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Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial

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ABSTRACT

Introduction: Insomnia is a prevalent sleep disorder that causes substantial personal and societal harm. Open-label placebo treatment (OLP) has been proposed as a method of using the placebo effect ethically, but the efficacy and acceptability of OLP for insomnia is currently unknown.

Methods and analysis: This study uses a cohort multiple randomised controlled trial design to compare OLP, conventional placebo (CP), and no treatment for insomnia. Two-hundred and sixty-seven participants with at least moderate insomnia (Insomnia Severity Index, ISI≥10) will be recruited into an observational study and have their sleep monitored over a two-week period. Participants will then be randomised to one of three groups: invite to OLP, invite to CP described deceptively as a new pharmacological agent, or no invite/observational control (OC). Those in OLP and CP accepting the invite receive identical placebos for a two-week treatment period while sleep is monitored in all participants. The primary outcome is insomnia severity (ISI) at the end of the treatment period. Secondary outcomes include treatment uptake, objective and subjective sleep parameters, fatigue, mood, expectancy, treatment satisfaction and side effects. Predictors of uptake and responses to OLP and CP will be explored.

Ethics and dissemination: The trial has been approved by The University of Sydney Human Research Ethics Committee. Written informed consent is obtained from every participant. OLP and CP participants accepting the invite undergo an additional information and consent process. Results will be disseminated via peer-reviewed conference proceedings and publications.

Trial registration: ANZCTRXXXXXX [pending, final will be provided prior to publication]

Strengths and limitations of this study:

- This will be the first study to test whether open-label placebo (OLP) is effective and acceptable for insomnia.
- The use of a cohort multiple RCT design provides a more ecologically valid no treatment comparison and will allow us to compare the efficacy and uptake of OLP relative to conventional placebo.
- The inclusion of actigraphy means that we can assess the effect of OLP on both self-report and objective sleep outcomes.
- Predictors of uptake and responding will be explored, including expectancy.
- Because of the nature of the study, participants and researchers cannot be blind to treatment allocation, but the data analysis will be conducted by a blind researcher.

INTRODUCTION

Insomnia is the most common sleep disorder, with an estimated prevalence of 10% in the adult population[1]. It is characterised by difficulty initiating or maintaining sleep along with daytime impairment and/or distress and carries substantial personal and socioeconomic burden[2 3]. People with insomnia have poorer quality of life, greater risk of experiencing other medical conditions and psychiatric disorders, increased healthcare utilisation, and reduced work productivity[4-6]. While a range of pharmacological treatments are available for insomnia, those that demonstrate efficacy are associated with significant risks in terms of adverse effects and the potential for dependence (e.g. benzodiazepines)[7] whereas those with lower risk profiles have limited efficacy (e.g. melatonin.)[8]. As such, there remains a pressing need to identify safe and effective treatments to combat the burden of insomnia.

Interestingly, many randomised placebo-controlled trials of insomnia interventions find that participants allocated to receive placebo treatment experience significant symptom improvement.[9-11]. This suggests that insomnia may be responsive to the placebo effect, whereby the treatment context itself elicits positive expectancies that trigger improvement[12-14]. Importantly, improvement in placebo groups of these trials holds even when directly compared with no treatment[15], which is important because it indicates that placebo treatment generates more improvement in insomnia than can be accounted for by other factors, such as, spontaneous recovery and regression to the mean[16]. Therefore, it may be possible to harness the placebo effect in order to reduce the burden of insomnia.

Placebo interventions are likely to carry fewer adverse events than pharmacological interventions and have lower cost than psychological interventions[17]. On the other hand, the deception that is typically associated with placebo administration presents a significant barrier to

its clinical use because of the violation of patient trust and informed consent[18]. However, this barrier is based on the assumption that deception is necessary to elicit a placebo effect, which has recently been called into question by 'open-label placebo' trials [19].

Open-label placebo (OLP) trials involve administering placebo treatment with full disclosure that the treatment is in fact a placebo, meaning there is no deception. Only a handful of randomized controlled trials (RCTs) testing open-label placebo have been conducted to date and none with insomnia, but the available data suggest some promising results. For example, in an RCT comparing three weeks' of open-label placebo with 'treatment as usual' (TAU) for chronic pain, Carvalho and colleagues'[20] found that OLP significantly reduced pain and disability, with moderate to large effect sizes. Similar results have been found in RCTs of open-label placebo for irritable bowel syndrome[21], depression[22], and allergic rhinovirus[23]. As a result, there have been increasing calls to explore the potential efficacy of open label-placebos in clinical practice[19 24].

Despite the promising preliminary findings, several criticisms of existing open-label placebo trials have been raised. The most common criticism concerns the types of control group used in these studies, typically either TAU or waitlist control. The very nature of OLP treatment means that participants and treatment administrators are not blind to treatment allocation, which could introduce problems to do with demand characteristics and experimenter bias[19]. While that may be difficult to avoid, a further problem with existing controls is that knowingly being allocated to receive no treatment may induce nocebo effects and thereby poorer outcomes in the control group that artificially inflates the apparent efficacy of the open-label placebo treatment[19 25]. In addition to concerns regarding the type of control groups used, a second potential important limitation is the fact that participants in OLP trials are typically recruited via advertisements that

explicitly describe the intervention as a 'novel mind-body treatment'[20 21]. Little is known about the characteristics of individuals who volunteer to participate in 'novel mind-body treatment' research, but differences between such samples and the general population could significantly limit the generalisability of existing OLP trials. For example, if only those who already hold strong beliefs about the power of the mind are enrolled, then this could overestimate the efficacy of OLP effects in the general population. A final limitation is that existing OLP trials have failed to include a comparison with conventional deceptive placebo treatment, which is important to evaluate the relative cost-benefit of open-label versus conventional placebo.

To address these gaps, the current study tests the efficacy of open-label placebo for insomnia (OPIN) using a novel cohort multiple randomised controlled trial (cmRCT) design comparing OLP, conventional (deceptive) placebo (CP), and no treatment to address limitations raised concerning existing open-label placebo trials. The cmRCT involves a two-stage consent process whereby participants are first recruited to an observational study (with no mention of intervention) and are then randomised to be invited to the treatment arms or to remain in the observational arm (i.e. act as controls). This design will allow us to compare the efficacy and uptake of open-label versus conventional placebo, relative to a no treatment group, in a more generalisable sample of participants who are not specifically interested in mind-body treatments, and in a scenario in which participants in the control group are unaware that they are missing out on a potentially desirable treatment. The protocol and study design are guided by the recommendations set out in the SPIRIT 2013 Statement[26]. The results of this research will provide first ever evidence concerning whether open-label placebo is an effective treatment for insomnia and the strongest test of open-label placebo effects in general to date.

Objectives

Primary Objectives

1. Determine whether open-label placebo is associated with a reduction in self-report insomnia symptoms in people with at least moderate insomnia compared to conventional placebo and no treatment.

Secondary Objectives

1. Determine the rate of uptake of open-label placebo relative to conventional placebo
2. Determine whether open-label placebo is associated with improvements in objective and subjective sleep parameters, as well as daytime fatigue, depression, anxiety, and stress, expectancy, treatment satisfaction and side effects, relative to conventional placebo and no treatment.
3. Identify which demographic, individual, and clinical, characteristics predict uptake of and responses to open-label and conventional placebo.

METHOD AND ANALYSIS

Trial Design

As shown in Figure 1, The OPIN trial will use a parallel three arm cmRCT design[27] comparing open-label placebo, conventional (deceptive) placebo, and no treatment for insomnia. In the first stage, a cohort of participants with at least moderate insomnia will be recruited into an observational study, with no mention of potential later randomisation to treatment. Following an initial two-week baseline observation period, in the second stage, participants will be randomised

to one of three groups; invite to open-label placebo treatment (OLP), invite to conventional placebo treatment (CP), or no invite, observational control group (OC). Randomisation will be on a 2:2:1 ratio (full details below). The OLP treatment will be openly described as consisting of no active ingredient and instead aiming to capitalise on the placebo effect. The CP treatment will be described as a new pharmacological agent designed to promote sleep. Those invited into open-label and conventional placebo treatment who consent to receive treatment will be asked to take evening dosages of placebo medication for two weeks, while those not invited will remain in the observational cohort for those two weeks, without the potential disappointment of missing out on a treatment.

Participants

To be eligible, participants must report insomnia symptoms of moderate or greater severity (determined by a ≥10 on the Insomnia Severity Index; ISI[28]), be at least 18 years old, be proficient in English, and able to attend the study clinic three times over one month. The following exclusion criteria will apply: (1) sleep disorder other than insomnia, (2) currently pregnant, planning to conceive in the next 3 months, or <1 year post-partum, (3) serious medical illness requiring invasive treatment/surgery (e.g. cancer) or heavy substance use, (4) severe psychiatric co-morbidity (e.g. psychosis, bipolar disorder, depression) or risk of self-harm or suicidality, (5) currently receiving psychological treatment or taking regular (i.e. ≥1/week) medication for sleep (including prescription or over-the-counter medications, herbal supplements, homeopathic formulations), (6) undertaking regular shift work, and/or (7) intending to travel to a destination >2 hours' time difference in the next three months**.** Participants will be reimbursed AUD$60 upon completion of the study and will be provided with 12 months free

access to Sleepio [29], a commercially available digital cognitive behaviour therapy app that has been found to reduce insomnia symptoms.

[FIGURE 1 HERE]

Study Setting

The study will take place at The University of Sydney, Australia. The study will be advertised online (e.g. University research volunteer sites, Facebook) with a link to the study website. The study website includes information about the observational component of the study, researcher contact details, and a link to complete the online screening. Eligible participants will then be contacted and invited to attend the study site to provide consent and commence participation.

Materials and Measures

Placebo capsules

Participants in the OLP and CP arms will receive a bottle containing 28 blue and white plant-based capsules filled with the inactive ingredient microcrystalline cellulose. Capsules in the OLP and CP groups are identical in appearance. Bottles for the OLP and CP treatment arms will be labelled "Open-label Placebo Capsules" and "[Codename[1]] Capsules", respectively. All participants will be asked to return bottles with any unused capsules at the final study visit as a measure of treatment compliance.

[1]The codename is a 7-digit alphanumeric sequence that will be the same for all participants allocated to CP, but is omitted here to avoid the protocol appearing in any internet searchers participants may undertake.

Primary outcome

Insomnia Severity Index (ISI)[28]. The ISI is a brief, validated 7-item self-report questionnaire assessing insomnia symptomatology using a 5-point Likert scale. Three items address the severity of insomnia within the last two weeks regarding difficulty falling asleep, staying asleep or waking up too early, with each item rated from '0' = 'none' to '4' = 'very severe'. Other items include questions such as "How satisfied/dissatisfied you are with your current sleep pattern?" and "How worried/distressed are you about your current sleep problem?" with ratings from '0' = very satisfied or not at all to '4' = very dissatisfied or very much worried. All scores are summed to a total score with scores above 8 indicating clinically meaningful insomnia. Psychometric evaluation demonstrates the ISI as a reliable and valid measure in both clinical and research outcome settings, with internal consistency coefficients ranging from 0.74 – 0.78, and moderate concurrent validity (correlations ranging from 0.32 - 0.91) between the ISI and daily sleep diary, across studies [27].

Secondary outcome measures

Uptake of OLP and CP. Uptake of open-label and conventional placebo will be measured simply as the proportion of participants accepting the invite to each treatment arm.

Actigraphy. Objective sleep-wake data will be calculated from actigraphy watches (GENEActive, Activinsights Ltd., Cambridgeshire, UK). These are small, wrist-worn accelerometers that record daily movement and can be used to calculate a range of objective sleep parameters such as sleep onset latency (i.e. the time taken to fall asleep each night),

number and duration of awakenings, and total sleep time. Participants will receive an actigraphy watch at the first study visit and be instructed to wear them continuously for the duration of their study participation. Actigraphy watches have established validity against gold standard sleep assessment (i.e. polysomnography.)[29]**.** Sleep-wake data collected from actigraphy watches will be used to calculate objective sleep parameters including sleep onset latency, total sleep duration, and overall sleep quality.

Consensus Sleep Diary (CSD)[30]. The CSD is a widely used instrument used to assess participants' self-reported sleep patterns. The CSD includes questions such as time in bed, time to sleep, and number and duration of awakenings. As a secondary measure of self-reported insomnia, subjective sleep parameters such as sleep onset latency, total sleep time, total time in bed, and number and duration of awakenings, will be collected using the CSD. As an additional measure of treatment compliance, participants in the open-label and placebo treatment arms will complete an additional diary item asking whether, and when, they took the capsules the previous night.

Fatigue Symptom Inventory (FSI)[31]. The FSI is a 14-item self-report inventory assessing the intensity, duration, impact and daily pattern of fatigue over a one-week period. For each item, participants rate their fatigue from '0', indicating no fatigue to '10', the most fatigue with respect to severity, duration and interference. Individual items are scored to assess least, most and average fatigue in the past week, and current fatigue. Severity items can be averaged to obtain a composite FSI score [32]. Items addressing fatigue interference with daily functioning or psychosocial wellbeing are averaged to obtain an interference scale score [33]. The FSI has good internal consistency across studies for the interference and severity subscales (coefficients ranged from 0.91 - 0.96), and demonstrated concurrent, convergent and discriminant validity [33].

