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Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)

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Abstract

Introduction: Insomnia is a prevalent sleep disorder that negatively affects quality of life. Multicomponent cognitive-behavioural therapy (CBT) is the recommended treatment but access remains limited, particularly in primary care. Sleep restriction therapy (SRT) is one of the principal active components of CBT and could be delivered by generalist staff in primary care. The aim of this randomised controlled trial is to establish whether nurse-delivered SRT for insomnia disorder in primary care is clinically and cost-effective compared to sleep hygiene advice.

Methods and Analysis: In the HABIT trial, 588 participants meeting criteria for insomnia disorder will be recruited from primary care in England and randomised (1:1) to either nurse-delivered SRT (plus sleep hygiene booklet) or sleep hygiene booklet on its own. SRT will be delivered over four weekly sessions; total therapy time is approximately 1 hour. Outcomes will be collected at baseline, 3, 6 and 12 months post-randomisation. The primary outcome is self-reported insomnia severity using the insomnia severity index (ISI) at six months. Secondary outcomes include health-related and sleep-related quality of life, depressive symptoms, use of prescribed sleep medication, diary and actigraphy-recorded sleep parameters, and work productivity. Analyses will be intention to treat. Moderation and mediation analyses will be conducted and a cost-utility analysis and process evaluation will be performed.

Ethics and dissemination: Ethical approval was granted by the Yorkshire & the Humber - Bradford Leeds Research Ethics Committee (reference: 18/YH/0153). We will publish our primary findings (on clinical and cost-effectiveness) in high-impact, peer-reviewed journals. There will be further outputs in relation to process evaluation and secondary analyses focused on moderation and mediation. Trial results could make the case for the introduction of nurse-

delivered sleep therapy in primary care, increasing access to evidence-based treatment for people with insomnia disorder.

Trial registration: ISRCTN42499563

Key words: Insomnia disorder; sleep restriction therapy; primary care.

Strengths and Limitations of this study

- This multi-centre RCT will recruit 588 participants and will be the largest trial of sleep restriction therapy for insomnia.
- If found to be effective, brief nurse-delivered sleep restriction therapy is scalable and has the potential to be deployed in primary care.
- Owing to the nature of the intervention participants will not be blind to treatment allocation.

Introduction

Insomnia disorder is characterised by persistent problems with sleep initiation and maintenance, significantly impairing quality of life (1-3). Persistent insomnia affects approximately 10% of the adult population (4) and is a risk factor for several mental and physical health problems, particularly depression and cardiometabolic disease (5,6). Insomnia is also an expensive condition, associated with substantial direct and indirect costs; chiefly reflecting increased healthcare utilisation, work-related absenteeism, reduced work productivity and elevated accident risk (7-9).

Insomnia is treatable. The principal treatment options are hypnotic medication and cognitive behavioural therapy (CBT). The former is indicated for short-term use only, while the latter is the recommended first-line treatment and has been shown to engender sustained improvement in self-reported sleep and insomnia severity (10). Despite national and international clinical guidelines recommending CBT (11-13), access is almost non-existent in routine care across many health systems. In the absence of available treatment, general practitioners (GPs) are limited to administering sleep hygiene guidelines, hypnotics, and (off-label) sedative antidepressants (14-15); yet none are evidence-based for persistent insomnia (12;16), and hypnotics have well-defined side-effects (4). Barriers to wide-scale adoption of CBT for insomnia in routine healthcare relate to limited training, expertise and funding. A major development in the insomnia field, therefore, has been the dismantling of multicomponent, multisession CBT into brief and focussed treatment packages (17), and the training of non-specialists to deliver such therapies (18-20).

SRT has emerged as one of the primary active ingredients within multi-component CBT. The therapy involves restricting and standardising a patient's time in bed with the aim of

increasing homoeostatic sleep pressure, over-riding cognitive and physiological arousal, and strengthening circadian regulation of sleep (21). Tailored prescription of bed and rise-times over several weeks leads to improved sleep consolidation and reduction in insomnia severity. Its short length and simplicity renders SRT ideally suited for delivery by generalist staff in primary care.

A systematic review of trials comparing single-component SRT to waitlist control or sleep hygiene advice found medium-to-large effects on sleep continuity measures (22). Moreover, recent trials suggest SRT may be as effective as multicomponent CBT (23-24). One primary care trial compared brief SRT delivered by one GP with sleep hygiene advice (25). The participants were highly selected so that they were free from comorbidity or medication use. SRT significantly reduced insomnia severity at 6 months (Cohen's d=0.54). While this was an important first study, a pragmatic trial in primary care testing a scalable model of treatment delivery is clearly required.

We have developed a brief SRT protocol based upon 1) our extensive research using multicomponent CBT (18-20) and 2) systematic examination of the patient experience of SRT (26). We aim to test whether brief SRT (alongside sleep hygiene advice) 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 (18-20) 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 the delivery of brief behavioural interventions in primary care (27). While previous studies in UK primary care show multicomponent CBT to be effective when delivered by nurses (18,19), counsellors (28), or through self-help CBT booklets (29), there has been no large-scale evaluation of the clinical and cost-effectiveness of a brief and scalable behavioural intervention.

Study Objectives

The primary objective of the Health-professional Administered Brief Insomnia Therapy (HABIT) trial is to establish whether nurse-delivered SRT(+sleep hygiene [SH]) for insomnia disorder in primary care improves insomnia more than SH alone. We hypothesise that participants allocated to SRT(+SH) will demonstrate lower insomnia severity at 6 months post-randomisation compared with those allocated to SH alone.

Our secondary hypotheses are as follow:

1. Compared to SH, participants allocated to SRT(+SH) will report improvements in health-related quality of life, sleep-related quality of life, depressive symptoms, work productivity, pre-sleep arousal and sleep effort (at 3, 6 and 12 months).
2. Compared to SH, participants allocated to SRT(+SH) will demonstrate improvements in sleep parameters (diary and actigraphy-recorded) and report a reduction in use of sleep-promoting medication (6 and 12 months)
3. The effect of SRT(+SH) on insomnia severity will be mediated via reduction in sleep effort and pre-sleep arousal, consistent with theoretical models (21)

Other objectives:

4. To establish whether nurse-delivered SRT(+SH) for insomnia disorder in primary care is cost-effective compared to SH, from NHS and societal perspectives.
5. To undertake a process evaluation to understand intervention delivery, fidelity and acceptability.
6. To test whether insomnia phenotype moderates clinical benefit obtained from SRT(+SH). One prominent model posits that participants with short sleep duration are less likely to experience improvement in insomnia relative to those with normal sleep

duration (5). We will examine whether actigraphy-defined sleep duration (< 6hrs vs. ≥ 6hrs) at baseline moderates the effect of SRT on clinical outcomes (at 6 months)

7. To test whether SRT adherence mediates degree of clinical change (ISI) from baseline to 3 months, and from baseline to 6 months.

Methods and Analysis

Trial design

This is a pragmatic, multicentre, individually, randomised, parallel group, superiority trial to test whether nurse-delivered SRT(+SH), compared to SH alone, reduces insomnia severity. Both groups will receive treatment as usual without restriction. Participants will be recruited from general practices across three regions in the UK (Thames Valley, Greater Manchester and Lincolnshire). Assessments will take place at baseline, 3, 6 and 12 months post-randomisation (see Figure 1 for trial flow). The trial is prospectively registered with the ISRCTN (ISRCTN42499563). There is a Trial Steering Committee and Data Monitoring and Ethics Committee, both comprised of majority independent members.

[INSERT Figure 1]

Participants and recruitment

We aim to recruit participants aged 18 years and above in primary care practices who meet criteria for insomnia disorder. Since insomnia is not commonly coded within practice records we will search records for broad sleep-related terms, sleep-related medications and associated conditions to identify those most likely to be eligible, while applying exclusionary diagnoses. We will send invitations to identified individuals. 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); b) placing posters in practices (containing study contact details) and c) posting study adverts on the internet (e.g., practice websites, Facebook).

