4c: Manuscript write-up									
WP4d: HTA final report									
MS6: Analysis & report completed								MS6	

Table 1: Project schedule. WP=work package; MS=milestone

PROJECT MANAGEMENT

The trial will be led by the Primary Care Clinical Trials Unit (PC-CTU) at Oxford, which is part of Oxford Primary Care and Vaccines Collaborative Clinical Trials Unit (UKCRC registered trials unit). The CTU will submit the approval applications and develop the practice induction materials; set up and maintain the Trial Master File and Investigator Site Files; manage all amendments, adverse event/progress reporting to the Sponsor, communicating recruitment metrics and performance; data collection; supplies management; close-out procedures and archiving. Each site will be responsible for recruitment and induction of local site practices; for managing any issues that arise during the trial at a local level; for monitoring site recruitment rates; and for overseeing the regular searches on practice databases to identify further eligible cases. A central Trial Management Group (TMG) will oversee the day-to-day co-ordination and progress of the trial, managing any key issues and tasks to be addressed. A regular meeting will occur every month throughout the trial involving team members from all three sites, using face-to-face meetings, Skype meetings and teleconferences. Monitoring of the trial will be overseen by the quality assurance manager and study monitor who will work with local monitoring staff at each site to ensure participant safety, study quality and data integrity. An expert Data management team at the PC-CTU will ensure verification of the data for high quality trial results. The Chief Investigator will have dedicated time allocated in his job plan to steer the trial, and will be supported in this task by experienced co-applicants, an independent Trial Steering Committee (TSC) and Independent Data Monitoring Committee (IDMC).

We will appoint an independent Trial Steering Committee (TSC) chaired by a leading researcher, and including PPI representatives, to provide oversight of major operational management decisions. We will also appoint a Data Monitoring Committee (DMC) to monitor trial safety and draw up a DMC Charter according to the DAMOCLES guideline. We anticipate that the TSC will meet monthly initially during the set up phase and every 6 months thereafter.

We will also work closely with our NIHR CRN partners to optimise recruitment of practices and participants and good clinical practice.

APPROVAL BY ETHICS COMMITTEES

Full approval will be obtained via HRA. The trial be will conducted in accordance with the Declaration of Helsinki.

PUBLIC AND PATIENT INVOLVEMENT (PPI)

Our view is that meaningful public involvement will enhance the relevance, quality and value of our research. PPI has thus been central to the preparation of trial design and will continue to inform study procedures.

A draft of the study proposal and plain English summary were circulated to the Healthier Ageing Public and Patient Involvement (HAPPI) group, University of Lincoln. Four people provided detailed comments, helping to shape our proposal. They emphasised the importance of patient support during the early stages of treatment to promote adherence. Our treatment includes four brief nurse-contacts to support therapy titration and behavioural adherence. The group considered both sleep and quality of life (QoL) as important outcomes; we now ensure comprehensive coverage of both. It was also noted that QoL should be assessed in a patient-centred manner, capturing factors relevant to each individual. We now add the Glasgow Sleep Impact Index, a patient-generated measure of sleep-related QoL. It was remarked that sleep and QoL improvement may take time to evolve. We agree and now include follow-up assessments at 3, 6 and 12 months to appraise long-term gains, making our study the longest follow-up of SRT to date. The group raised the issue that "sleep restriction therapy" may not be attractive to prospective participants. We will refer to *sleep consolidation therapy* in our written materials.

PPI ACTIVITIES

Three members of HAPPI have agreed to join a participant advisory group, supporting project preparation, study progress review, and dissemination. Specifically, PPI representatives will review all patient-facing materials, including participant information sheets, consent forms, therapy workbooks and questionnaire measures. They will also advise on recruitment procedures and methods to engage prospective participants. Finally they will support the dissemination of trial results through review of the final HTA report, lay summary (which we will send to trial participants on completion of analysis), and media releases via the University of Oxford. Based on INVOLVE guidelines we have incorporated PPI costs into the proposal to cover travel, subsistence and honorarium for activities. We have not requested monies for training since our PPI representatives have previously undergone training as part of their involvement with HAPPI.

EXPERTISE

We have assembled a multi-disciplinary team, comprising world-leading expertise in sleep, CBT/SRT, primary care, and trials methodology. Applicant expertise is appropriately distributed across centres, ensuring that our trial will be executed successfully in all geographical regions while centrally co-ordinated from Oxford. Our team has extensive experience in trials of complex interventions within primary care. Such work has directly influenced NHS policy and practice.

COAPPLICANTS

CI Kyle is a Senior Research Fellow in the Sleep and Circadian Neuroscience Institute and Director of the Oxford Online Programme in Sleep Medicine. He is a leading authority on Sleep Restriction Therapy, daytime functioning/quality of life in insomnia, and the evaluation of insomnia treatments. He has extensive experience of clinical trials of sleep therapies, including through NIHR-HTA funding. He will be responsible for overall trial management and will be closely mentored by senior co-applicants Espie, Aveyard and Bower, who are leading trial methodologists with a history of successfully executing large NIHR-Funded clinical trials.