Depression Anxiety Stress Scales (DASS-21)[34]. The DASS-21 is a well-validated 21-item self-report measure consisting of three 7-item scales measuring symptoms of depression, anxiety and stress. Each item is rated on a scale from '0' = 'did not apply to me at all' to '4' = 'applied to me very much, or most of the time'. Item scores are summed and multiplied by two to calculate a final score ranging from 0 to 42 for each scale. Psychometric properties indicate adequate construct validity and excellent internal consistency for the depression (0.88), anxiety (0.82) and stress (0.90) scales [35].

Expectancy Measure. A purpose-built expectancy measure was developed for this study. All participants are asked how much they expect their insomnia symptoms to change as a result of taking part of the study at two time points: prior to the 2-week baseline period and, prior to the 2-week treatment period (after randomisation). Responses are completed on a scale from '-10' = 'much worse' to '0' = 'no change to '10' = 'much better'.

Generic Assessment of Side Effects (GASE)[36]. The GASE is a standardised self-report measure of 36 commonly-reported side effects observed in clinical trials (e.g. headache, dry mouth). Participants rate the intensity of these symptoms from '0' = 'not present' to '3' = 'severe' and are asked to indicate whether each symptom is related to their current medication. The symptom intensity ratings are summed to obtain a total GASE score (reflecting overall symptom burden) and a medication-attributed score can be calculated by summing the symptoms that have rated as being related to the medication[36]. Because OC does not receive any medication, an amended version of the attribution question will be administered in the current study, whereby for any symptoms present participants in all three arms (OLP, CP and OC) are asked whether each symptom is related to study participation first, then only those participants in

the OLP and CP arms indicate whether they believe any such symptom is related to the study medication.

Treatment Satisfaction Questionnaire for Medication (TSQM)[37]. The TSQM is a 14-item self-report measure of participants' perceived effectiveness, convenience, side effects and overall satisfaction with medication use. The measure will be administered specifically to participants enrolled in the OLP or CP arms because it focuses on treatment/medication. Scores for the specific domains of effectiveness, side effects, convenience, and global satisfaction are summed from domain items and then transformed to a composite score ranging from 0 to 100. The TSQM has demonstrated construct validity and internal consistency coefficients ranging from 0.88-0.94 across domains[37].

Potential predictors of uptake and the placebo effect

Life Orientation Test-Revised (LOT-R)[38]. The LOT-R is a 10-item measure that assesses dispositional optimism. Responses are made on a 5-point scale from '0' = 'strongly disagree' to '4' = 'strongly agree' to items such as "I'm always optimistic about my future", with six of the items then being summed to achieve an overall optimism score. Psychometric properties indicate adequate construct validity and modest internal consistency correlations ranging from 0.43 to 0.63.[34]

Big-Five Inventory – openness to experience[39] . The Big-Five Inventory (BFI) is a widely used taxonomy of personality traits. Ten self-report items assessing the domain openness to experience were selected for this trial. The BFI psychometric properties indicate good construct validity and convergent validity with other similar personality measures[35].

Insomnia treatment history. A purpose-designed measure was developed to assess participants' self-reported history of treatments for insomnia (pharmacological, psychological, complementary/alternative, etc.) and their perceived efficacy of these past treatments.

Procedure

Figure 1 shows the study flow. Participants who complete screening and are eligible will be contacted by the researchers to schedule their first study visit (Visit 1). At Visit 1, all participants will be given an actigraphy watch and CSD to wear and complete, respectively, for 14 days, constituting the baseline period. Participants will return to the study site for Visit 2 (Day 14) and will complete outcome measures. At Visit 2, they will be randomised to one of three conditions: OLP, CP, or OC. In the case of the placebo arms, the researcher will discuss the relevant treatment with each participant according to five points, summarised in Table 1, including: 'What is this treatment?', 'What does previous research say?', 'What are the mechanisms of action?', 'How should I take the capsules?', and 'How long do they take to work?', with the OLP information guided by previous OLP trials[19,20] In the OLP arm there will be an additional emphasis on explaining that most placebo research in the past has involved deception, whilst those in the CP arm will be provided with information about the fake medication.

Table 1. Summary of descriptions and discussion points for OLP and CP.

Discussion point	Open-label Placebo (OLP)	Conventional Placebo (CP)

What is this treatment?	Placebo capsules containing no active ingredient	A new pharmacological agent, [Drug codename]
What does previous research say?	Placebo effects have been found to reduce insomnia symptoms, but deception is typically involved. Some recent studies in other countries have shown OLP effects outside of sleep	Some recent studies in other countries have shown that [Drug codename] can reduce insomnia symptoms
What are the mechanisms of action?	Placebo effects trigger the brain to release neurotransmitters that can improve symptoms. These responses can be automatic.	[Drug codename] triggers the brain to release neurotransmitters that can improve sleep.
How should I take the capsules?	Work best if taken exactly as prescribed. A positive attitude helps, but is not essential.	
How long will it take to work?	Generally work quickly, but can take longer for some people.	

Participants who accept an invite to the OLP or CP arms will be provided with placebo capsules and the dosage instructions, which require them to take two placebo capsules 10-15 minutes prior to going to bed. Participants will also be asked to record their daily treatment adherence in the CSD. After Visit 2, all participants will continue completing the CSD and wearing the actigraphy watch for another 14 days, constituting the treatment period. At Visit 3, participants will return to the study site with the CSD and actigraphy watches; participants in the

two placebo arms will return the capsule bottles and any unused capsules as an additional measure of treatment adherence. All participants will complete post-treatment outcome measures and be debriefed at the end of their study participation.

Sample Size

Charlesworth and colleagues'[19] meta-analysis of open-label placebo for other conditions (e.g. chronic pain, irritable bowel syndrome) found a large effect size of d=.88 relative to no treatment. To obtain 80% power with alpha=.05 we would require 22 participants to detect this effect size comparing OLP and OC arms. However, we are also seeking to determine whether open-label placebos differ in efficacy relative to conventional placebos – which has not been investigated systematically. We hypothesise that the OLP will be less effective CP and that the effect size for this comparison will be weaker than the effect size for OLP versus OC. To detect an effect size for OLP versus CP of d=.5, we will require 64 participants per type of placebo treatment to achieve 80% power with alpha=.05. Therefore, using an allocation ratio of 2:2:1 we would require 64, 64, 32 (total N=160) participants OLP, CP, and OC respectively to obtain sufficient power for both of the critical comparisons. However, because the cmRCT involves two stage consent process we will recruit N=267 participants into the initial cohort aiming to randomise 107 to each placebo arm and 53 to OC, which assumes at least two-thirds (67%) uptake in the placebo arms, including allowance for 10% attrition. This will provide us with sufficient power for both intent-to-treat (primary) and per protocol (sensitivity) analyses.

Randomisation and blinding

Randomisation tables will be generated using randomizer.org. Randomisation will be conducted on a 2:2:1 ratio (OLP, CP, OC) and will be stratified according to gender and scores on the ISI (<15 and ≥ 15). Randomisation will take place after the eligibility screening and baseline assessment (allocation concealment) at Visit 2. Blinding of the participant and researcher administering the treatment is not possible, however, the data analysis will be performed by a blinded member of the team.

Statistical analysis

Primary Outcome

Insomnia severity index. Intent-to-treat analysis (ITT) will be used as the primary analysis to compare the effect of OLP, CP and OC on insomnia symptoms. The primary endpoint (mean scores on the ISI at post-treatment) will be assessed using a multilevel model with group (offered OLP, offered CP, OC) and baseline (Visit 2) ISI score included as factors. Consistent with previous analysis methods in cmRCTs, the ITT population for the OLP and CP arms will consist of all participants who receive an offer of treatment, regardless of treatment uptake. As a sensitivity analysis, a per-protocol approach will also be implemented as secondary analysis and this will include only those participants in the placebo arms who accept the invite and complete the study and only those randomised to OC who complete the study. The analyses will include all participants who scored ≥10 on the ISI at the eligibility screen (inclusion criterion), but we will also conduct sensitivity analysis excluding any participants who fall below this threshold during the baseline period (assessed at Visit 2).

Secondary Outcomes

Uptake. A Chi-squared test of independence will be used to determine whether rates of accepting treatment differ when open-label versus conventional placebo is offered.

Other sleep parameters and outcomes. Other sleep measures (self-report and objective), daytime fatigue, depression, anxiety, stress, treatment satisfaction, expectancy, and side effects will be assessed as per the primary ISI outcome.

Predictors of uptake and the placebo effect

Potential predictors of uptake and the placebo effect will be assessed using a combination of logistic and linear regressions to identify which clinical, demographic and personality characteristics predict uptake (logistic) of and responses (linear) to open-label and conventional placebo

For all analyses, results will be considered statistically significant when $p < .05$.

Patient and public involvement

Neither patients nor members of the public had any involvement in the design of the OPIN trial.

ETHICS AND DISSEMINATION

The study is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTRXXXXXX), and the ethical aspects of this trial have been reviewed and approved by The University of Sydney Human Research Ethics Committee. Written informed consent is obtained from every participant, and those in the OLP and CP conditions undergo an additional information and consent process if they decide to accept the relevant invite. Results from this trial will be disseminated in the form of peer-reviewed conference proceedings and publications.

Author Contributions

BC conceptualised the study. All authors contributed to designing the study. BC and DC were responsible for the power calculations and statistical analysis plan. BC, AS, and ZA were responsible for creating the first draft of this manuscript. All authors provided feedback and approved the final draft of this manuscript.

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Competing Interests Statement

The authors report no competing interests in relation to this research.

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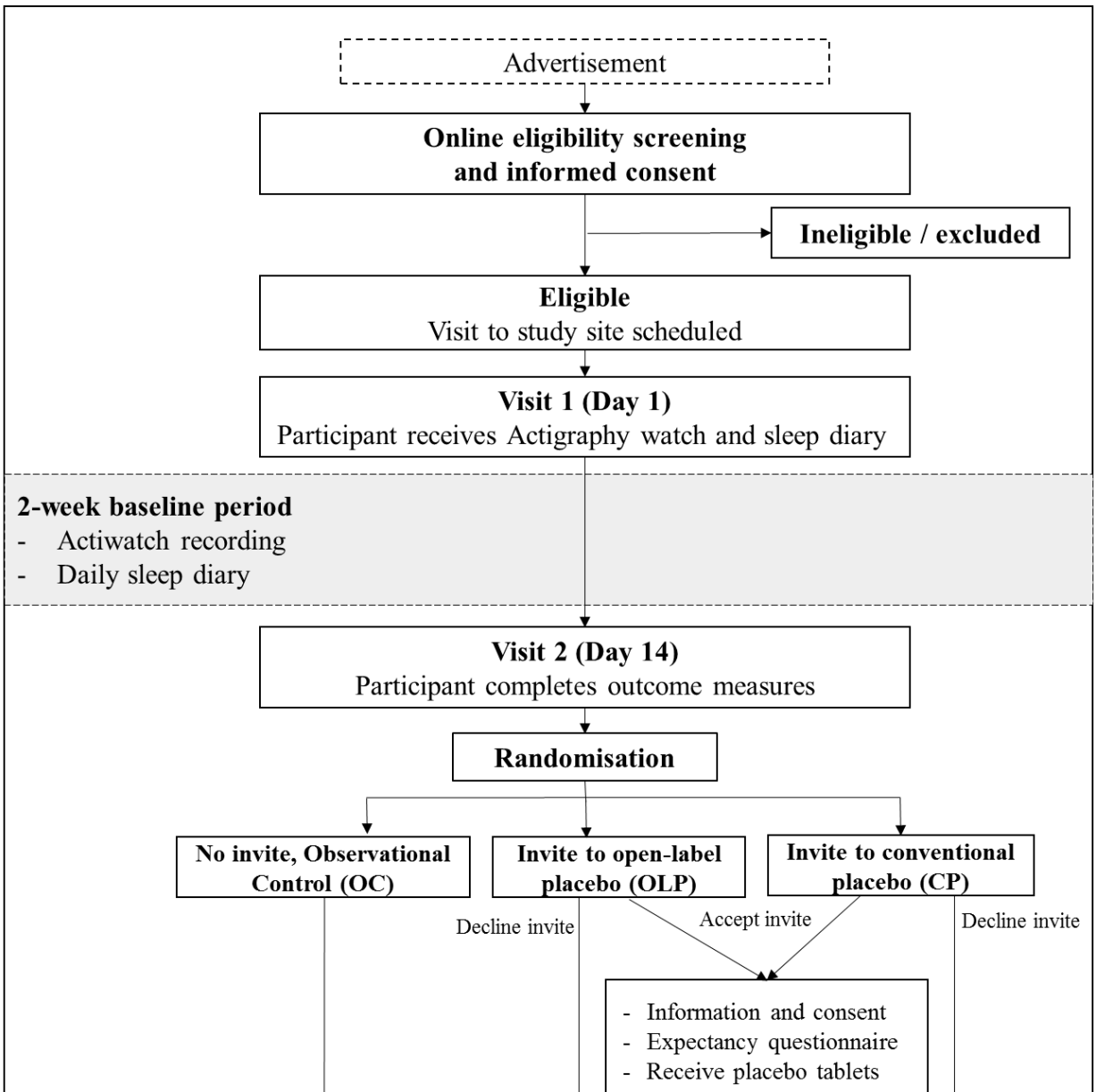
Figure captions

Figure 1. Study flow chart.