Participants will be screened for eligibility over the phone by the research team, or through self-completion of an online questionnaire. The inclusion criteria are as follows: a) participant is willing and able to give informed consent for participation; b) screen positive for insomnia symptoms on the Sleep Condition Indicator (SCI; 30) and meet DSM-5 criteria for insomnia disorder; c) self-reported sleep efficiency < 85% over the past month; d) age ≥18 years; and e) 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.

Exclusions will be limited principally to conditions which may be contraindicated for SRT, or render SRT inappropriate or ineffective: a) pregnant/pregnancy planning in the next 6 months; b) additional sleep disorder diagnosis (e.g., restless legs syndrome, obstructive sleep apnoea, narcolepsy) or "positive" screen on screening questionnaire (31); c) dementia or mild cognitive impairment; d) diagnosis of epilepsy, schizophrenia or bipolar disorder; e) current suicidal ideation with intent (32) or attempted suicide within past 2 months; f) currently receiving cancer treatment or planned major surgery during treatment phase; g) night, evening, early morning or rotating shift-work; h) currently receiving psychological treatment for insomnia from a health professional or taking part in an online treatment programme for insomnia; and i) life expectancy of <2 years.

Interventions

Sleep hygiene (SH)

Usual care for persistent insomnia typically involves sleep hygiene advice, repeat hypnotic prescription, and use of sedative antidepressants or antihistamines (14,15). For those aged

55+ years, melatonin may also be prescribed for insomnia, consistent with English guidelines from the National Institute for Health and Care Excellence (NICE; 13). Evidence shows that access to and awareness of CBT for insomnia in primary care is very limited (14).

Since NICE recommends that individuals with persistent insomnia should receive sleep hygiene advice, it is likely that some participants will have been exposed to such information in the past. Therefore, to avoid bias, all participants in both arms will be provided with the same standardised sleep hygiene information. We will provide a booklet comprising standard behavioural guidance about lifestyle and environmental factors associated with sleep and sleeplessness (33). Participants randomised to the SH arm will be sent their booklet via email or post.

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 (+treatment as usual, TAU) vs. SH (+TAU), permitting clear judgment to be made regarding the relative clinical utility of SRT in routine clinical practice.

Sleep restriction therapy (SRT)

Participants in the intervention arm will be offered nurse-delivered insomnia therapy in the form of SRT, a manualised behavioural intervention. See *Supplementary Table 1* for a detailed description of the intervention according to the template for intervention description and replication (TIDieR) checklist (34). Nurses will receive a four-hour training session on insomnia and the delivery of SRT as well as access to supporting resources (e.g. recorded video clips and a list of frequently asked questions and answers in relation to treatment delivery). Trained nurses will deliver manualised SRT over four brief, weekly sessions [total contact time = approximately 1hr 5 mins]. In session 1 the nurse will work through slides with the participant to introduce the rationale for SRT alongside a review of sleep diaries,

selection of bed and rise-times, management of daytime sleepiness (including implications for driving), 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. Participants will be provided with diaries and sleep efficiency calculation grids to support implementation of SRT instructions and permit weekly review of progress. Sessions 2, 3 and 4 will be brief sessions (10-15 minutes) to review progress, trouble-shoot any difficulties and advise upon adaptation of the sleep schedule (35). Sessions 1 and 3 will be in-person at the practice while sessions 2 and 4 will be over the phone.

Randomisation and blinding

Participants will be randomised (1:1) to SRT+SH or SH using a fully validated web-based randomisation program (Sortition), with a non-deterministic minimisation algorithm to balance region (Thames Valley, Lincolnshire, Greater Manchester), use of prescribed sleep promoting medication (yes/no), age (18-65 yrs vs > 65yrs), sex, baseline insomnia severity (ISI [36] score <22 vs. 22-28) and depression symptom severity (PHQ-9 [37] score <10 vs. 10-27) across the two groups.

This is an open-label study and therefore both participants and nurses will be aware of allocation. The participant information sheet 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. It will be impractical to blind the research team. The statisticians will remain blind to group allocation.

Assessments

The primary outcome is insomnia severity assessed by the insomnia severity index (ISI; 36), and will be measured at baseline, 3, 6, and 12 months post-randomisation. Secondary outcomes will similarly be measured at all four time-points and they are health-related quality of life (SF-36; 38), sleep-related quality of life (GSII; 3), depressive symptoms (PHQ-9; 37), work productivity and activity impairment (WPAI; 39), sleep effort (GSES; 40) and pre-sleep arousal (PSAS; 41). Questionnaires will be completed online or on paper, depending on participant preference. Self-reported sleep and use of sleep medication will be captured over 7 days using the consensus sleep diary (42) collected at baseline, 6 and 12 months. The consensus sleep diary will also be completed by the SRT group during the 4-week intervention phase. Actigraphy-defined sleep (CamNtech Ltd., MotionWatch 8) will be measured at baseline, 6 and 12 months. A modified version of the client service receipt inventory (CSRI; 43) and the EQ-5D-3L (44) will be administered at baseline, 3, 6 and 12 months to inform the cost-effectiveness evaluation. Participants will receive vouchers for completion of outcomes at each assessment point [vouchers = £5 at baseline, £10 at 3 months, £15 at 6 months and £10 at 12 months]. A summary of outcomes in relation to study objectives can be found in Table 1.

[INSERT Table 1]

Process evaluation

Consistent with MRC guidance for trials of complex interventions we will conduct a process evaluation (45). The aim of the process evaluation is to explore nurse-delivered SRT in the primary care setting by examining implementation, mechanisms of impact, and contextual factors that facilitate or impede intervention delivery. This will complement the outcomes evaluation, helping to understand the trial results through exploring:

(i) nurse perceptions of SRT, including training and support

(ii) fidelity of intervention delivery by nurses

(iii) whether participants in the control group also receive SRT (i.e. contamination)

(iv) the participant experience of SRT, including reflections on implementing the sleep schedule and perceptions of benefit, as well as any unexpected consequences

(v) whether level of adherence mediates degree of clinical improvement

(vi) views of primary care staff in relation to the implementation of SRT beyond the context of the trial.

In order to capture experiences and perceptions of SRT semi-structured interviews will be conducted by the research team with a sample of practice nurses (n=15), trial participants (n=15) and practice managers or GPs (n=15) across the three study sites. These will be in-depth semi-structured telephone, *Skype* or face-to-face interviews 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. Participant interviews will take place after the intervention phase. Participants will receive a £10 voucher for interview participation.

To enable fidelity assessment, all in-person SRT sessions will be recorded (if participants consent). A sample of these sessions will be rated by a trained member of the research team. We will monitor potential for control group contamination (i.e. SH participants accessing SRT via the trained practice nurse) through questionnaire (43) completion at 3 and 6 months follow-up. SRT engagement will be measured with respect to number of treatment sessions attended, while adherence to therapeutic instructions (prescribed bed and rise-times) will be quantified from sleep diaries recorded during the 4-week intervention phase.

Sample size

To detect a difference on the ISI of 1.35 points (standard deviation=4.50) 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 based on the results from the primary care evaluation of SRT conducted by Falloon and colleagues (25). Accounting for 20% attrition the total number of participants required to be recruited is 588 (294 per group). Should attrition be higher, at 25% or 30%, the total number of participants required would be 628 (314 per group) or 672 (336 per group), respectively.

Most CBT evaluations show large effects on the ISI (46) but these studies have small samples, are tightly controlled and recruit participants from the community, who are generally 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 (25) 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 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 (47)] 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 (48) and guidelines recommending that a minimum of 12 interviews are needed to achieve data saturation (49).

Adverse events

The likelihood of serious adverse events (SAEs) occurring due to treatment is low since neither CBT-I/SRT nor sleep hygiene advice have been reported to cause them. We define SAEs as any untoward medical occurrence that either: a) results in death; b) is life-threatening; c) requires inpatient hospitalisation or prolongation of existing hospitalisation; d) results in persistent or significant disability/incapacity; or d) consists of a congenital anomaly or birth defect. Therapists and participants will be prompted to self-report SAEs. Along with self-reporting of SAEs, we will also use responses on the CSRI (43) - which includes questions on hospitalisations - to follow-up participants who report being hospitalised. We will record planned hospital admissions at baseline and, when they occur, these will not be counted as SAEs. SAEs will be assessed for severity, seriousness and relatedness to study procedures by a medically qualified member of the team. SAEs will be reported after date of randomisation until either the date of trial withdrawal or 6-month follow-up completion, whichever is earlier.