Co-Applicant Espie is Professor of Sleep Medicine, Emeritus Professor of Clinical Psychology and a Consultant Clinical Psychologist. He is internationally renowned for his work on the development and evaluation of insomnia treatments, and in making treatments more widely available through e.g., stepped care models, digital therapy. He has extensive experience in the evaluation of CBT for insomnia, in the primary care context specifically, and training nurses to deliver such therapies. He will support therapist training, provide clinical supervision and trial management mentorship to CI Kyle, whom he has worked with for >10 years.

Co-Applicant Aveyard is Professor of Behavioural Medicine and a General Practitioner. He is a leading expert in behavioural medicine and behaviour change, and has led multiple randomised trials in primary care (e.g., Aveyard et al., 2016 The Lancet). He will provide mentorship to CI Kyle, advise on nurse training, and support practice integration of study procedures.

Co-Applicant Bower is Professor of Health Services Research and a leading expert in clinical trials methodology, specifically design of and recruitment to randomised trials of complex interventions, and models of service delivery in primary care. He will provide mentorship to PI Kyle, act as centre lead (Manchester) and advise on recruitment strategies.

Co-Applicant Siriwardena is a Professor of Primary & Pre-Hospital Health Care and General Practitioner. He is the UK's leading expert in insomnia management in primary care and has published multiple qualitative and quantitative studies in this area. He will be centre lead (Lincoln), and support training and supervision of nurses in SRT delivery.

Co-applicant van Marwijk is a Professor of General Practice and GP. He is an expert in behaviour change and implementation, and the design and conduct of randomized trials in primary care. He will support nurse training and practice integration of study procedures.

Co-Applicant Yu is the Deputy Director and Lead Trial Statistician at the Oxford's Primary Care Clinical Trials Unit. She has over 20 years of experience as a medical statistician and specifically in clinical trials in the past 14 years. She has worked in a wide range of national and international trials, and as lead trial statistician on multiple NIHR-funded studies. She will lead the statistical aspects of the design, analysis and interpretation of the trial.

Co-applicant Ogburn is a Senior Clinical Trials Manager with extensive clinical trials management experience. She will lead clinical trial management.

Co-applicant Middlemass is a registered nurse and research fellow. She is an experienced qualitative researcher and has a background in qualitative insomnia research. With co-applicant NS, she will lead the process evaluation and PPI activities.

Co-applicant Abel is an experienced primary care health economist. She will lead the economic evaluation of SRT, mentored by Dr Jane Wolstenholme (Health Economics Research Centre, Oxford) and Dr Yaling Yang (Department of Primary Care Health Sciences, Oxford), who developed the EQ-5D+sleep bolt-on.

RESEARCH-RELATED STAFF

Dedicated researchers in Manchester and Lincoln (1.0 FTE, 42 months) will be responsible for study-set up within each region, participant recruitment and consent, eligibility screening, assessments, and qualitative evaluation.

One experienced post-doctoral sleep researcher based at the SCNi, Oxford (1.0 FTE, 18 months) will conduct blind scoring of actigraphy and sleep diaries.

The Trial Manager, under the supervision of co-applicant Ogburn, will work closely with the Lead Applicant to coordinate the project from set-up through to publication; be responsible for ensuring all

ethics and regulatory approvals are in place before the study commences, train and supervise the study coordinator, assist with the training of the site staff, liaise with the Sponsor to ensure that appropriate site contracts are in place, assist in the design of trial documents, will monitor recruitment and data submission, will assist in data checking and cleaning, and will organise and coordinate meetings of investigators and the TSC and DMC.

The Statistician will, under the supervision of co-applicant Yu, provide statistical input into the protocol, CRF and database development, preparation of the statistical analysis plan to ensure all data-points required for analysis are appropriately captured. The statistician will be responsible for conducting interim and final analysis as detailed in the statistical analysis plan, in addition to preparing reports for TSC and DMC meetings when required.

The IT Programmer will develop, build, validate and maintain a trial specific database along with providing training for trials staff in data entry. Duties will include ensuring database security and backups and providing the Data Manager and Statistician with quality control reports and statistical reports for the Investigators. In addition the programmer will assist with the design and updating of trial specific pages within the PC-CTU website.

The Data Manager will be responsible for ensuring the accuracy, consistency, completeness and above all validity of all trial data; oversee all central monitoring of data collected, raising data queries and following them to resolution, maintaining an audit trail according to the trial Standard Operating Procedures and liaise with the Programmer and Statistician to provide necessary reports to the Investigators. They will oversee all data entry (by the Research Assistant and the QA Monitor) and liaise with the Trial Manager and Statistician to decide when data should be locked and exported for analysis. He will ensure the appropriate archiving of all essential documents and data at the end of the trial, so it is available at a later date for inspection or further analysis.

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