Advertisement
Online eligibility screening and informed consent
Ineligible / excluded
Eligible
Visit to study site scheduled
Visit 1 (Day 1)
Participant receives Actigraphy watch and sleep diary
2-week baseline period
- Actiwatch recording
- Daily sleep diary
Visit 2 (Day 14)
Participant completes outcome measures
Randomisation
No invite, Observational Control (OC)
Invite to open-label placebo (OLP)
Invite to conventional placebo (CP)
Decline invite
Accept invite
Decline invite
- Information and consent
- Expectancy questionnaire
- Receive placebo tablets
2-week treatment period
- Actiwatch recording
- Daily sleep diary
- Treatment compliance (CP / OLP)
Visit 3 (day 28)
- Participant completes outcome measures
- Participants debriefed

1

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	2
	2b	All items from the World Health Organization Trial Registration Data Set	NA
Protocol version	3	Date and version identifier	NA
Funding	4	Sources and types of financial, material, and other support	20
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	10
	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	NA
	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)	20

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	___4-7_____
	6b	Explanation for choice of comparators	____4-7_____
Objectives	7	Specific objectives or hypotheses	____4-7_____
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	____10_____
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	____10,15_____
	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)	____NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____16_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____8_____
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	____10-14_____
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)	____16_____

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	____17_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	____NA_____
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	____17_____
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	___17_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	____17_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	____17_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	____17_____
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	_____18-19____
	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	____18-19_____

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	18-19
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	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
	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)	18-19
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	NA
	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	NA
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	13
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	19
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)	19

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	NA
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	NA
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	20
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	NA
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	8
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	19
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

BMJ Open

Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial

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Words: 3,814 Figures: 1 Tables: 1

Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial

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ABSTRACT

Introduction: Insomnia is a prevalent sleep disorder that causes substantial personal and societal harm. There is evidence that placebo interventions can reduce insomnia symptoms, but this research has involved deceptively administering the placebo under the guise of a real medication (conventional placebo, CP), which has obvious ethical constraints. Open-label placebo treatment (OLP), in which a placebo is administered with full disclosure that there are no active ingredients, has been proposed as a method of using the placebo effect ethically, but the efficacy and acceptability of OLP for insomnia is currently unknown.

Methods and analysis: This study uses a cohort multiple randomised controlled trial design to compare OLP, CP, and no treatment for insomnia. Two-hundred and sixty-seven participants with self-reported insomnia symptoms (Insomnia Severity Index, ISI≥10) will be recruited into an observational study and have their sleep monitored over a two-week period. Participants will then be randomised to one of three groups: invite to OLP, invite to CP described deceptively as a new pharmacological agent, or no invite/observational control (OC). Those in OLP and CP accepting the invite receive identical placebos for a two-week treatment period while sleep is monitored in all participants. The primary outcome is ISI at the end of the treatment period. Secondary outcomes include treatment uptake and clinically significant response rates, objective and subjective sleep parameters, fatigue, mood, expectancy, treatment satisfaction and side effects. Predictors of uptake and responses to OLP and CP will be explored.

Ethics and dissemination: The trial has been approved by The University of Sydney Human Research Ethics Committee. Written informed consent is obtained from every participant. OLP

and CP participants accepting the invite undergo an additional consent process. Results will be disseminated via peer-reviewed conference proceedings and publications.

Trial registration: ANZCTRN12620001080910

Strengths and limitations of this study:

- This will be the first study to test whether open-label placebo (OLP) is effective and acceptable for insomnia.
- The use of a cohort multiple RCT design provides a more ecologically valid no treatment comparison and will allow us to compare the efficacy and uptake of OLP relative to conventional placebo.
- The inclusion of actigraphy means that we can assess the effect of OLP on both self-report and objective sleep outcomes.
- Predictors of uptake and any resulting placebo effect will be explored, including expectancy and baseline insomnia severity.
- Because of the nature of the study, participants and researchers cannot be blind to treatment allocation, but the data analysis will be conducted by a blind researcher.

INTRODUCTION

Insomnia is the most common sleep disorder, with an estimated diagnostic prevalence of 10% [1-3] and symptom prevalence of 30%[3 4] in adults. Higher prevalence rates have been reported in medical settings, ranging from 20 to 56%[2-6], with up to 90% of patients being prescribed pharmacotherapy [7 8]. Insomnia is characterised by difficulty initiating or maintaining sleep along with daytime impairment and/or distress and carries substantial personal and socioeconomic burden[9 10]. People with insomnia have poorer quality of life, greater risk of experiencing other medical conditions and psychiatric disorders, increased healthcare utilisation, and reduced work productivity[11-13]. While a range of pharmacological treatments are available for insomnia, those that demonstrate efficacy are associated with significant risks in terms of adverse effects and the potential for dependence (e.g. benzodiazepines)[14] whereas those with lower risk profiles have limited efficacy (e.g. melatonin.)[15]. Cognitive Behaviour Therapy for Insomnia (CBT-I) has been recommended as first line treatment for insomnia[2 3], however, CBT-I is not always accessible[3] and both practitioners and people with insomnia appear more willing to persist with pharmacological rather than psychological interventions [6 8 16 17]. As such, there remains a pressing need to identify safe and effective treatments to combat the burden of insomnia.

Interestingly, many randomised placebo-controlled trials of insomnia interventions find that participants allocated to placebo treatment experience significant improvement.[18-20]. This suggests that insomnia may be responsive to the placebo effect, whereby the treatment context itself elicits positive expectancies that trigger improvement[21-23]. Importantly, improvement in placebo groups of these trials holds even when directly compared with no treatment[24], indicating that placebo treatment generates more improvement in insomnia than can be accounted for by

other factors, such as, spontaneous recovery and regression to the mean[25]. Therefore, it may be possible to harness the placebo effect to reduce the burden of insomnia.

Placebo interventions likely carry fewer adverse events than pharmacological interventions and have lower cost than psychological interventions[26]. On the other hand, the deception typically associated with placebo administration presents a significant barrier to its clinical use because of the violation of patient trust and informed consent[27]. However, this barrier is based on the assumption that deception is necessary to elicit a placebo effect, which has recently been called into question by 'open-label placebo' trials [28].

Open-label placebo (OLP) trials involve administering placebo treatment with full disclosure that the treatment is in fact a placebo, meaning there is no deception. Only a handful of randomised controlled trials (RCTs) testing OLP have been conducted to date and none with insomnia, but the available data suggest some promising results. For example, in an RCT comparing three weeks' of OLP with 'treatment as usual' (TAU) for chronic pain, Carvalho and colleagues'[29] found that OLP significantly reduced pain and disability, with moderate to large effect sizes. Similar results have been found in RCTs of OLP for irritable bowel syndrome[30], depression[31], and allergic rhinovirus[32]. As a result, there have been increasing calls to explore the potential efficacy of OLP in clinical practice[28 33].

Despite the promising preliminary findings, several criticisms of existing OLP trials have been raised. The most common criticism concerns the types of control group used, typically TAU or waitlist control. The very nature of OLP treatment means that participants and researchers are not blind to treatment allocation, potentially introducing problems with demand characteristics and experimenter bias[28]. While that may be difficult to avoid, a further problem is that knowingly being allocated to receive no treatment may induce nocebo effects and thereby

poorer outcomes in the control group, artificially inflating the apparent efficacy of OLP treatment[28 34]. In addition to concerns regarding the type of control groups used, a second potential important limitation is that participants in OLP trials are usually recruited via advertisements explicitly describing the intervention as a 'novel mind-body treatment'[29 30]. Little is known about the characteristics of individuals who volunteer to participate in 'novel mind-body treatment' research, but differences between such samples and the general population could significantly limit the generalisability of existing OLP trials. If only those who already hold strong beliefs about the power of the mind are enrolled, then this could overestimate the efficacy of OLP effects in the general population. A final limitation is that existing OLP trials have failed to include a comparison with conventional (deceptive) placebo (CP) treatment, which is important to evaluate the relative cost-benefit of open-label versus conventional placebo.

To address this, the current study tests the efficacy of OLP for insomnia (OPIN) using a novel cohort multiple randomised controlled trial (cmRCT) design comparing OLP, CP, and no treatment. The cmRCT involves a two-stage consent process whereby participants are first recruited to an observational study (with no mention of intervention) and are then randomised to be invited to the treatment arms or to remain in the observational arm (i.e. act as controls). This design allows us to compare the efficacy and uptake of open-label versus conventional placebo, relative to a no treatment group, in a more generalisable sample of participants not specifically interested in mind-body treatments, and in a scenario whereby participants in the control group are unaware they are missing out on a potentially desirable treatment. The protocol and study design are guided by the recommendations set out in the SPIRIT 2013 Statement[35]. The results will provide first ever evidence concerning whether OLP is an effective treatment for insomnia and the strongest test of OLP effects in general to date.

Objectives

Primary Objectives

1. Determine whether OLP is associated with reductions in self-report insomnia symptoms, measured by the Insomnia Severity Index (ISI), compared to CP and no treatment.

Secondary Objectives

1. Determine whether OLP is associated with improvements in objective and subjective sleep parameters, daytime fatigue, depression, anxiety, and stress, expectancy, treatment satisfaction and side effects, relative to CP and no treatment.
2. Determine whether OLP is associated with clinically significant improvements in insomnia (response rate), relative to CP and no treatment.
3. Determine the rate of uptake of OLP relative to CP
4. Identify which demographic, individual, and clinical, characteristics predict uptake and the placebo effect (e.g. ISI scores, number of responders) following OLP and CP.

METHOD AND ANALYSIS

Trial Design

As shown in Figure 1, the OPIN trial will use a parallel three-arm cmRCT design[36] comparing OLP, CP, and no treatment/observational control (OC) for insomnia. In the first stage, a cohort of participants with self-reported insomnia symptoms will be recruited into a 2-week observational (baseline) period. In the second stage, participants will be randomised to one of three groups; invite to OLP, invite to CP, or no invite, OC. OLP will be openly described as

consisting of no active ingredient and instead aiming to capitalise on the placebo effect. CP will be described as a new pharmacological agent designed to promote sleep. Participants consenting to OLP or CP will be administered placebo medication while those allocated to OC will continue to be observed for the 2-week treatment period.

The study Steering Committee (principal investigator (PI), associate investigators, study coordinator and statistician) will meet every six months to review the study, ensuring adherence to all ethical, regulatory, and clinical trial guidelines. If higher-than-anticipated attrition rates occur, the Steering Committee will investigate whether the sample size needs to be increased to maintain power, and if so, will seek the appropriate modifications. A Data Monitoring Committee will not be implemented because all participants receive placebos and adverse events are anticipated to be low. Although early study termination is unanticipated, if deemed necessary, only the PI will have the authority to terminate the study.

Participants

To be eligible, participants must report an Insomnia Severity Index (ISI) ≥10, be at least 18 years old, be proficient in English, and able to attend the study site three times over one month. The following exclusion criteria will apply: (1) sleep disorder other than insomnia, (2) currently pregnant, planning to conceive in the next 3 months, breastfeeding, or <1 year post-partum, (3) serious medical illness requiring invasive treatment/surgery (e.g. cancer) or heavy substance use, (4) severe psychiatric co-morbidity (e.g. psychosis, bipolar disorder, depression) or risk of self-harm or suicidality, (5) currently receiving psychological treatment or taking regular (i.e. ≥1/week) medication for sleep (including prescription or over-the-counter medications, herbal supplements, homeopathic preparations), (6) undertaking shift work (fixed

or rotating, including regular night shifts), and/or (7) intending to travel to a destination >2 hours' time difference in the next three months**.** An ISI score of ≥10 was chosen because it has been suggested to indicate clinically significant insomnia[37], with high sensitivity and specificity in community samples[38], and is frequently used in RCTs of sleep interventions[39 40]. Participants will be reimbursed AUD$60 upon completion of the study and will be provided with 12 months free access to Sleepio[41], a commercially available digital CBT app found to reduce insomnia symptoms.

Study Setting

The study will take place at The University of Sydney, Australia. The study will be advertised online (e.g. University research volunteer sites, Facebook) with a link to the study website. The study website includes information about the observational component of the study, researcher contact details, the information sheet and consent form, and a link to complete the online screening measures. Eligible and consenting participants will be contacted and invited to attend the study site to commence participation.

Materials and Measures

Placebo capsules

Participants in the OLP and CP arms will receive a bottle containing identical 28 blue and white plant-based capsules containing microcrystalline cellulose. Bottles for the OLP and CP

treatment arms will be labelled "Open-label Placebo Capsules" and "[Codename[1]] Capsules", respectively.