Because implementation of SRT may be associated with increased sleepiness we will also record 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.

Analysis Plan

Statistical Analysis

The primary statistical analysis will be carried out on the basis of intention-to-treat (ITT). We will endeavour to obtain full follow-up data on every participant to allow full ITT analysis, but we will inevitably experience the problem of missing data due to withdrawal, loss to follow-up, or nonresponse to some questionnaire items. The results from the trial will be prepared as comparative summary statistics with 95% confidence intervals. All the tests will

be performed at a 5% two-sided significance level. The study results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (50). A full detailed statistical analysis plan will be prepared and finalised before data collection is complete.

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 (alongside reasons for missingness where available) and the missing data pattern will be explored, though the mixed effects model implicitly accounts 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 effect models with appropriate link function. We will undertake pre-specified sub-group analysis of the primary outcome by actigraphy-defined sleep duration at baseline (< 6hrs vs. ≥ 6hrs). Mediation analyses will be conducted using the approach of Baron and Kenny (51) but will follow the adaptation in Freeman et al (52) 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 for 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.

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 NICE guidelines (53). Additional analyses will examine costs from a societal perspective, quantifying productivity losses in relation to absenteeism and presenteeism.

From trial records we will quantify participants' attendance at SRT sessions and hence nurse time and also assess the resources used in training. We will collect data on health care usage through GP records (medication use) and a self-reported version of CSRI (43). The Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care (54) and NHS Reference Costs (55) will be used to apply national average unit costs to service utilisation and construct a cost profile per participant. Productivity will be quantified from the Work Productivity and Activity Impairment (WPAI; 39) questionnaire, 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 (44) at baseline, 3, 6 and 12 months, and

calculating the area under the curve. An incremental cost-effectiveness ratio will be calculated using costs-per-QALY with a 12-month time horizon. We will add a sleep dimension (56) to the standard EQ-5D-3L allowing us to examine, in exploratory analysis, the relationship between sleep bolt-on responses and other measures of insomnia severity, to identify whether the sleep question correlates with other measures of sleep satisfaction and self-reported health. Probabilistic and deterministic sensitivity analysis will be conducted to characterise the uncertainty around the cost-effectiveness estimates.

Qualitative analysis

We will use a Framework approach (57) for qualitative data analysis supported by QSR NVivo (version 11), 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 occur as the interviews are transcribed and this analysis will allow schedules and data collection to be further developed. We will analyse qualitative process data prior to knowing trial outcomes to avoid biased interpretation.

Patient and public involvement

Four people from the Healthier Ageing Public and Patient Involvement (HAPPI) group, University of Lincoln, read and provided detailed comments on the original grant proposal, helping to shape key methodological choices (e.g., measurement selection). Two individuals will contribute during the trial by reviewing participant information sheets, consent form, therapy workbooks and questionnaire measures. They will advise on recruitment procedures and methods to engage prospective participants/ retain enrolled participants. Finally they will support the dissemination of trial results through review of the final report to the funder, lay summary (which we will send to trial participants on completion of analysis), and media releases by the University of Oxford.

Ethics and dissemination

The trial has received both Health Research Authority approval (IRAS: 238138) and ethical approval (Yorkshire & the Humber - Bradford Leeds Research Ethics Committee, reference: 18/YH/0153). We will publish our findings in high-impact, peer-reviewed journals. We will send trial participants a summary of study outcomes.

Trial status

The trial commenced recruitment in August 2018 and will continue recruiting until approximately March 2020, with final outcome data expected around April 2021.

Contributors

SDK is the Chief Investigator, conceived the project, had overall responsibility for the trial design and treatment design, and drafted the trial protocol. CM contributed to the trial protocol and drafted the manuscript. PA, CAE, PB, NS, LMY, LA, EO, SA contributed to trial design. SDK, CAE and NS contributed to treatment design. LMY is responsible for statistical analysis. LA is responsible for economic analysis. NS/SA are responsible for the process evaluation analysis. NB is the Trial Manager. Centre leads are SDK/PA (Oxford), PB (Greater Manchester) and NS (Lincoln).

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are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Competing interests

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 (the Sleepio programme). This study is in no way connected to Big Health Ltd or Sleepio. SDK declares non-financial support from Big Health Ltd. in relation to no-cost access to Sleepio for use in clinical trial research. All other authors declare no competing interests.

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List of tables and figures

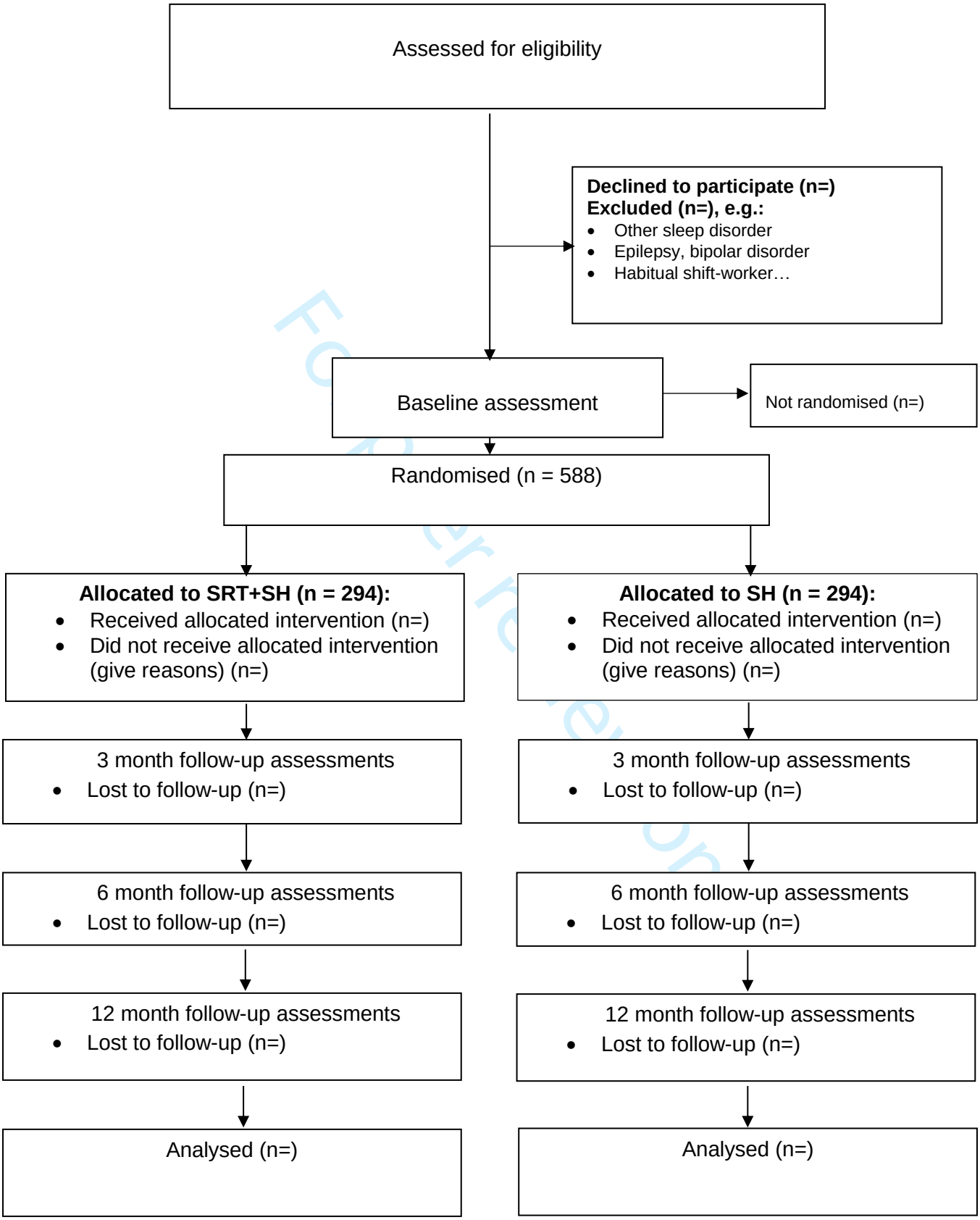
Table 1: Objectives and outcome measures