Primary outcome

Insomnia Severity Index (ISI)[37]. The ISI is a brief, validated 7-item self-report questionnaire assessing insomnia symptomatology on a 5-point scale. Items addressed include the severity of sleep onset, maintenance and early awakening difficulties in the last two weeks and are rated from '0' = 'none' to '4' = 'very severe'. Other items rate sleep dissatisfaction, distress, interference and noticeability to others. Scores are summed to obtain a total score from 0 to 28, with the following clinical cut-offs: no clinically significant insomnia (0 to 7), subthreshold insomnia (8 to 14), moderate insomnia (15 to 21), and severe insomnia (22 to 28). The ISI as a reliable and valid measure in clinical and research settings, with sound internal consistency coefficients (0.74 – 0.78), and moderate concurrent validity (0.32 - 0.91) between the ISI and daily sleep diary [37].

Secondary outcome measures

Uptake of OLP and CP. Uptake of open-label and conventional placebo will be measured simply as the proportion of participants accepting the invite to each treatment arm.

Response rate. Clinically significant improvements in insomnia will be defined as the rate of participants obtaining a 6-point or greater reduction on the ISI from baseline to post-

[1]The codename is a 7-digit alphanumeric sequence that will be the same for all participants allocated to CP, but is omitted here to avoid the protocol appearing in any internet searchers participants may undertake.

treatment[42] and/or who have an ISI score below the cut-off of 10 at post-treatment[38], relative to CP and no treatment.

Actigraphy. Objective sleep-wake data will be calculated from actigraphy watches (GENEActive, Activinsights Ltd., Cambridgeshire, UK). These are small, wrist-worn accelerometers that record daily movement and can be used to calculate a range of objective sleep parameters. Actigraphy watches have established validity against gold standard sleep assessment (i.e. polysomnography.)[29] **A**ctigraphy data will be used to calculate objective sleep parameters including sleep onset latency, total sleep duration, and overall sleep quality.

Consensus Sleep Diary (CSD)[43]. The CSD is widely used to assess participants' self-reported sleep patterns. The CSD includes questions about time in bed, time to sleep, and number and duration of awakenings. As a measure of treatment adherence, OLP and CP participants will complete items asking whether, and when, they took the capsules the previous night.

Fatigue Symptom Inventory (FSI)[44]. The FSI is a 14-item self-report inventory assessing the intensity, duration, impact and daily pattern of fatigue over a 1-week period. Participants rate their fatigue from '0'= no fatigue to '10'= the most fatigue with respect to severity, duration and interference. Individual items are scored to assess least, most and average fatigue in the past week, and current fatigue. Severity items can be averaged to obtain a composite FSI score[45]. Items addressing fatigue interference with daily functioning or psychosocial wellbeing are averaged to obtain an interference scale score[46]. The FSI has good internal consistency (0.91 - 0.96), and demonstrated concurrent, convergent and discriminant validity[46].

Depression Anxiety Stress Scales (DASS-21)[47]. The DASS-21 is a 21-item self-report measure consisting of three 7-item scales measuring symptoms of depression, anxiety and stress. Each item is rated on a scale from 0 = 'did not apply to me at all' to 4 = 'applied to me very

much, or most of the time'. Item scores are summed and multiplied by two to calculate a final score ranging from 0 to 42 for each scale. Psychometric properties indicate adequate construct validity and excellent internal consistency for the depression (0.88), anxiety (0.82) and stress (0.90) scales [48].

Expectancy Measure. A purpose-built expectancy measure was developed for this study. All participants are asked how much they expect their insomnia symptoms to change as a result of taking part of the study at two time points: prior to the 2-week baseline period and, prior to the 2-week treatment period (after randomisation). Responses are completed on a scale from -10 = 'much worse' through 0 = 'no change to 10 = 'much better'.

Generic Assessment of Side Effects (GASE)[49]. The GASE is a standardised self-report measure of 36 commonly reported side effects observed in clinical trials (e.g. headache, dry mouth). Participants rate the intensity of these symptoms from 0 = 'not present' to 3 = 'severe' and indicate whether each symptom is related to their treatment. The intensity ratings are summed to obtain a total GASE score and a medication-attributed score is calculated by summing symptoms scores rated as related to treatment[49]. Because OC does not receive any medication, an amended version of the attribution question will be administered, whereby for any symptoms present participants in all three arms (OLP, CP and OC) indicate whether each symptom is related to study participation first, then only those participants in the OLP and CP arms indicate whether they believe any such symptom is related to the study medication.

Treatment Satisfaction Questionnaire for Medication – Version II (TSQM-II)[50]. The TSQM-II is an 11-item self-report measure of participants' perceived effectiveness, convenience, side effects and overall satisfaction with medication use. The measure will be administered specifically to participants enrolled in the OLP or CP arms because it focuses on

treatment/medication. Domain items are summed and then transformed to a composite score ranging from 0 to 100. The TSQM-II has demonstrated construct validity and internal consistency coefficients ranging from 0.88-0.94 across domains [50 51].

Potential predictors of uptake and the placebo effect

Life Orientation Test-Revised (LOT-R)[52]. The LOT-R is a 10-item measure assessing dispositional optimism. Responses are made on a 5-point scale from 0 = 'strongly disagree' to 4 = 'strongly agree' to items such as "I'm always optimistic about my future", with six of the items summed to achieve an overall optimism score. Psychometric properties indicate adequate construct validity and modest internal consistency correlations ranging from 0.43 to 0.63.[34]

Big-Five Inventory – openness to experience[53] . The Big-Five Inventory (BFI) is a widely used taxonomy of personality traits. Ten self-report items assessing the domain openness to experience were selected for this trial. The BFI has good construct validity and convergent validity with other similar personality measures[35].

Insomnia treatment history. A purpose-designed measure was developed to assess participants' self-reported history of treatments for insomnia (pharmacological, psychological, complementary) and their perceived efficacy of these treatments.

Procedure

Figure 1 shows the study flow. Eligible participants will be invited to attend their first on-site visit (Visit 1). At Visit 1, all participants will be given an actigraphy watch to wear and CSD to complete, for the 2-week baseline period. Participants will return to the study site for Visit 2 (Day 14) and complete outcome measures. At Visit 2, they will be randomised to one of three

conditions: OLP, CP, or OC. In the case of the placebo arms, the researcher will discuss the relevant treatment with each participant according to five points, summarised in Table 1, with the OLP information guided by previous OLP trials[19,20] In the OLP arm there will be an additional emphasis on explaining that most placebo research in the past has involved deception, whilst those in the CP arm will be provided with information about the fake medication.

Table 1. Summary of descriptions and discussion points for OLP and CP.

Discussion point	**Open-label Placebo (OLP)**	**Conventional Placebo (CP)**
What is this treatment?	Placebo capsules containing no active ingredient	A new pharmacological agent, [Drug codename]
What does previous research say?	Placebo effects have been found to reduce insomnia symptoms, but deception is typically involved. Some recent studies in other countries have shown OLP effects outside of sleep	Some recent studies in other countries have shown that [Drug codename] can reduce insomnia symptoms
What are the mechanisms of action?	Placebo effects trigger the brain to release neurotransmitters that can improve symptoms. These responses can be automatic.	[Drug codename] triggers the brain to release neurotransmitters that can improve sleep.

How should I take the capsules?	Work best if taken exactly as prescribed. A positive attitude helps, but is not essential.
How long will it take to work?	Generally work quickly, but can take longer for some people.

Participants who accept an invite to OLP or CP will be provided with placebo capsules and the dosage instructions, which require them to take two placebo capsules 10-15 minutes prior to going to bed for the 2-week treatment period. Participants will be asked to record their daily treatment adherence in the CSD. Participants who decline an invite to the OLP or CP arms will continue in the study, unless they choose to withdraw. During the treatment period, all participants will continue completing the CSD and wearing the actigraphy watch. At the final study visit (Visit 3), all participants will return the CSD and actigraphy watches, and participants in the OLP and CP arms will return the capsule bottles and any unused capsules as an additional measure of treatment adherence. All participants will complete post-treatment outcome measures and be debriefed at the end of their study participation. On-site study visits may be replaced with video-link visits in the event that COVID-19 social distancing requirements prevent face-to-face interactions, with study materials being couriered if necessary.

Sample Size

There have been no previous studies on OLP for insomnia. Charlesworth and colleagues'[28] meta-analysis of open-label placebo for other conditions (e.g. chronic pain, irritable bowel syndrome) found a large effect size of d=.88 relative to no treatment. Assuming a similar

effect size, to obtain 80% power with alpha=.05 we would require 22 participants to detect this effect size comparing OLP and OC arms. However, we are also seeking to determine whether open-label placebos differ in efficacy relative to conventional placebos – which has not been investigated systematically. We hypothesise that the OLP will be less effective CP and that the effect size for this comparison will be weaker than the effect size for OLP versus OC. To detect an effect size for OLP versus CP of d=.5, we will require 64 participants per type of placebo treatment to achieve 80% power with alpha=.05. Therefore, using an allocation ratio of 2:2:1 we would require 64, 64, 32 (total N=160) participants OLP, CP, and OC respectively to obtain sufficient power for both of the critical comparisons. However, because the cmRCT involves two stage consent process we will recruit N=267 participants into the initial cohort aiming to randomise 107 to each placebo arm and 53 to OC, which assumes at least two-thirds (67%) uptake in the placebo arms, including allowance for 10% attrition. This will provide us with sufficient power for both intent-to-treat (primary) and per protocol (sensitivity) analyses.

Randomisation and blinding

Randomisation tables will be generated using randomizer.org. Randomisation will be conducted on a 2:2:1 ratio (OLP, CP, OC) and stratified according to gender and scores on the ISI (<15 and ≥ 15). Randomisation will take place after the eligibility screening and baseline assessment (allocation concealment) at Visit 2. Blinding of the participant and researcher administering the treatment is not possible, however, data analysis will be performed by a blinded member of the team.

Statistical analysis

Primary Outcome

Insomnia severity index. Intent-to-treat analysis (ITT) will be used as the primary analysis to compare the effect of OLP, CP and OC on insomnia symptoms. The primary endpoint (mean scores on the ISI post-treatment) will be assessed using a multilevel model with group (OLP, CP, OC) and baseline (Visit 2) ISI score included as factors. Consistent with previous analysis methods in cmRCTs, the ITT population for the OLP and CP arms will consist of all participants who receive an offer of treatment, regardless of treatment uptake. As a secondary, sensitivity analysis, a per-protocol approach will also be implemented including only those participants in the OLP, CP and OC arms who complete the study. The analyses will include participants who scored ≥10 on the ISI at screening, but we will also conduct sensitivity analysis excluding any participants who fall below this threshold during the baseline period (assessed at Visit 2).

Secondary Outcomes

Uptake. A chi-squared test of independence will be used to determine whether rates of accepting treatment differ when OLP versus CP is offered.

Response rate: Group differences in the proportion of participants achieving a clinically significant response (i.e. ≥ 6-point reduction and/or < 10 on the ISI) will be analysed using a chi-squared test of independence.

Other sleep parameters and outcomes. Other sleep measures (self-report and objective), daytime fatigue, depression, anxiety, stress, treatment satisfaction, expectancy, and side effects will be assessed as per the primary ISI outcome.

Predictors of uptake and the placebo effect

Potential predictors of uptake and the placebo effect will be assessed using a combination of logistic and linear regressions to identify which clinical, demographic and personality characteristics predict uptake (logistic) of and the placebo effect (linear: ISI scores and related outcomes; logistic: response rates) to OLP and CP.

For all analyses, results will be considered statistically significant when $p < .05$.

Patient and public involvement

Neither patients nor members of the public had any involvement in the design of the OPIN trial.

ETHICS AND DISSEMINATION

The study is registered with the Australian and New Zealand Clinical Trial Registry (ANZCTRN12620001080910; see Supplementary Data 1). The study protocol (version 6 dated 10 September 2020) and relevant materials, and the ethical aspects of this trial have been reviewed and approved by The University of Sydney Human Research Ethics Committee (HREC 2019/552). Study data will be collected and stored using the University's Research Electronic

Data Capture (REDCap) system, with password-protected access provided to relevant research personnel only. All data will be securely stored for a minimum of 15 years. The PI will be responsible for communicating important protocol modifications. The final dataset will be maintained by the PI and provided de-identified to interested researchers upon reasonable request. Results from this trial will be disseminated in the form of peer-reviewed conference proceedings and publications.

Author Contributions

BC conceptualised the study. BC, LS, ZA, NG, DB, and AS contributed to designing the study. BC and DC were responsible for the power calculations and statistical analysis plan. BC, AS, and ZA were responsible for creating the first draft of this manuscript. BC, LS, ZA, NG, DB, and AS provided feedback and approved the final draft of this manuscript.

Funding Statement

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Competing Interests Statement

The authors report no competing interests in relation to this research. The University of Sydney is the study sponsor. All decisions regarding the study design, collection, management, analysis or interpretation of data, and publication remain the PIs.

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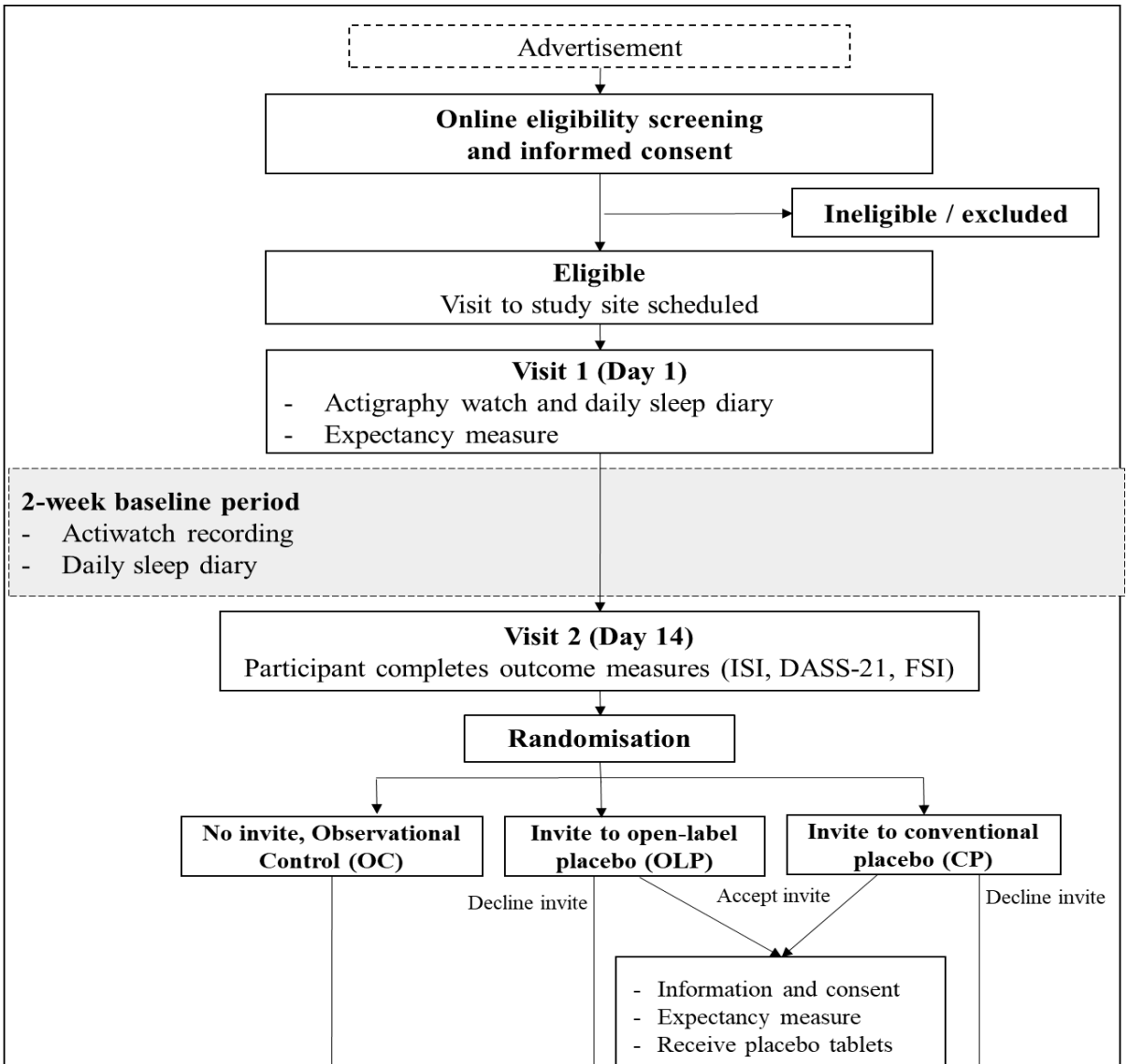
Figure captions

Figure 1. Study design and flowchart


Advertisement
Online eligibility screening and informed consent
Ineligible / excluded
Eligible
Visit to study site scheduled
Visit 1 (Day 1)
- Actigraphy watch and daily sleep diary
- Expectancy measure
2-week baseline period
- Actiwatch recording
- Daily sleep diary
Visit 2 (Day 14)
Participant completes outcome measures (ISI, DASS-21, FSI)
Randomisation
No invite, Observational Control (OC)
Invite to open-label placebo (OLP)
Invite to conventional placebo (CP)
Decline invite
Accept invite
Decline invite
- Information and consent
- Expectancy measure
- Receive placebo tablets
2-week treatment period
- Actiwatch recording
- Daily sleep diary
- Treatment compliance (CP / OLP)
Visit 3 (day 28)
- Participant completes outcome measures (ISI, DASS-21, FSI, TSQM-II, GASE)
- Participants debriefed

BMJ Open Supplementary Material 1

SPIRIT Item2b: WHO Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	Anzctr.org.au ANZCTRN 12620001080910
Date of registration in primary registry	20 October 2020
Secondary identifying numbers	2019/552
Source(s) of monetary or material support	School of Psychology, The University of Sydney
Primary sponsor	The University of Sydney
Secondary sponsor(s)	N/A
Contact for public queries	A/Prof Ben Colagiuri PhD, +61 2 9351 4589, ben.colagiuri@sydney.edu.au
Contact for scientific queries	A/Prof Ben Colagiuri PhD, +61 2 9351 4589, ben.colagiuri@sydney.edu.au
Public Title	Open-label placebo for insomnia (OPIN)
Scientific Title	Open-label placebo for insomnia (OPIN): a cohort multiple randomized controlled trial in adults with moderate or severe insomnia
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Insomnia
Intervention(s)	Active comparator: open-label placebo capsules Placebo comparator: conventional (deceptive) placebo capsules
Key inclusion and exclusion criteria	Inclusion criteria: adult (≥ 18 years), self-reported insomnia symptoms with score on Insomnia Severity Index (ISI) ≥ 10 Exclusion criteria: sleep disorder other an insomnia (e.g. sleep apnoea), severe medical or psychiatric comorbidity, current regular (≥ 1/week) administration of sleep medication, current psychological treatment for sleep, currently pregnant, planning to conceive within 3 months, breastfeeding or 1 year post-partum, regular night shift work
Study type	Cohort multiple randomized controlled trial Allocation: randomized Intervention model: parallel assignment Masking: Open-label placebo arm (both participant and investigator are aware of treatment allocation, conventional placebo arm (participant is blind but investigator aware of treatment allocation)

	Primary purpose: Intervention outcome
Date of first enrolment	
Target sample size	267
Recruitment status	Not yet recruiting
Primary outcome(s)	Changes in self-reported insomnia symptoms measured with the Insomnia Severity Index (ISI)
Key secondary outcomes	Rate of uptake of open-label relative to conventional placebo; changes in objective and subjective sleep parameters; changes in daytime fatigue, anxiety, depression and stress; changes in expectancy; changes in treatment satisfaction; self-reported side effects

1

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	Supplementary File 1
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	11
	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	21
	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)	8

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	____4-6_____
Objectives	7	Specific objectives or hypotheses	____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)	____7-8_____
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	____11_____
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)	_____8-9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7-8,15-17__
	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)	____8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____12-14_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____8_____
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	____7-15_____
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_____

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	1
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18
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	18
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
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	11-17
	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	11-17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
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	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
	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)	18-19
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	8
	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	8
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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)	20

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	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	20
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	NA
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	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
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	NA

*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.

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Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial

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Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial

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ABSTRACT

Introduction: Insomnia is a prevalent sleep disorder that causes substantial personal and societal harm. There is evidence that placebo interventions can reduce insomnia symptoms, but this research has involved deceptively administering the placebo under the guise of a real medication (conventional placebo, CP), which has obvious ethical constraints. Open-label placebo treatment (OLP), in which a placebo is administered with full disclosure that there are no active ingredients, has been proposed as a method of using the placebo effect ethically, but the efficacy and acceptability of OLP for insomnia is currently unknown.

Methods and analysis: This study uses a cohort multiple randomised controlled trial design to compare OLP, CP, and no treatment for insomnia. Two-hundred and sixty-seven participants with self-reported insomnia symptoms (Insomnia Severity Index, ISI≥10) will be recruited into an observational study and have their sleep monitored over a two-week period. Participants will then be randomised to one of three groups: invite to OLP, invite to CP described deceptively as a new pharmacological agent, or no invite/observational control (OC). Those in OLP and CP accepting the invite receive identical placebos for a two-week treatment period while sleep is monitored in all participants. The primary outcome is ISI at the end of the treatment period. Secondary outcomes include treatment uptake and clinically significant response rates, objective and subjective sleep parameters, fatigue, mood, expectancy, treatment satisfaction and side effects. Predictors of uptake and responses to OLP and CP will be explored.

Ethics and dissemination: The trial has been approved by The University of Sydney Human Research Ethics Committee. Written informed consent is obtained from every participant. OLP

and CP participants accepting the invite undergo an additional consent process. Results will be disseminated via peer-reviewed conference proceedings and publications.

Trial registration: ACTRN12620001080910

Strengths and limitations of this study:

- This will be the first study to test whether open-label placebo (OLP) is effective and acceptable for insomnia.
- The use of a cohort multiple RCT design provides a more ecologically valid no treatment comparison and will allow us to compare the efficacy and uptake of OLP relative to conventional placebo.
- The inclusion of actigraphy means that we can assess the effect of OLP on both self-report and objective sleep outcomes.
- Predictors of uptake and any resulting placebo effect will be explored, including expectancy and baseline insomnia severity.
- Because of the nature of the study, participants and researchers cannot be blind to treatment allocation, but the data analysis will be conducted by a blind researcher.

INTRODUCTION

Insomnia is the most common sleep disorder, with an estimated diagnostic prevalence of 10% [1-3] and symptom prevalence of 30%[3 4] in adults. Higher prevalence rates have been reported in medical settings, ranging from 20 to 56%[2-6], with up to 90% of patients being prescribed pharmacotherapy [7 8]. Insomnia is characterised by difficulty initiating or maintaining sleep along with daytime impairment and/or distress and carries substantial personal and socioeconomic burden[9 10]. People with insomnia have poorer quality of life, greater risk of experiencing other medical conditions and psychiatric disorders, increased healthcare utilisation, and reduced work productivity[11-13]. While a range of pharmacological treatments are available for insomnia, those that demonstrate efficacy are associated with significant risks in terms of adverse effects and the potential for dependence (e.g. benzodiazepines)[14] whereas those with lower risk profiles have limited efficacy (e.g. melatonin.)[15]. Cognitive Behaviour Therapy for Insomnia (CBT-I) has been recommended as first line treatment for insomnia[2 3], however, CBT-I is not always accessible[3] and both practitioners and people with insomnia appear more willing to persist with pharmacological rather than psychological interventions [6 8 16 17]. As such, there remains a pressing need to identify safe and effective treatments to combat the burden of insomnia.

Interestingly, many randomised placebo-controlled trials of insomnia interventions find that participants allocated to placebo treatment experience significant improvement.[18-20]. This suggests that insomnia may be responsive to the placebo effect, whereby the treatment context itself elicits positive expectancies that trigger improvement[21-23]. Importantly, improvement in placebo groups of these trials holds even when directly compared with no treatment[24], indicating that placebo treatment generates more improvement in insomnia than can be accounted for by

other factors, such as, spontaneous recovery and regression to the mean[25]. Therefore, it may be possible to harness the placebo effect to reduce the burden of insomnia.

Placebo interventions likely carry fewer adverse events than pharmacological interventions and have lower cost than psychological interventions[26]. On the other hand, the deception typically associated with placebo administration presents a significant barrier to its clinical use because of the violation of patient trust and informed consent[27]. However, this barrier is based on the assumption that deception is necessary to elicit a placebo effect, which has recently been called into question by 'open-label placebo' trials [28].

Open-label placebo (OLP) trials involve administering placebo treatment with full disclosure that the treatment is in fact a placebo, meaning there is no deception. Only a handful of randomised controlled trials (RCTs) testing OLP have been conducted to date and none with insomnia, but the available data suggest some promising results. For example, in an RCT comparing three weeks' of OLP with 'treatment as usual' (TAU) for chronic pain, Carvalho and colleagues'[29] found that OLP significantly reduced pain and disability, with moderate to large effect sizes. Similar results have been found in RCTs of OLP for irritable bowel syndrome[30], depression[31], and allergic rhinovirus[32]. As a result, there have been increasing calls to explore the potential efficacy of OLP in clinical practice[28 33].

Despite the promising preliminary findings, several criticisms of existing OLP trials have been raised. The most common criticism concerns the types of control group used, typically TAU or waitlist control. The very nature of OLP treatment means that participants and researchers are not blind to treatment allocation, potentially introducing problems with demand characteristics and experimenter bias[28]. While that may be difficult to avoid, a further problem is that knowingly being allocated to receive no treatment may induce nocebo effects and thereby

poorer outcomes in the control group, artificially inflating the apparent efficacy of OLP treatment[28 34]. In addition to concerns regarding the type of control groups used, a second potential important limitation is that participants in OLP trials are usually recruited via advertisements explicitly describing the intervention as a 'novel mind-body treatment'[29 30]. Little is known about the characteristics of individuals who volunteer to participate in 'novel mind-body treatment' research, but differences between such samples and the general population could significantly limit the generalisability of existing OLP trials. If only those who already hold strong beliefs about the power of the mind are enrolled, then this could overestimate the efficacy of OLP effects in the general population. A final limitation is that existing OLP trials have failed to include a comparison with conventional (deceptive) placebo (CP) treatment, which is important to evaluate the relative cost-benefit of open-label versus conventional placebo.