Objectives	**Outcome Measures**	**Timepoint(s) of evaluation of this outcome measure**
Primary Objective: To compare the effect of SRT+SH versus SH on insomnia severity	Self-rated insomnia severity using the 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 HRQoL	Self-rated HRQoL using the SF-36 questionnaire (Total Score, MCS, PCS)	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 CSD (SOL;WASO;SE;TST;SQ)	Baseline, 6- and 12-months post-randomisation.
To compare the effect of SRT+SH versus SH on objective estimates of sleep	Actigraphy-defined 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 medications; and 6) pre-sleep arousal and sleep effort	1. Self-rated quality of life using the GSII [Ranks 1,2,3] 2. Self-rated depressive symptoms severity using the PHQ-9 3. Self-rated WPAI questionnaire 4. Use of prescribed hypnotics (quantified from 7-day diary) 5. Use of other prescribed sleep-promoting medications (quantified from 7-day diary) 6. Self-rated arousal and sleep effort using the PSAS and GSES	Baseline, 3, 6- and 12-months post-randomisation. Medication use will be quantified from diaries at baseline, 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), CSRI, ISI, WPAI, EQ-5D-3L	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 or practice managers.	Throughout the trial.
Moderator analysis:	Actigraphy, ISI, GSII, SF-36	Baseline and 6

Test whether objective short sleep duration at baseline (< 6hrs vs. ≥ 6hrs) moderates the effect of SRT on clinical outcomes (at 6 months)		months.
To compare the number of specified adverse events between the groups	Questionnaire	Baseline, 3, 6, and 12 months.

CSD = Consensus Sleep Diary; CSRI = client service receipt inventory; EQ-5D-3L = EuroQol questionnaire; GSES = Glasgow sleep effort scale; GSII = Glasgow sleep impact index; HRQoL = health-related quality of life; ISI = insomnia severity index; MCS = mental component summary score; PCS = physical component summary score; PHQ-9 = patient health questionnaire; PSAS = pre-sleep arousal scale; SE = sleep efficiency; SOL =sleep-onset latency; SF-36 = short-form 36 questionnaire; SH=sleep hygiene; SRT = sleep restriction therapy; SQ = sleep quality; TST= total sleep time; WASO = wake-time after sleep onset; WPAI = work productivity and activity impairment questionnaire.

Figure 1: Trial Flow



Supplementary Table 1: Template for Intervention Description and Replication (TIDieR) checklist

Name of intervention	Sleep Restriction Therapy (SRT) for Insomnia Disorder
Why	Insomnia is assumed to be maintained, in part, by excessive amounts of time in bed and irregular sleep-wake schedules, which serve to fragment sleep. Time in bed awake further contributes to insomnia because the bed/bedroom environment may become associated with wakefulness over time; subsequently acting as a trigger for arousal and sleep fragmentation. SRT aims to: 1) restrict time in bed (to enhance sleep efficiency); 2) regularise the timing of the sleep-wake cycle; and 3) recondition the bed-sleep association (21).
What: Materials	*Materials for patients*: patients will be provided with a folder at the beginning of the intervention. This folder contains: a copy of the slides used during session 1; worksheets to complete during sessions 1-4; sleep diaries and sleep efficiency grids to enable recording of sleep efficiency each day during the 4-week intervention period; and a booklet which contains enhanced information on the background and implementation of SRT, including quotes from patients who have previously underwent SRT, as well as guidance on sleep hygiene. This guidance briefly covers lifestyle behaviours (e.g., caffeine, alcohol use, exercise) and environmental factors (e.g., light, temperature) that influence sleep. *Materials for nurses*: nurses will be provided with a training folder (as part of a 4-hour training session) which contains background information on sleep, insomnia and SRT. The folder also contains a list of frequently asked questions in relation to trouble-shooting and specific patient scenarios that may arise, with standardised guidance on how to navigate. Nurses will be provided with access to two recorded videos that give an overview of insomnia and SRT implementation. Nurses will be provided with a power-point slide set to work through with each patient during session 1. They will also work through a structured checklist (completed online) for each session to guide content and structure.
What: Procedures	In session 1 the nurse will work through Power-Point slides with the participant to introduce the rationale for SRT alongside a review of (baseline) sleep diaries, selection of bed and rise-times (for the following seven nights), management of daytime sleepiness (including implications for driving), and discussion of barriers/facilitators to implementation. Participants will be provided with diaries and sleep efficiency calculation grids to support implementation of SRT instructions and permit weekly review of progress. Sessions 2, 3 and 4 will be brief sessions to review progress, trouble-shoot any difficulties and advise upon titration of the sleep schedule.
Who provided	Registered practice nurses in primary care and research nurses from clinical research networks will be trained to deliver SRT.
How provided	Intervention is delivered one-to-one, involving both face-to-face (sessions 1 and 3) and over the phone contacts (sessions 2 and 4).
Where	The face-to-face sessions will take place in a consultation room within general practice.
When and how much	Intervention will be delivered over four sessions. Duration and format of sessions is as follows: • session 1 (in-person, ~30 minutes) • session 2 (by phone, ~10 minutes) • session 3 (in-person, ~15 minutes) • session 4 (by phone, ~10 minutes).

<table>
<tr>
<td>Tailoring</td>
<td>The treatment will be tailored to each individual's sleep pattern but follows standardised instructions for setting and titrating time in bed (TIB):

<table>
<tr><th>Criterion</th><th>SRT</th></tr>
<tr><td>Calculation of prescribed time in bed (TIB)</td><td>Based on average total sleep time (TST) from baseline 7-day sleep diary. Minimum TIB = 5 hrs.</td></tr>
<tr><td>Rise time selection</td><td>Time that aligns with working schedule and can be adhered to 7 days a week</td></tr>
<tr><td>Bed time selection</td><td>Typically delayed in order to equal the prescribed TIB.</td></tr>
<tr><td>Weekly adjustments to TIB based on average sleep efficiency for 7 days (SE) (sessions 2-4)</td><td>a) SE ≥ 85% increase TIB by 15 minutes
b) SE = 80-84% no change to TIB
c) SE ≤ 79% decrease TIB by 15 minutes

Adjustments (advancing or delaying) are typically made to the prescribed bed-time.</td></tr>
<tr><td>Napping</td><td>Recommendation to eliminate all napping</td></tr>
</table>

The nurse will be encouraged to adapt the TIB prescription in the following circumstances: patient is struggling to adhere, or cannot tolerate the restriction; patient is excessively sleepy; or change in health precludes full implementation. In these circumstances nurses will be encouraged to agree a revised time in bed (increasing in 15 minute blocks) until the patient is content.

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

BMJ Open

Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)

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Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)

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Abstract

Introduction: Insomnia is a prevalent sleep disorder that negatively affects quality of life. Multicomponent cognitive-behavioural therapy (CBT) is the recommended treatment but access remains limited, particularly in primary care. Sleep restriction therapy (SRT) is one of the principal active components of CBT and could be delivered by generalist staff in primary care. The aim of this randomised controlled trial is to establish whether nurse-delivered SRT for insomnia disorder is clinically and cost-effective compared to sleep hygiene advice.

Methods and Analysis: In the HABIT trial, 588 participants meeting criteria for insomnia disorder will be recruited from primary care in England and randomised (1:1) to either nurse-delivered SRT (plus sleep hygiene booklet) or sleep hygiene booklet on its own. SRT will be delivered over four weekly sessions; total therapy time is approximately 1 hour. Outcomes will be collected at baseline, 3, 6 and 12 months post-randomisation. The primary outcome is self-reported insomnia severity using the insomnia severity index (ISI) at six months. Secondary outcomes include health-related and sleep-related quality of life, depressive symptoms, use of prescribed sleep medication, diary and actigraphy-recorded sleep parameters, and work productivity. Analyses will be intention to treat. Moderation and mediation analyses will be conducted and a cost-utility analysis and process evaluation will be performed.