To address this, the current study tests the efficacy of OLP for insomnia (OPIN) using a novel cohort multiple randomised controlled trial (cmRCT) design comparing OLP, CP, and no treatment. The cmRCT involves a two-stage consent process whereby participants are first recruited to an observational study (with no mention of intervention) and are then randomised to be invited to the treatment arms or to remain in the observational arm (i.e., act as controls). This design allows us to compare the efficacy and uptake of open-label versus conventional placebo, relative to a no treatment group, in a more generalisable sample of participants not specifically interested in mind-body treatments, and in a scenario whereby participants in the control group are unaware they are missing out on a potentially desirable treatment. The protocol and study design are guided by the recommendations set out in the SPIRIT 2013 Statement[35]. The results will provide first ever evidence concerning whether OLP is an effective treatment for insomnia and the strongest test of OLP effects in general to date.

Objectives

Primary Objectives

1. Determine whether OLP is associated with reductions in self-report insomnia symptoms, measured by the Insomnia Severity Index (ISI), compared to CP and no treatment.

Secondary Objectives

1. Determine whether OLP is associated with improvements in objective and subjective sleep parameters, daytime fatigue, depression, anxiety, and stress, expectancy, treatment satisfaction and side effects, relative to CP and no treatment.
2. Determine whether OLP is associated with clinically significant improvements in insomnia (response rate), relative to CP and no treatment.
3. Determine the rate of uptake of OLP relative to CP.
4. Identify which demographic, individual, and clinical characteristics predict uptake and the placebo effect (e.g., ISI scores, number of responders) following OLP and CP.

METHOD AND ANALYSIS

Trial Design

As shown in Figure 1, the OPIN trial will use a parallel three-arm cmRCT design[36] comparing OLP, CP, and no treatment/observational control (OC) for insomnia. In the first stage, a cohort of participants with self-reported insomnia symptoms will be recruited into a 2-week observational (baseline) period. In the second stage, participants will be randomised to one of three groups; invite to OLP, invite to CP, or no invite, OC. OLP will be openly described as

consisting of no active ingredient and instead aiming to capitalise on the placebo effect. CP will be described as a new pharmacological agent designed to promote sleep. Participants consenting to OLP or CP will be administered placebo medication while those allocated to OC will continue to be observed for the 2-week treatment period.

The study Steering Committee (principal investigator (PI), associate investigators, study coordinator and statistician) will meet every six months to review the study, ensuring adherence to all ethical, regulatory, and clinical trial guidelines. If higher-than-anticipated attrition rates occur, the Steering Committee will investigate whether the sample size needs to be increased to maintain power, and if so, will seek the appropriate modifications. A Data Monitoring Committee will not be implemented because all participants receive placebos and adverse events are anticipated to be low. Although early study termination is unanticipated, if deemed necessary, only the PI will have the authority to terminate the study.

Participants

To be eligible, participants must report an Insomnia Severity Index (ISI) ≥10, be at least 18 years old, be proficient in English, and able to attend the study site three times over one month. The following exclusion criteria will apply: (1) sleep disorder other than insomnia, (2) currently pregnant, planning to conceive in the next 3 months, breastfeeding, or <1 year post-partum, (3) serious medical illness requiring invasive treatment/surgery (e.g. cancer) or heavy substance use, (4) severe psychiatric co-morbidity (e.g. psychosis, bipolar disorder, depression) or risk of self-harm or suicidality, (5) currently receiving psychological treatment or taking regular (i.e. ≥1/week) medication for sleep (including prescription or over-the-counter

medications, herbal supplements, homeopathic preparations), (6) undertaking shift work (fixed or rotating, including regular night shifts), and/or (7) intending to travel to a destination >2 hours' time difference in the next three months**.** An ISI score of ≥10 was chosen because it has been suggested to indicate clinically significant insomnia[37], with high sensitivity and specificity in community samples[38], and is frequently used in RCTs of sleep interventions[39 40]. Participants will be reimbursed AUD$60 upon completion of the study and will be provided with 12 months free access to Sleepio[41], a commercially available digital CBT app found to reduce insomnia symptoms.

Study Setting

The study will take place at The University of Sydney, Australia. The study will be advertised online (e.g., University research volunteer sites, Facebook) with a link to the study website. The study website includes information about the observational component of the study, researcher contact details, the information sheet and consent form, and a link to complete the online screening measures. Eligible and consenting participants will be contacted and invited to attend the study site to commence participation.

Materials and Measures

Placebo capsules

Participants in the OLP and CP arms will receive a bottle containing identical 28 blue and white plant-based capsules containing microcrystalline cellulose. Bottles for the OLP and CP treatment arms will be labelled "Open-label Placebo Capsules" and "[Codename[1]] Capsules", respectively.

Primary outcome

Insomnia Severity Index (ISI)[37]. The ISI is a brief, validated 7-item self-report questionnaire assessing insomnia symptomatology on a 5-point scale. Items addressed include the severity of sleep onset, maintenance and early awakening difficulties in the last two weeks

[1]The codename is a 7-digit alphanumeric sequence that will be the same for all participants allocated to CP, however, is omitted here to avoid the protocol appearing in any internet searchers participants may undertake.

and are rated from '0' = 'none' to '4' = 'very severe'. Other items rate sleep dissatisfaction, distress, interference, and noticeability to others. Scores are summed to obtain a total score from 0 to 28, with the following clinical cut-offs: no clinically significant insomnia (0 to 7), subthreshold insomnia (8 to 14), moderate insomnia (15 to 21), and severe insomnia (22 to 28). The ISI as a reliable and valid measure in clinical and research settings, with sound internal consistency coefficients (0.74 – 0.78), and moderate concurrent validity (0.32 - 0.91) between the ISI and daily sleep diary [37].

Secondary outcome measures

Uptake of OLP and CP. Uptake of open-label and conventional placebo will be measured simply as the proportion of participants accepting the invite to each treatment arm.

Response rate. Clinically significant improvements in insomnia will be defined as the rate of participants obtaining a 6-point or greater reduction on the ISI from baseline to post-treatment[42] and/or who have an ISI score below the cut-off of 10 at post-treatment[38], relative to CP and no treatment.

Actigraphy. Objective sleep-wake data will be calculated from actigraphy watches (GENEActive, Activinsights Ltd., Cambridgeshire, UK). These are small, wrist-worn accelerometers that record daily movement and can be used to calculate a range of objective sleep parameters. Actigraphy watches have established validity against gold standard sleep assessment (i.e., polysomnography.)[29] **A**ctigraphy data will be used to calculate objective sleep parameters including sleep onset latency, total sleep duration, and overall sleep quality.

Consensus Sleep Diary (CSD)[43]. The CSD is widely used to assess participants' self-reported sleep patterns. The CSD includes questions about time in bed, time to sleep, and number and duration of awakenings. As a measure of treatment adherence, OLP and CP participants will complete items asking whether, and when, they took the capsules the previous night.

Fatigue Symptom Inventory (FSI)[44]. The FSI is a 14-item self-report inventory assessing the intensity, duration, impact, and daily pattern of fatigue over a 1-week period. Participants rate their fatigue from '0'= no fatigue to '10'= the most fatigue with respect to severity, duration, and interference. Individual items are scored to assess least, most, and average fatigue in the past week, and current fatigue. Severity items can be averaged to obtain a composite FSI score[45]. Items addressing fatigue interference with daily functioning or psychosocial wellbeing are averaged to obtain an interference scale score[46]. The FSI has good internal consistency (0.91 - 0.96), and demonstrated concurrent, convergent and discriminant validity[46].

Depression Anxiety Stress Scales (DASS-21)[47]. The DASS-21 is a 21-item self-report measure consisting of three 7-item scales measuring symptoms of depression, anxiety, and stress. Each item is rated on a scale from 0 = 'did not apply to me at all' to 4 = 'applied to me very much, or most of the time'. Item scores are summed and multiplied by two to calculate a final score ranging from 0 to 42 for each scale. Psychometric properties indicate adequate construct validity and excellent internal consistency for the depression (0.88), anxiety (0.82) and stress (0.90) scales [48].

Expectancy Measure. A purpose-built expectancy measure was developed for this study. All participants are asked how much they expect their insomnia symptoms to change as a result of taking part of the study at two time points: prior to the 2-week baseline period and, prior to the

2-week treatment period (after randomisation). Responses are completed on a scale from -10 = 'much worse' through 0 = 'no change to 10 = 'much better'.

Generic Assessment of Side Effects (GASE)[49]. The GASE is a standardised self-report measure of 36 commonly reported side effects observed in clinical trials (e.g., headache, dry mouth). Participants rate the intensity of these symptoms from 0 = 'not present' to 3 = 'severe' and indicate whether each symptom is related to their treatment. The intensity ratings are summed to obtain a total GASE score and a medication-attributed score is calculated by summing symptoms scores rated as related to treatment[49]. Because OC does not receive any medication, an amended version of the attribution question will be administered, whereby for any symptoms present participants in all three arms (OLP, CP and OC) indicate whether each symptom is related to study participation first, then only those participants in the OLP and CP arms indicate whether they believe any such symptom is related to the study medication.

Treatment Satisfaction Questionnaire for Medication – Version II (TSQM-II)[50]. The TSQM-II is an 11-item self-report measure of participants' perceived effectiveness, convenience, side effects and overall satisfaction with medication use. The measure will be administered specifically to participants enrolled in the OLP or CP arms because it focuses on treatment/medication. Domain items are summed and then transformed to a composite score ranging from 0 to 100. The TSQM-II has demonstrated construct validity and internal consistency coefficients ranging from 0.88-0.94 across domains [50 51].

Potential predictors of uptake and the placebo effect

In addition to demographic data, the following personality and clinical history measures will be administered as part of the online screening measures completed prior to study enrolment.

Life Orientation Test-Revised (LOT-R)[52]. The LOT-R is a 10-item measure assessing dispositional optimism. Responses are made on a 5-point scale from 0 = 'strongly disagree' to 4 = 'strongly agree' to items such as "I'm always optimistic about my future", with six of the items summed to achieve an overall optimism score. Psychometric properties indicate adequate construct validity and modest internal consistency correlations ranging from 0.43 to 0.63.[34]

Big-Five Inventory – openness to experience[53] . The Big-Five Inventory (BFI) is a widely used taxonomy of personality traits. Ten self-report items assessing the domain openness to experience were selected for this trial. The BFI has good construct validity and convergent validity with other similar personality measures[35].

Insomnia treatment history. A purpose-designed measure was developed to assess participants' self-reported history of treatments for insomnia (pharmacological, psychological, complementary) and their perceived efficacy of these treatments.

Procedure

Figure 1 shows the study flow. Eligible participants will be invited to attend their first on-site visit (Visit 1). At Visit 1, all participants will be given an actigraphy watch to wear and CSD to complete, for the 2-week baseline period. Participants will return to the study site for Visit 2 (Day 14) and complete outcome measures. At Visit 2, they will be randomised to one of three conditions: OLP, CP, or OC. In the case of the placebo arms, the researcher will discuss the relevant treatment with each participant according to five points, summarised in Table 1, with the

OLP information guided by previous OLP trials[19,20] In the OLP arm there will be an additional emphasis on explaining that most placebo research in the past has involved deception, whilst those in the CP arm will be provided with information about the fake medication.

Table 1. Summary of descriptions and discussion points for OLP and CP.

Discussion point	**Open-label Placebo (OLP)**	**Conventional Placebo (CP)**
What is this treatment?	Placebo capsules containing no active ingredient	A new pharmacological agent, [Drug codename]
What does previous research say?	Placebo effects have been found to reduce insomnia symptoms, but deception is typically involved. Some recent studies in other countries have shown OLP effects outside of sleep	Some recent studies in other countries have shown that [Drug codename] can reduce insomnia symptoms
What are the mechanisms of action?	Placebo effects trigger the brain to release neurotransmitters that can improve symptoms. These responses can be automatic.	[Drug codename] triggers the brain to release neurotransmitters that can improve sleep.
How should I take the capsules?	Work best if taken exactly as prescribed. A positive attitude helps, but is not essential.	
How long will it take to work?	Generally work quickly, but can take longer for some people.	