Ethics and dissemination: Ethical approval was granted by the Yorkshire & the Humber - Bradford Leeds Research Ethics Committee (reference: 18/YH/0153). We will publish our primary findings (on clinical and cost-effectiveness) in high-impact, peer-reviewed journals. There will be further outputs in relation to process evaluation and secondary analyses focused on moderation and mediation. Trial results could make the case for the introduction of nurse-delivered sleep therapy in primary care, increasing access to evidence-based treatment for people with insomnia disorder.

Trial registration: ISRCTN42499563

Key words: Insomnia disorder; sleep restriction therapy; primary care.

Strengths and Limitations of this study

- This multi-centre RCT will recruit 588 participants and will be the largest trial of sleep restriction therapy (SRT) for insomnia.
- This study will test whether brief, nurse-delivered SRT in primary care is clinically and cost-effective.
- The control group will be provided with a sleep hygiene booklet while the SRT arm will receive both nurse-delivered SRT and a sleep hygiene booklet
- The primary outcome is self-reported insomnia severity while secondary outcomes include actigraphy-defined sleep, use of sleep medication, quality of life and depressive symptoms.
- Owing to the nature of the intervention participants will not be blind to treatment allocation.

Introduction

Insomnia disorder is characterised by persistent problems with sleep initiation and maintenance, significantly impairing quality of life (1-3). Persistent insomnia affects

approximately 10% of the adult population (4) and is a risk factor for several mental and physical health problems, particularly depression and cardiometabolic disease (5,6). Insomnia is also an expensive condition, associated with substantial direct and indirect costs; chiefly reflecting increased healthcare utilisation, work-related absenteeism, reduced work productivity and elevated accident risk (7-9).

Insomnia is treatable. The principal treatment options are hypnotic medication and cognitive behavioural therapy (CBT). The former is indicated for short-term use only, while the latter is the recommended first-line treatment and has been shown to engender sustained improvement in self-reported sleep and insomnia severity (10). Despite national and international clinical guidelines recommending CBT (11-13), access is almost non-existent in routine care across many health systems. In the absence of available treatment, general practitioners (GPs) are limited to administering sleep hygiene guidelines, hypnotics, and (off-label) sedative antidepressants (14-15); yet none are evidence-based for persistent insomnia (12;16), and hypnotics have well-defined side-effects (4). Barriers to wide-scale adoption of CBT for insomnia in routine healthcare relate to limited training, expertise and funding. A major development in the insomnia field, therefore, has been the dismantling of multicomponent, multisession CBT into brief and focussed treatment packages (17), and the training of non-specialists to deliver such therapies (18-20).

SRT has emerged as one of the primary active ingredients within multi-component CBT. The therapy involves restricting and standardising a patient's time in bed with the aim of increasing homoeostatic sleep pressure, over-riding cognitive and physiological arousal, and strengthening circadian regulation of sleep (21). Tailored prescription of bed and rise-times over several weeks leads to improved sleep consolidation and reduction in insomnia severity.

Its short length and simplicity renders SRT ideally suited for delivery by generalist staff in primary care.

A systematic review of trials comparing single-component SRT to waitlist control or sleep hygiene advice found medium-to-large effects on sleep continuity measures (22). Moreover, recent trials suggest SRT may be as effective as multicomponent CBT (23-24). One primary care trial compared brief SRT delivered by one GP with sleep hygiene advice (25). The participants were highly selected so that they were free from comorbidity or medication use. SRT significantly reduced insomnia severity at 6 months (Cohen's d=0.54). While this was an important first study, a pragmatic trial in primary care testing a scalable model of treatment delivery is clearly required.

We have developed a brief SRT protocol based upon 1) our extensive research using multicomponent CBT (18-20) and 2) systematic examination of the patient experience of SRT (26). We aim to test whether brief SRT (alongside sleep hygiene advice) 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 (18-20) 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 the delivery of brief behavioural interventions in primary care (27). While previous studies in UK primary care show multicomponent CBT to be effective when delivered by nurses (18,19), counsellors (28), or through self-help CBT booklets (29), there has been no large-scale evaluation of the clinical and cost-effectiveness of a brief and scalable behavioural intervention.

Study Objectives

The primary objective of the Health-professional Administered Brief Insomnia Therapy (HABIT) trial is to establish whether nurse-delivered SRT(+sleep hygiene [SH]) for insomnia disorder in primary care improves insomnia more than SH alone. We hypothesise that participants allocated to SRT(+SH) will demonstrate lower insomnia severity at 6 months post-randomisation compared with those allocated to SH alone.

Our secondary hypotheses are as follow:

1. Compared to SH, participants allocated to SRT(+SH) will report improvements in health-related quality of life, sleep-related quality of life, depressive symptoms, work productivity, pre-sleep arousal and sleep effort (at 3, 6 and 12 months).
2. Compared to SH, participants allocated to SRT(+SH) will demonstrate improvements in sleep parameters (diary and actigraphy-recorded) and report a reduction in use of sleep-promoting medication (6 and 12 months)
3. The effect of SRT(+SH) on insomnia severity will be mediated via reduction in sleep effort and pre-sleep arousal, consistent with theoretical models (21)

Other objectives:

4. To establish whether nurse-delivered SRT(+SH) for insomnia disorder in primary care is cost-effective compared to SH, from NHS and societal perspectives.
5. To undertake a process evaluation to understand intervention delivery, fidelity and acceptability.
6. To test whether insomnia phenotype moderates clinical benefit obtained from SRT(+SH). One prominent model posits that participants with objective short sleep duration are less likely to experience improvement in insomnia relative to those with normal sleep duration (5). We will examine whether actigraphy-defined sleep duration

(< 6hrs vs. ≥ 6hrs) at baseline moderates the effect of SRT on clinical outcomes (at 6 months)

7. To test whether SRT adherence mediates degree of clinical change (ISI) from baseline to 3 months, and from baseline to 6 months.

Methods and Analysis

Trial design

This is a pragmatic, multicentre, individually randomised, parallel group, superiority trial to test whether nurse-delivered SRT(+SH), compared to SH alone, reduces insomnia severity. Both groups will receive treatment as usual without restriction. Participants will be recruited from general practices across three regions in the UK (Thames Valley, Greater Manchester and Lincolnshire). Assessments will take place at baseline, 3, 6 and 12 months post-randomisation (see Figure 1 for trial flow). The trial is prospectively registered with the ISRCTN (ISRCTN42499563). There is a Trial Steering Committee and Data Monitoring and Ethics Committee, both comprised of majority independent members.

[INSERT Figure 1]

Participants and recruitment

We aim to recruit participants aged 18 years and above in primary care practices who meet criteria for insomnia disorder. Since insomnia is not commonly coded within practice records we will search records for broad sleep-related terms, sleep-related medications and associated conditions to identify those most likely to be eligible, while applying exclusionary diagnoses. We will send invitations to identified individuals. 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); b) placing posters in practices (containing study contact details) and c) posting study adverts on the internet (e.g., practice websites, Facebook).

Participants will be screened for eligibility over the phone by the research team, or through self-completion of an online questionnaire. The inclusion criteria are as follows: a) participant is willing and able to give informed consent for participation; b) screen positive for insomnia symptoms on the Sleep Condition Indicator (SCI; 30) and meet DSM-5 criteria for insomnia disorder; c) self-reported sleep efficiency < 85% over the past month; d) age ≥18 years; and e) 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.

Exclusions will be limited principally to conditions which may be contraindicated for SRT, or render SRT inappropriate or ineffective: a) pregnant/pregnancy planning in the next 6 months; b) additional sleep disorder diagnosis (e.g., restless legs syndrome, obstructive sleep apnoea, narcolepsy) or "positive" screen on screening questionnaire (31); c) dementia or mild cognitive impairment; d) diagnosis of epilepsy, schizophrenia or bipolar disorder; e) current suicidal ideation with intent (32) or attempted suicide within past 2 months; f) currently receiving cancer treatment or planned major surgery during treatment phase; g) night, evening, early morning or rotating shift-work; h) currently receiving psychological treatment for insomnia from a health professional or taking part in an online treatment programme for insomnia; and i) life expectancy of <2 years. On completion of screening, eligible participants will be invited to a baseline appointment with a member of the research team where they will provide written informed consent (see *appendices*), complete baseline questionnaires (see *assessments* section) and asked to complete a sleep diary and wear an actigraph watch for the following week. Participants will return the completed diary and actigraph watch to the research team via postal mail.

Interventions

Sleep hygiene (SH)

Usual care for persistent insomnia typically involves sleep hygiene advice, repeat hypnotic prescription, and use of sedative antidepressants or antihistamines (14,15). For those aged 55+ years, melatonin may also be prescribed for insomnia, consistent with English guidelines from the National Institute for Health and Care Excellence (NICE; 13). Evidence shows that access to and awareness of CBT for insomnia in primary care is very limited (14).

Since NICE recommends that individuals with persistent insomnia should receive sleep hygiene advice, it is likely that some participants will have been exposed to such information in the past. Therefore, to avoid bias, all participants in both arms will be provided with the same standardised sleep hygiene information. We will provide a booklet comprising standard behavioural guidance about lifestyle and environmental factors associated with sleep and sleeplessness (33). Participants randomised to the SH arm will be sent their booklet via email or post.

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 (+treatment as usual, TAU) vs. SH (+TAU), permitting clear judgment to be made regarding the relative clinical utility of SRT in routine clinical practice.

Sleep restriction therapy (SRT)

Participants in the intervention arm will be offered nurse-delivered insomnia therapy in the form of SRT, a manualised behavioural intervention. See *Supplementary Table 1* for a detailed description of the intervention according to the template for intervention description and replication (TIDieR) checklist (34). We will initially aim to train practice nurses to deliver SRT

but in order to overcome scheduling issues that may arise, or limitations on practice capacity, we will also train research nurses from clinical research networks to support delivery. Nurses will receive a four-hour training session on insomnia and the delivery of SRT as well as access to supporting resources (e.g. recorded video clips and a list of frequently asked questions and answers in relation to treatment delivery). Trained nurses will deliver manualised SRT over four brief, weekly sessions [total contact time = approximately 1hr 5 mins]. In session 1 the nurse will work through slides with the participant to introduce the rationale for SRT alongside a review of sleep diaries, selection of bed and rise-times, management of daytime sleepiness (including implications for driving), 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 (identical to those provided to the control arm). Participants will be provided with diaries and sleep efficiency calculation grids to support implementation of SRT instructions and permit weekly review of progress. Sessions 2, 3 and 4 will be brief sessions (10-15 minutes) to review progress, trouble-shoot any difficulties and advise upon adaptation of the sleep schedule (35). Sessions 1 and 3 will be in-person at the practice while sessions 2 and 4 will be over the phone.

Randomisation and blinding

Following completion of baseline assessments participants will be randomised (1:1) to SRT+SH or SH using a fully validated web-based randomisation program (Sortition), with a non-deterministic minimisation algorithm to balance region (Thames Valley, Lincolnshire, Greater Manchester), use of prescribed sleep promoting medication (yes/no), age (18-65 yrs vs > 65yrs), sex, baseline insomnia severity (ISI [36] score <22 vs. 22-28) and depression symptom severity (PHQ-9 [37] score <10 vs. 10-27) across the two groups. Members of the research team will inform participants of their allocation.

This is an open-label study and therefore both participants and nurses will be aware of allocation. The participant information sheet 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. It will be impractical to blind the research team. The statisticians will remain blind to group allocation.

Assessments

The primary outcome is insomnia severity assessed by the insomnia severity index (ISI; 36), and will be measured at baseline, 3, 6, and 12 months post-randomisation. Secondary outcomes will similarly be measured at all four time-points and they are health-related quality of life (SF-36; 38), sleep-related quality of life (GSII; 3), depressive symptoms (PHQ-9; 37), work productivity and activity impairment (WPAI; 39), sleep effort (GSES; 40) and pre-sleep arousal (PSAS; 41). Questionnaires will be completed online or on paper, depending on participant preference. Self-reported sleep and use of sleep medication will be captured over 7 days using the consensus sleep diary (42) collected at baseline, 6 and 12 months. The consensus sleep diary will also be completed by the SRT group during the 4-week intervention phase. Actigraphy-defined sleep (CamNtech Ltd., MotionWatch 8) will be measured at baseline, 6 and 12 months. A modified version of the client service receipt inventory (CSRI; 43) and the EQ-5D-3L (44) will be administered at baseline, 3, 6 and 12 months to inform the cost-effectiveness evaluation. Participants will receive vouchers for completion of outcomes at each assessment point [vouchers = £5 at baseline, £10 at 3 months, £15 at 6 months and £10 at 12 months]. A summary of outcomes in relation to study objectives can be found in Table 1.

[INSERT Table 1]

Process evaluation

Consistent with MRC guidance for trials of complex interventions we will conduct a process evaluation (45). The aim of the process evaluation is to explore nurse-delivered SRT in the primary care setting by examining implementation, mechanisms of impact, and contextual factors that facilitate or impede intervention delivery. This will complement the outcomes evaluation, helping to understand the trial results through exploring:

(i) nurse perceptions of SRT, including training and support

(ii) fidelity of intervention delivery by nurses

(iii) whether participants in the control group also receive SRT (i.e. contamination)

(iv) the participant experience of SRT, including reflections on implementing the sleep schedule and perceptions of benefit, as well as any unexpected consequences

(v) whether level of adherence mediates degree of clinical improvement

(vi) views of primary care staff in relation to the implementation of SRT beyond the context of the trial.

In order to capture experiences and perceptions of SRT semi-structured interviews will be conducted by the research team with a sample of practice nurses (n=15), trial participants (n=15) and practice managers or GPs (n=15) across the three study sites. Interview participants will be invited from 5 practices from each of the three trial recruitment centres. The practices will be selected to reflect a range of practice types (e.g., based on practice size, or membership of a consortium) and, for each selected practice, one nurse, one trial participant and one GP or practice manager will be interviewed. These will be in-depth semi-structured telephone, *Skype* or face-to-face interviews 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. Participant

interviews will take place after the intervention phase. Participants will receive a £10 voucher for interview participation.

To enable fidelity assessment, all in-person SRT sessions will be recorded (if participants consent). A sample of these sessions will be rated by a trained member of the research team using a bespoke rating scale. We will monitor potential for control group contamination (i.e. SH participants accessing SRT via the trained practice nurse) through questionnaire (43) completion at 3 and 6 months follow-up. SRT engagement will be measured with respect to number of treatment sessions attended, while adherence to therapeutic instructions (prescribed bed and rise-times) will be quantified from sleep diaries recorded during the 4-week intervention phase.

Sample size

To detect a difference on the ISI of 1.35 points (standard deviation=4.50) 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. This equates to a standardised effect size of 0.3. The standard deviation was based on the results from the primary care evaluation of SRT conducted by Falloon and colleagues (25). Accounting for 20% attrition the total number of participants required to be recruited is 588 (294 per group). Should attrition be higher, at 25% or 30%, the total number of participants required would be 628 (314 per group) or 672 (336 per group), respectively.

Most CBT evaluations show large effects on the ISI (46) but these studies have small samples, are tightly controlled and recruit participants from the community, who are generally 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 (25) 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 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 (47)] 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 (48) and guidelines recommending that a minimum of 12 interviews are needed to achieve data saturation (49).

Adverse events

The likelihood of serious adverse events (SAEs) occurring due to treatment is low since neither CBT/SRT nor sleep hygiene advice have been reported to cause them. We define SAEs as any untoward medical occurrence that either: a) results in death; b) is life-threatening; c) requires inpatient hospitalisation or prolongation of existing hospitalisation; d) results in persistent or significant disability/incapacity; or d) consists of a congenital anomaly or birth defect. Therapists and participants will be prompted to self-report SAEs. Along with self-reporting of SAEs, we will also use responses on the CSRI (43) - which includes questions on hospitalisations - to follow-up participants who report being hospitalised. We will record planned hospital admissions at baseline and, when they occur, these will not be counted as SAEs. SAEs will be assessed for severity, seriousness and relatedness to study procedures by a medically qualified member of the team. SAEs will be reported after date of randomisation until either the date of trial withdrawal or 6-month follow-up completion, whichever is earlier.