Participants who accept an invite to OLP or CP will be provided with placebo capsules and the dosage instructions, which require them to take two placebo capsules 10-15 minutes prior to going to bed for the 2-week treatment period. Participants will be asked to record their daily treatment adherence in the CSD. Participants who decline an invite to the OLP or CP arms will continue in the study, unless they choose to withdraw. During the treatment period, all participants will continue completing the CSD and wearing the actigraphy watch. At the final study visit (Visit 3), all participants will return the CSD and actigraphy watches, and participants in the OLP and CP arms will return the capsule bottles and any unused capsules as an additional measure of treatment adherence. All participants will complete post-treatment outcome measures and be debriefed at the end of their study participation. On-site study visits may be replaced with video-link visits in the event that COVID-19 social distancing requirements prevent face-to-face interactions, with study materials being couriered if necessary.

Sample Size

There have been no previous studies on OLP for insomnia. Charlesworth and colleagues'[28] meta-analysis of open-label placebo for other conditions (e.g. chronic pain, irritable bowel syndrome) found a large effect size of d=.88 relative to no treatment. Assuming a similar effect size, to obtain 80% power with alpha=.05 we would require 22 participants to detect this effect size comparing OLP and OC arms. However, we are also seeking to determine whether open-label placebos differ in efficacy relative to conventional placebos – which has not been investigated systematically. We hypothesise that the OLP will be less effective than CP and that the effect size for this comparison will be weaker than the effect size for OLP versus OC. To detect an effect size for OLP versus CP of d=.5, we will require 64 participants per type of

placebo treatment to achieve 80% power with alpha=.05. Therefore, using an allocation ratio of 2:2:1 we would require 64, 64, 32 (total N=160) participants OLP, CP, and OC respectively to obtain sufficient power for both of the critical comparisons. However, because the cmRCT involves two stage consent process we will recruit N=267 participants into the initial cohort aiming to randomise 107 to each placebo arm and 53 to OC, which assumes at least two-thirds (67%) uptake in the placebo arms, including allowance for 10% attrition. This will provide us with sufficient power for both intent-to-treat (primary) and per protocol (sensitivity) analyses.

Randomisation and blinding

Randomisation tables will be generated using randomizer.org. Randomisation will be conducted on a 2:2:1 ratio (OLP, CP, OC) and stratified according to gender and scores on the ISI (<15 and ≥ 15). Randomisation will take place after the eligibility screening and baseline assessment (allocation concealment) at Visit 2. Blinding of the participant and researcher administering the treatment is not possible, however, data analysis will be performed by a blinded member of the team.

Statistical analysis

Primary Outcome

Insomnia severity index. Intent-to-treat analysis (ITT) will be used as the primary analysis to compare the effect of OLP, CP and OC on insomnia symptoms. The primary endpoint (mean scores on the ISI post-treatment) will be assessed using a multilevel model with group (OLP, CP, OC) and baseline (Visit 2) ISI score included as factors. Consistent with previous

analysis methods in cmRCTs, the ITT population for the OLP and CP arms will consist of all participants who receive an offer of treatment, regardless of treatment uptake. As a secondary, sensitivity analysis, a per-protocol approach will also be implemented including only those participants in the OLP, CP and OC arms who complete the study. The analyses will include participants who scored ≥10 on the ISI at screening, but we will also conduct sensitivity analysis excluding any participants who fall below this threshold during the baseline period (assessed at Visit 2).

Secondary Outcomes

Uptake. A chi-squared test of independence will be used to determine whether rates of accepting treatment differ when OLP versus CP is offered.

Response rate: Group differences in the proportion of participants achieving a clinically significant response (i.e., ≥ 6-point reduction and/or < 10 on the ISI) will be analysed using a chi-squared test of independence.

Other sleep parameters and outcomes. Other sleep measures (self-report and objective), daytime fatigue, depression, anxiety, stress, treatment satisfaction, expectancy, and side effects will be assessed as per the primary ISI outcome.

Predictors of uptake and the placebo effect

Potential predictors of uptake and the placebo effect will be assessed using a combination of logistic and linear regressions to identify which clinical, demographic and personality

characteristics predict uptake (logistic) of and the placebo effect (linear: ISI scores and related outcomes; logistic: response rates) to OLP and CP.

For all analyses, results will be considered statistically significant when $p < .05$.

Patient and public involvement

Neither patients nor members of the public had any involvement in the design of the OPIN trial.

ETHICS AND DISSEMINATION

The study is registered with the Australian and New Zealand Clinical Trial Registry (ACTRN12620001080910; see Supplementary Material 1). The study protocol (version 6 dated 10 September 2020), participant information sheets and consent forms (see Supplementary Material 2) and relevant materials, and the ethical aspects of this trial have been reviewed and approved by The University of Sydney Human Research Ethics Committee (HREC 2019/552). Study data will be collected and stored using the University's Research Electronic Data Capture (REDCap) system, with password-protected access provided to relevant research personnel only. All data will be securely stored for a minimum of 15 years. The PI will be responsible for communicating important protocol modifications. The final dataset will be maintained by the PI, with de-identified participant data available on request following publication to researchers providing a methodologically and ethically sound proposal, in addition to the full study protocol,

statistical analysis plan and analytic code. Results from this trial will be disseminated in the form of peer-reviewed conference proceedings and publications.

Author Contributions

BC conceptualised the study and is the princial investigator and grant holder. BC, AS, LS, NG, DC, DB and ZA made significant contributions to designing the study. BC, AS, LS, NG, DB and ZA contributed to developing the screening procedures. BC and DC were responsible for the power calculations and statistical analysis plan. BC, AS, and ZA were responsible for creating the first draft of this manuscript. BC, AS, LS, NG, DC, DB and ZA provided input and feedback, and approved the final draft of this manuscript.

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Competing Interests Statement

The authors report no competing interests in relation to this research. The University of Sydney is the study sponsor. All decisions regarding the study design, collection, management, analysis or interpretation of data, and publication remain the PIs.

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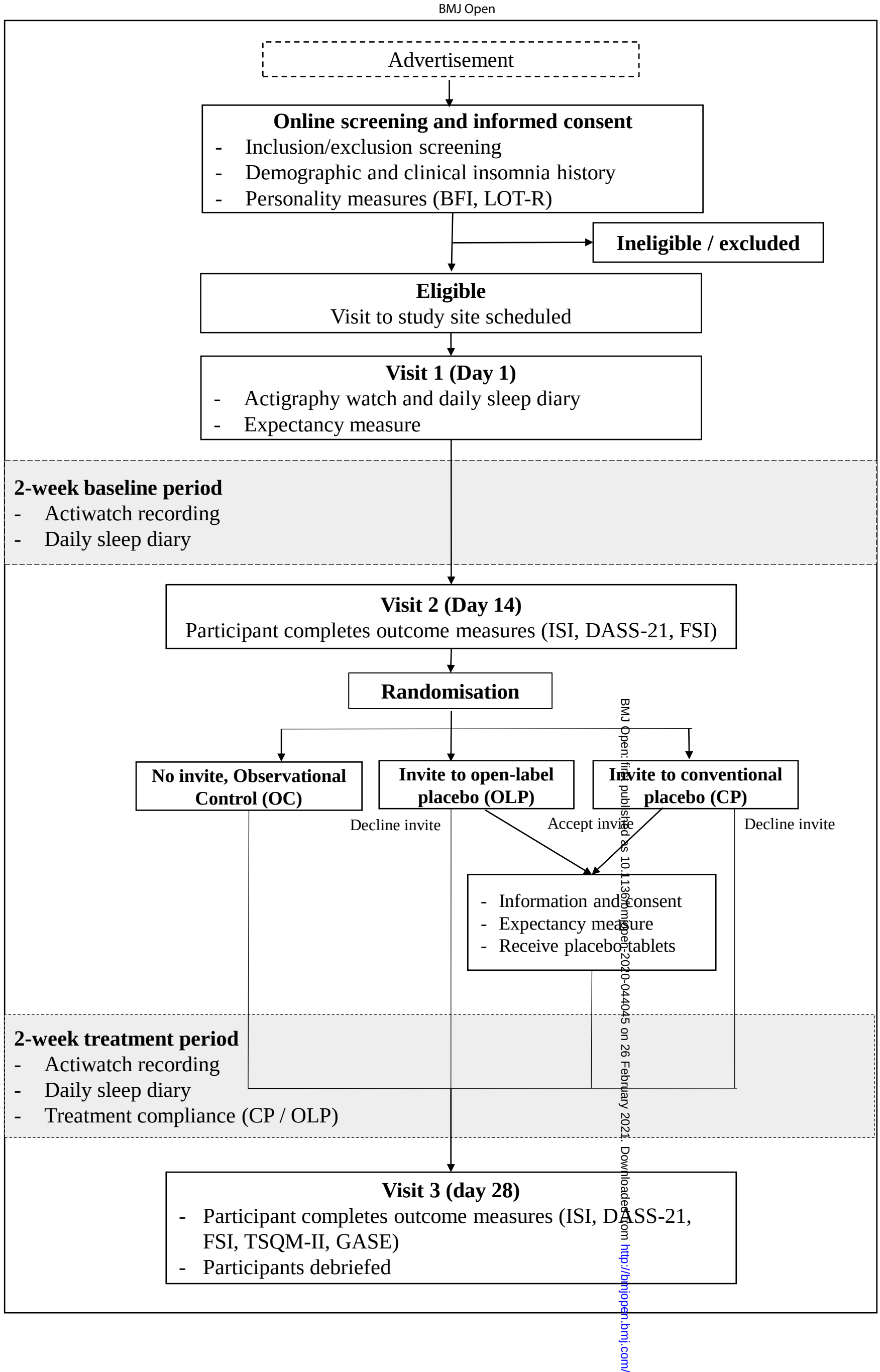

BMJ Open Supplementary Material 1

SPIRIT Item2b: WHO Trial Registration Data Set

Data Category	Information
Primary registry and trial identifying number	Australian New Zealand Clinical Trial Registry https://www.anzctr.org.au Trial ID: ACTRN12620001080910
Date of registration in primary registry	20 October 2020
Secondary identifying numbers	2019/552
Source(s) of monetary or material support	School of Psychology, The University of Sydney
Primary sponsor	The University of Sydney
Secondary sponsor(s)	N/A
Contact for public queries	A/Prof Ben Colagiuri PhD, +61 2 9351 4589, ben.colagiuri@sydney.edu.au
Contact for scientific queries	A/Prof Ben Colagiuri PhD, +61 2 9351 4589, ben.colagiuri@sydney.edu.au
Public Title	Open-label placebo for insomnia (OPIN)
Scientific Title	Open-label placebo for insomnia (OPIN): a cohort multiple randomised controlled trial in adults with moderate or severe insomnia
Countries of recruitment	Australia

Health condition(s) or problem(s) studied	Insomnia
Intervention(s)	Active comparator: open-label placebo (OLP) capsules Placebo comparator: conventional (deceptive) placebo (CP) capsules
Key inclusion and exclusion criteria	Inclusion criteria: adult (≥ 18 years), self-reported insomnia symptoms with score on Insomnia Severity Index (ISI) ≥ 10 Exclusion criteria: sleep disorder other an insomnia, severe medical or psychiatric comorbidity, current regular (≥ 1/week) administration of sleep medication, current psychological treatment for sleep, currently pregnant, planning to conceive within 3 months, breastfeeding or 1-year post-partum, regular night shift work
Study type	Cohort multiple randomised controlled trial Allocation: randomised Intervention model: parallel assignment Masking: Open-label placebo arm (both participant and investigator are aware of treatment allocation, conventional placebo arm (participant is blind but investigator aware of treatment allocation) Primary purpose: Intervention outcome
Date of first enrolment	
Target sample size	267
Recruitment status	Not yet recruiting

Primary outcome(s)	Determine whether OLP is associated with reductions in self-reported insomnia symptoms measured with the Insomnia Severity Index (ISI), compared to CP and no treatment.
Key secondary outcomes	Improvements in objective and subjective sleep parameters, daytime fatigue, anxiety, depression and stress, expectancy, treatment satisfaction and self-reported side effects; clinically significant improvements in insomnia in OLP, relative to CP and no treatment; rate of uptake of OLP relative to CP; predictors of uptake and placebo effect

BMJ Open Supplementary Material 2

OPIN Information Sheet_1, Version 3 dated 18 August 2020

THE UNIVERSITY OF SYDNEY

ABN 15 211 513 464

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Email:
ben.colagiuri@sydney.edu.au

Insomnia Symptoms Study

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part in a research study examining the sleeping patterns of people who experience insomnia symptoms. We are interested to understand how insomnia symptoms (such as difficulty falling asleep, or frequent awakenings) change over time. We hope to use the data collected in this study to inform how people might respond to different treatments for insomnia.

You have been invited to participate in this study because you have expressed interest in taking part and identify as having insomnia symptoms. This Participant Information Statement tells you about the research. Knowing what is involved will help you decide if you want to take part. Please read this sheet carefully and get in touch with the researchers to ask questions about anything that you don't understand or want to know more about. Contact details can be found at the end of this information sheet. Participation in this research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

✓ Understand what you have read.

- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described

(2) Who is running the study?

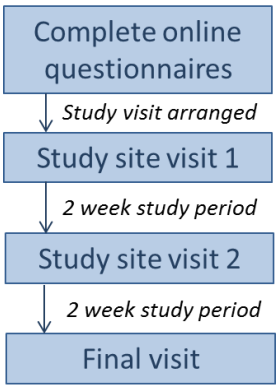
The study is being carried out by the following researchers:

- Ben Colagiuri, Associate Professor, The University of Sydney School of Psychology
- Louise Sharpe, Professor, The University of Sydney School of Psychology
- Nick Glozier, Professor of Psychological Medicine, Central Clinical School of Medicine and Brain & Mind Centre, University of Sydney
- Delwyn Bartlett, Associate Professor, Central Clinical School of Medicine, University of Sydney
- Amelia Scott, PhD, The University of Sydney School of Psychology
- Daniel Costa, Honorary Research Fellow, Pain Management Research Institute, University of Sydney
- Zahava Ambarchi, Study Coordinator, The University of Sydney, School of Psychology

This study is being funded by The University of Sydney and the Australian Research Council.

(3) What will the study involve for me?

The study will take place over four weeks. You will firstly be required to complete an online questionnaire to determine whether you are eligible to take part. If you are eligible, you will be contacted to schedule a time to attend the study site.



The screening questionnaire asks about basic details such as your age and gender, your current insomnia symptoms and treatment, and some brief questions about your mental and physical health. Participating in the study involves wearing a watch-like sleep monitoring device, as well as completing a daily sleep diary and questions about your mental and physical health.

If you agree to participate, you will be asked to attend three visits:

1) On visit one, you will collect the watch and a sleep diary

2) On the second visit, you will complete some brief questionnaires about sleep and other symptoms over the previous two weeks

3) On the final visit you will return the watch and complete some brief questionnaires about sleep and other symptoms over the previous two weeks

Prior to your attendance to any of the three face-to-face study visits, the study coordinator will contact you and ask you some questions regarding cold and flu-like symptoms and contact with positive or potential cases of COVID-19. If necessary, your visit will be rescheduled or conducted via phone, in which case the watch and sleep diary will be mailed to you.

The sleep monitoring device is called an Actiwatch. It is a safe, non-invasive and accurate way to measure people's sleep-wake patterns. You will be asked to wear it continuously (day and night). You will also be asked to complete a brief sleep diary each morning that should take you approximately 2 minutes. An SMS text reminder will be sent to you each morning to remind you to complete the sleep diary.

At visit two and the final visit, you will be required to complete a longer survey. This survey includes questions about your insomnia symptoms, fatigue, mood, other physical symptoms experienced. These questionnaires will take approximately 25 minutes.

You may be asked to take part in Phase 2 of the study. This invitation will be randomly determined so that some people are invited into Phase 2 while others are not. It will be entirely your decision as to whether you choose to participate in Phase 2 and you will be provided with an additional information sheet and consent form regarding this at your second site visit.

(4) How much of my time will the study take?

This screening questionnaire should take you approximately 20 minutes. We estimate that attending the study site on three occasions and completing testing will take 1 hour and 15 minutes in total (i.e., <30min each visit, see the above diagram), excluding travel time. Completing the sleep diary each morning will take approximately 2 minutes per day. Therefore, the total time commitment is approximately 2 ½ hours.

(5) Who can take part in the study?

People eligible to take part will be adults (age over 18), proficient in English, who experience insomnia symptoms of at least moderate severity. People cannot take part if they are currently receiving treatment (such as psychological therapy, prescription or over-the-counter medications, herbal supplements or homeopathic formulations), undertake regular night shift work, are currently pregnant, intending to fall pregnant in the next 3 months, breastfeeding or less than 1 year post-partum, if they seem to have a different kind of sleep disorder (e.g. sleep apnoea), if they are currently experiencing a significant medical condition requiring invasive treatment or surgery, and/or psychiatric condition.

(6) Do I have to be in the study? Can I withdraw from the study once I've started?

Being in this study is completely voluntary and you do not have to take part. Your decision whether to participate will not affect your current or future relationship with the researchers or anyone else at the University of Sydney. If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by informing the study coordinator (by phone or by e-mail) that you no longer wish to take part. If you decide to withdraw from the study, we will not collect any more information from you. Please let us know at the time when you withdraw what you would like us to do with the information we have collected about you up to that point. If you wish your information will be removed from our study records and will not be included in the study results, up to the point that we have analysed and published the results.

(7) Are there any risks or costs associated with being in the study?

Aside from giving up your time, we do not expect that there will be any risks or costs associated with taking part in this study.

(8) Are there any benefits associated with being in the study?

You will receive $60 after you complete the study. This will be provided to you in the form of cash. In terms of other benefits associated with participation, we anticipate that our results will provide benefit to our understanding of insomnia symptoms and their treatment.

(9) What will happen to information about me that is collected during the study?

During the study, we will be collecting various types of information from you. This includes your responses on survey questions, your daily sleep diary, and data that is collected from actigraphy watches.

In order to send you SMS reminders to complete your sleep diary, your phone number (but not your name or other personal details) will be provided to a third-party SMS service provider to perform this service. The SMS provider will only be used to send you reminder texts to complete the sleep diary for the duration of your involvement in the study, and only for that purpose. No other text messages will be sent to you during or after your participation in the study.

Data collected from this study will be published in journal articles and/or conference presentations in summary form without any personally identifying information. In addition, de-identified data may be shared with other researchers or research groups for the purpose of conducting extra analyses of our data, or comparing our results against similar studies. Under no circumstances will we provide identifying information (e.g. names, contact details) to other researchers.

By providing your consent, you are agreeing to us collecting personal information about you for the purposes of this research study. Your information will only be used for the purposes outlined in this Participant Information Statement, unless you consent otherwise. Your information will be stored securely and your identity/information will be kept strictly confidential, except as required by law. Study finding may be published, but you will not be individually identified in these publications.

(10) Can I tell other people about the study?

Yes, you are welcome to tell other people about the study. However, if you know other people participating in the study, it is best to talk with them about the study after you have all completed your sessions, in case your experiences influence theirs.

(11) What if I would like further information about the study?

When you have read this information, please get in touch with the researchers if you have any further questions. You can contact either the study coordinator on [redacted] or at psychology.sleepstudy@sydney.edu.au, or Ben Colagiuri at ben.colagiuri@sydney.edu.au or (02) 9351 4589.

(12) Will I be told the results of the study?

You have a right to receive feedback about the overall results of this study. You can tell us that you wish to receive feedback by ticking the relevant box below. This feedback will be in the form of a one page summary of the study findings. You will receive this feedback after the study is finished.

As well as the overall results of the study, you will be provided with specific feedback about your sleep-wake patterns based on reporting in a sleep diary as well as wearing the Actiwatch. This will be provided shortly after your participation in the study has been completed.

(13) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney [2019/552]. As part of this process, we

have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** ro.humanethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep

OPIN Consent Form_1, Version 2 dated 10 September 2020

Insomnia Symptoms Study

CONSENT FORM

If you have read the participant information sheet and would like to take part, you may complete the consent process below.

1) I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.	Yes / No
2) I understand that participation involves three visits to the University of Sydney, Camperdown, Sydney, and that a researcher will contact me by phone and/or e-mail to arrange this.	Yes / No
3) I understand that my mobile number will be shared with a third-party SMS provider for the sole purpose of sending me a daily text reminder while I am part of the study.	Yes / No
4) First name	
5) Surname	
6) Contact phone: (Note, include area code if using a landline)	

7) Please indicate any preferences regarding a suitable day or time to contact you:	
8) Contact email (please note that we will automatically send you a copy of the participant information statement for you to keep).	
9) I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.	Yes No
10) I understand that I can withdraw from the study at any time.	Yes No
11) I would like to receive feedback about the overall results of the study.	Yes No

Insomnia Symptoms Study

Optional additional participation - [redacted] for Insomnia Symptoms

PARTICIPANT INFORMATION STATEMENT

(1) What is this study about?

You are invited to take part phase 2 of the study you are currently participating in. The aim of this part is to determine whether [redacted] to improve your insomnia symptoms.

You have been invited to take part in this study by chance. In other words, your participant ID has been randomly selected via a computer programme.

This Participant Information Statement tells you about *the additional parts of this research*.

Participation in this part of the research study is voluntary.

By giving your consent to take part in this study you are telling us that you:

- ✓ Understand what you have read.
- ✓ Agree to take part in the research study as outlined below.
- ✓ Agree to the use of your personal information as described.

(2) What will this part of the study involve?

For the remaining two weeks of the study, your participation in the study will not change, with the exception of two parts;

- You will be required to take [redacted]
- You will be asked to record your [redacted] intake along with your sleep diary

(3) Will this take additional time?

We anticipate that the above additions to your research participation will take very little extra time.

(4) Do I have to be in this part of the study? Can I withdraw from the study once I've started?

At this point in the study, you have a few choices available to you:

A. You may take part in the additional component of the study that involves [redacted]

B. You may choose not to take part in the additional component of the study but continue in the way that you previously agreed to

C. You may choose to withdraw altogether, which you can do at any time

You do not have to agree to take part in this component of the research study, and your decision whether to participate or not will not affect your current or future relationship with the researchers or anyone else at the University of Sydney.

If you decide to take part in the study and then change your mind later, you are free to withdraw at any time. You can do this by informing the researchers (by phone or by e-mail) that you no longer wish to take part. If you decide to withdraw from the study, we will not collect any more information from you. Please let us know at the time when you withdraw what you would like us to do with the information we have collected about you up to that point. If you wish your information will be removed from our study records and will not be included in the study results, up to the point that we have analysed and published the results.

(5) Are there any risks or costs associated with being in this part of the study?

There are no known risks of taking [redacted]

(6) Are there any benefits associated with being in the study?

It is possible that you will experience improvements to your insomnia symptoms after taking [redacted]. You will not receive additional reimbursement for this additional component of the study – i.e. you will still receive $60 at the end of the study.

(7) What will happen to information about me that is collected during the study?

We will collect some additional information from you if you take part in this part of the study. This includes your thoughts and expectations about taking [redacted], and your compliance with [redacted]. Otherwise, there are no differences to the way that your information is collected and managed in this part of the study.

(8) Can I tell other people about the study?

You are welcome to speak to others about this study (e.g. a friend, family member, GP), but we ask that you do not speak to other people who may be participating in the study. This is because other people will not have been invited to this part of the study, and we do not wish for this knowledge to affect them in any way.

(9) What if I have a complaint or any concerns about the study?

Research involving humans in Australia is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this study have been approved by the HREC of the University of Sydney [2019/552]. As part of this process, we have agreed to carry out the study according to the *National Statement on Ethical Conduct in Human Research (2007).* This statement has been developed to protect people who agree to take part in research studies.

If you are concerned about the way this study is being conducted or you wish to make a complaint to someone independent from the study, please contact the university using the details outlined below. Please quote the study title and protocol number.

The Manager, Ethics Administration, University of Sydney:

- **Telephone:** +61 2 8627 8176
- **Email:** ro.humanethics@sydney.edu.au
- **Fax:** +61 2 8627 8177 (Facsimile)

This information sheet is for you to keep

OPIN Consent Form_2, Version 2 dated 10 September 2020

Insomnia Symptoms Study

Optional Additional Consent

PARTICIPANT INFORMATION STATEMENT

I, ... [PRINT NAME], agree to take part in the additional component of this research study.

In giving my consent I state that:

- I understand the purpose of the study, what I will be asked to do, and any risks/benefits involved.
- I have read the Participant Information Statement and have been able to discuss my involvement in the study with the researchers if I wished to do so.
- The researchers have answered any questions that I had about the study and I am happy with the answers.
- I understand that being in this study is completely voluntary and I do not have to take part. My decision whether to be in the study will not affect my relationship with the researchers or anyone else at the University of Sydney now or in the future.
- I understand that I can withdraw from the study at any time.
- I understand that personal information about me that is collected over the course of this project will be stored securely and will only be used for purposes that I have agreed to. I understand that information about me will only be told to others with my permission, except as required by law.

☐ I give consent for the researchers to contact me about future opportunities to participate in research relating to the current study (e.g. to be interviewed about my experiences)

☐ I give consent for the researchers to contact me to see whether I am interested in taking part in any media stories related to the current study

☐ I give consent for the researchers to contact me about future opportunities to participate in research not directly related to the current study

Please note: under no circumstance would we forward your information onto another party without your prior consent.

.....

Signature

.....

PRINT name

.....

Date

1

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	Supplementary File 1
Protocol version	3	Date and version identifier	20
Funding	4	Sources and types of financial, material, and other support	21
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1
	5b	Name and contact information for the trial sponsor	11
	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	21
	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)	8

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	____4-6_____
Objectives	7	Specific objectives or hypotheses	____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)	____7-8_____
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	____11_____
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)	_____8-9_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	__7-8,15-17__
	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)	____8_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	____12-14_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	____8_____
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	____7-15_____
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_____

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	17
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	11
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	18
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	18
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	18
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	18
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	18
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	11-17
	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	11-17

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	20
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	18-19
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	18-19
	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)	18-19
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	8
	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	8
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
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	8
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	20
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)	20

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	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	20
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	21
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	20
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	NA
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	20
	31b	Authorship eligibility guidelines and any intended use of professional writers	NA
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Supplementary File 2
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	NA

*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.