Because implementation of SRT may be associated with increased sleepiness we will also record 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.

Analysis Plan

Statistical Analysis

The primary statistical analysis will be carried out on the basis of intention-to-treat (ITT). We will endeavour to obtain full follow-up data on every participant to allow full ITT analysis, but we will inevitably experience the problem of missing data due to withdrawal, loss to follow-up, or nonresponse to some questionnaire items. The results from the trial will be prepared as comparative summary statistics with 95% confidence intervals. All the tests will be performed at a 5% two-sided significance level. The study results will be reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) guidelines (50). A full detailed statistical analysis plan will be prepared and finalised before data collection is complete.

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 (alongside reasons for missingness where available) and the missing data pattern will be explored, though the mixed effects model implicitly accounts 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 effect models with appropriate link function. We will undertake pre-specified sub-group analysis of the primary outcome by actigraphy-defined sleep duration at baseline (< 6hrs vs. ≥ 6hrs). Mediation analyses will be conducted using the approach of Baron and Kenny (51) but will follow the adaptation in Freeman et al (52) 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 for 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.

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 NICE guidelines (53). Additional analyses will examine costs from a societal perspective, quantifying productivity losses in relation to absenteeism and presenteeism.

From trial records we will quantify participants' attendance at SRT sessions and hence nurse time and also assess the resources used in training. We will collect data on health care usage through GP records (medication use) and a self-reported version of CSRI (43). The Personal Social Services Research Unit (PSSRU) Costs of Health and Social Care (54) and NHS Reference Costs (55) will be used to apply national average unit costs to service utilisation and construct a cost profile per participant. Productivity will be quantified from the Work Productivity and Activity Impairment (WPAI; 39) questionnaire, 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 (44) at baseline, 3, 6 and 12 months, and calculating the area under the curve. An incremental cost-effectiveness ratio will be calculated using costs-per-QALY with a 12-month time horizon. We will add a sleep dimension (56) to the standard EQ-5D-3L allowing us to examine, in exploratory analysis, the relationship between sleep bolt-on responses and other measures of insomnia severity, to identify whether the sleep question correlates with other measures of sleep satisfaction and self-reported health. Probabilistic and deterministic sensitivity analysis will be conducted to characterise the uncertainty around the cost-effectiveness estimates.

Qualitative analysis

We will use a Framework approach (57) for qualitative data analysis supported by QSR NVivo (version 11), 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 occur as the interviews are transcribed and this analysis will allow schedules and

data collection to be further developed. We will analyse qualitative process data prior to knowing trial outcomes to avoid biased interpretation.

Patient and public involvement

Four people from the Healthier Ageing Public and Patient Involvement (HAPPI) group, University of Lincoln, read and provided detailed comments on the original grant proposal, helping to shape key methodological choices (e.g., measurement selection). Two individuals will contribute during the trial by reviewing participant information sheets, consent form, therapy workbooks and questionnaire measures. They will advise on recruitment procedures and methods to engage prospective participants/ retain enrolled participants. Finally they will support the dissemination of trial results through review of the final report to the funder, lay summary (which we will send to trial participants on completion of analysis), and media releases by the University of Oxford.

Ethics and dissemination

The trial has received both Health Research Authority approval (IRAS: 238138) and ethical approval (Yorkshire & the Humber - Bradford Leeds Research Ethics Committee, reference: 18/YH/0153). We will publish our findings in high-impact, peer-reviewed journals. We will send trial participants a summary of study outcomes.

Trial status

The trial commenced recruitment in August 2018 and will continue recruiting until approximately March 2020, with final outcome data expected around April 2021.

Contributors

SDK is the Chief Investigator, conceived the project, had overall responsibility for the trial design and treatment design, and drafted the trial protocol. CM contributed to the trial protocol and drafted the manuscript. PA, CAE, PB, AS, LMY, LA, EO, SA contributed to trial design. SDK, CAE and AS contributed to treatment design. LMY is responsible for statistical analysis. LA is responsible for economic analysis. AS/SA are responsible for the process evaluation analysis. NB is the Trial Manager and helped draft the manuscript. Centre leads are SDK/PA (Oxford), PB (Greater Manchester) and AS (Lincoln). All authors inputted to the trial protocol and commented on the manuscript.

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Competing interests

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 (the Sleepio programme). This study is in no way connected to Big Health Ltd or Sleepio. SDK declares non-financial support from Big Health Ltd. in relation to no-cost access to Sleepio for use in clinical trial research. All other authors declare no competing interests.

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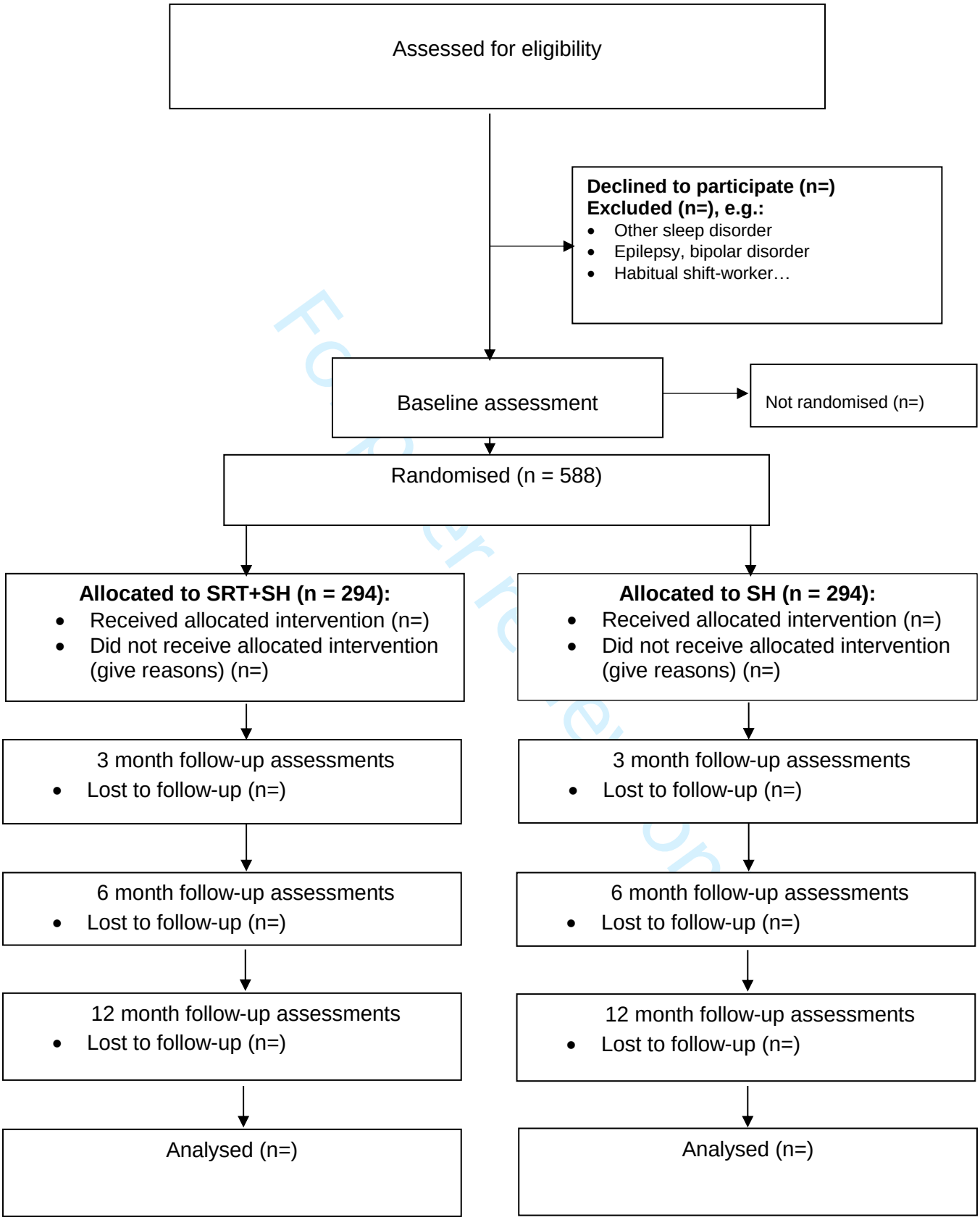
List of tables and figures

Objectives	Outcome Measures	Timepoint(s) of evaluation of this outcome measure
Primary Objective: To compare the effect of SRT+SH versus SH on insomnia severity	Self-rated insomnia severity using the 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 HRQoL	Self-rated HRQoL using the SF-36 questionnaire (Total Score, MCS, PCS)	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 CSD (SOL;WASO;SE;TST;SQ)	Baseline, 6- and 12-months post-randomisation.
To compare the effect of SRT+SH versus SH on objective estimates of sleep	Actigraphy-defined 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 medications; and 6) pre-sleep arousal and sleep effort	1. Self-rated quality of life using the GSII [Ranks 1,2,3] 2. Self-rated depressive symptoms severity using the PHQ-9 3. Self-rated WPAI questionnaire 4. Use of prescribed hypnotics (quantified from 7-day diary) 5. Use of other prescribed sleep-promoting medications (quantified from 7-day diary) 6. Self-rated arousal and sleep effort using the PSAS and GSES	Baseline, 3, 6- and 12-months post-randomisation. Medication use will be quantified from diaries at baseline, 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), CSRI, ISI, WPAI, EQ-5D-3L	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 or practice managers.	Throughout the trial.
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 on the ISI	ISI, PSAS, GSES Sleep diary during intervention phase, ISI	Baseline, 3 and 6 months.
To compare the number of specified adverse events between the groups	Questionnaire	Baseline, 3, 6, and 12 months.

CSD = Consensus Sleep Diary; CSRI = client service receipt inventory; EQ-5D-3L = EuroQol questionnaire; GSES = Glasgow sleep effort scale; GSII = Glasgow sleep impact index; HRQoL = health-related quality of life; ISI = insomnia severity index; MCS = mental component summary score; PCS = physical component summary score; PHQ-9 = patient health questionnaire; PSAS = pre-sleep arousal scale; SE = sleep efficiency; SOL =sleep-onset latency; SF-36 = short-form 36 questionnaire; SH=sleep hygiene; SRT = sleep restriction therapy; SQ = sleep quality; TST= total sleep time; WASO = wake-time after sleep onset; WPAI = work productivity and activity impairment questionnaire.

Figure 1: Trial Flow



Supplementary Table 1: Template for Intervention Description and Replication (TIDieR) checklist

Name of intervention	Sleep Restriction Therapy (SRT) for Insomnia Disorder
Why	Insomnia is assumed to be maintained, in part, by excessive amounts of time in bed and irregular sleep-wake schedules, which serve to fragment sleep. Time in bed awake further contributes to insomnia because the bed/bedroom environment may become associated with wakefulness over time; subsequently acting as a trigger for arousal and sleep fragmentation. SRT aims to: 1) restrict time in bed (to enhance sleep efficiency); 2) regularise the timing of the sleep-wake cycle; and 3) recondition the bed-sleep association (21).
What: Materials	*Materials for patients*: patients will be provided with a folder at the beginning of the intervention. This folder contains: a copy of the slides used during session 1; worksheets to complete during sessions 1-4; sleep diaries and sleep efficiency grids to enable recording of sleep efficiency each day during the 4-week intervention period; and a booklet which contains enhanced information on the background and implementation of SRT, including quotes from patients who have previously underwent SRT, as well as guidance on sleep hygiene. This guidance briefly covers lifestyle behaviours (e.g., caffeine, alcohol use, exercise) and environmental factors (e.g., light, temperature) that influence sleep. *Materials for nurses*: nurses will be provided with a training folder (as part of a 4-hour training session) which contains background information on sleep, insomnia (including its development and maintenance) and SRT. The folder also contains a list of frequently asked questions in relation to trouble-shooting and specific patient scenarios that may arise, with standardised guidance on how to navigate. Nurses will be provided with access to two recorded videos that give an overview of insomnia and SRT implementation. Nurses will be provided with a power-point slide set to work through with each patient during session 1. They will also work through a structured checklist (completed online) for each session to guide content and structure.
What: Procedures	In session 1 the nurse will work through Power-Point slides with the participant to introduce the rationale for SRT alongside a review of (baseline) sleep diaries, selection of bed and rise-times (for the following seven nights), management of daytime sleepiness (including implications for driving), and discussion of barriers/facilitators to implementation. Participants will be provided with diaries and sleep efficiency calculation grids to support implementation of SRT instructions and permit weekly review of progress. Sessions 2, 3 and 4 will be brief sessions to review progress, trouble-shoot any difficulties and advise upon titration of the sleep schedule.
Who provided	Registered practice nurses in primary care and research nurses from clinical research networks will be trained to deliver SRT.
How provided	Intervention is delivered one-to-one, involving both face-to-face (sessions 1 and 3) and over the phone contacts (sessions 2 and 4).
Where	The face-to-face sessions will take place in a consultation room within general practice.
When and how much	Intervention will be delivered over four sessions. Duration and format of sessions is as follows: • session 1 (in-person, ~30 minutes) • session 2 (by phone, ~10 minutes) • session 3 (in-person, ~15 minutes) • session 4 (by phone, ~10 minutes).

<table>
<tr>
<td>Tailoring</td>
<td>The treatment will be tailored to each individual's sleep pattern but follows standardised instructions for setting and titrating time in bed (TIB):
<table>
<tr><th>Criterion</th><th>SRT</th></tr>
<tr><td>Calculation of prescribed time in bed (TIB)</td><td>Based on average total sleep time (TST) from baseline 7-day sleep diary. Minimum TIB = 5 hrs.</td></tr>
<tr><td>Rise time selection</td><td>Time that aligns with working schedule and can be adhered to 7 days a week</td></tr>
<tr><td>Bed time selection</td><td>Typically delayed in order to equal the prescribed TIB.</td></tr>
<tr><td>Weekly adjustments to TIB based on average sleep efficiency for 7 days (SE) (sessions 2-4)</td><td>a) SE ≥ 85% increase TIB by 15 minutes
b) SE = 80-84% no change to TIB
c) SE ≤ 79% decrease TIB by 15 minutes

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

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

Study Title: HABIT (**H**ealth professional **A**dministered **B**rief **I**nsomnia **T**herapy) Study

Chief Investigator: Dr Simon Kyle
The University of Oxford
Email: habit.study@phc.ox.ac.uk
Tel: 01865-289-591

Research Ethics Committee: Yorkshire and The Humber – Bradford Leeds

PARTICIPANT INFORMED CONSENT FORM

	Please INITIAL each box	
1. I confirm I have read and understood the patient information sheet dated 29.07.19 (version 3.0) for the HABIT study and have had the opportunity to consider the information ask questions and had these answered satisfactorily.		
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, and without my medical care or legal rights being affected.		
3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the University of Oxford, University of Manchester, University of Lincoln, regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. This information will be transferred to the above named Universities and stored securely. I give permission for these individuals to have access to my records.		
4. I agree for members of the research team to access my medical notes for the purposes of data collection relevant to this study.		
5. Depending on the study group that I am assigned to, I agree for my sessions with the nurse to be digitally voice recorded. *(Optional)*	Yes	No
6. I agree to take part in a more in depth discussion about my experiences of being part of the HABIT study and that this will be audio-recorded and sent to an external transcription company for transcribing and analysed by researchers. I understand that my anonymised quotations may be used in publications and training materials. *(This part of the study is optional)*	Yes	No
7. I agree to be contacted via email, post and phone by the research team only about the study.		
8. I would like to receive summary of the study findings at the end of the study. *(Optional)*	Yes	No
9. I agree to take part in the above study.		

PRINT Participant name	Participant signature	Date
PRINT Researcher name	Researcher signature	Date

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

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

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	3
	2b	All items from the World Health Organization Trial Registration Data Set	
Protocol version	3	Date and version identifier	
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1,19
	5b	Name and contact information for the trial sponsor	
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19

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

Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	____10, Figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	___13_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____7,8_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	_____10_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	_____10-11____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_____10-11____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_____11_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_____11_____

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	11
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	15-17
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15-17
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	7
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14-15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	19
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appended
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	

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