PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)
AUTHORS	Kyle, Simon; Madigan, Claire; Begum, Nargis; Abel, Lucy; Armstrong, S; Aveyard, Paul; Bower, Peter; Ogburn, Emma; Siriwardena, Aloysius; Yu, Ly-Mee; Espie, Colin

VERSION 1 – REVIEW

REVIEWER	Christina Sandlund Karolinska Institutet, Sweden Academic Primary Health Care Centre, Stockholm Region, Sweden
REVIEW RETURNED	20-Dec-2019

GENERAL COMMENTS	Dear Authors, I have had the privilege of reviewing your manuscript, "Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)" for BMJ Open. Brief summary: The manuscript is a study protocol for a randomized controlled trial that aims to evaluate the effectiveness of nurse-delivered sleep restriction therapy in primary care. The main objective is to investigate whether nurse-delivered sleep restriction therapy and sleep hygiene advice reduce insomnia severity more than sleep hygiene advice alone. Other objectives are a cost-effectiveness evaluation and a process evaluation that includes but is not limited to qualitative analyses of participants' and nurses' experiences of sleep restriction therapy. Overall impression: The manuscript outlines a well-thought-out, comprehensive project. The study plan is well-described and scientifically credible. There is sufficient detail to instil confidence that the study will be properly conducted and analysed. However, I have some minor points that I think should be considered and some minor comments that I think should be addressed prior to publication in BMJ Open. Yours sincerely, Christina Sandlund Comments

	1. According to the methods section, you plan to identify potential participants in a variety of ways, including direct face-to-face GP referral (page 7, row 59). It may also be relevant to consider nurse referral. Nurses are often patients' first point of contact in primary care. Moreover, as you note (page 5, rows 46-51), practice nurses are increasingly involved in chronic disease management. They may therefore be well-placed to identify potential study participants. 2. The plan is for the research team to screen participants for eligibility (page 8, row 11). This seems out of keeping with the goal of assessing effectiveness in routine primary care. The research team includes insomnia experts, but in routine care, the patient's health care provider must be able to assess whether the patient is a candidate for sleep restriction or not. Have you considered letting the nurses perform the screening? I would also like more information about the reasoning behind the decision to screen through an online questionnaire. Was the decision made for practical reasons, or was there additional motivation? I ask because this decision also seems out of keeping with the assessment of effectiveness in routine care, where insomnia assessment is performed clinically, with questionnaires as a complement. 3. Ability and willingness to give informed consent is an inclusion criteria (page 8, row 16). How and by whom will informed consent be obtained? Will consent be verbal or written? 4. There is a discrepancy between the exclusion criteria presented in the ISRCTN registry (updated 17 September 2019) and in the manuscript: "Trans-meridian travel planned during the baseline assessments or for > 3 nights during treatment phase" is missing from the manuscript. I suggest adding this criterion to the study protocol, as it is a relevant reason for exclusion, both in the study and clinically. 5. Nurse training will include information about insomnia (page 9, row 50). Please consider adding a brief description of whether the information includes how to identify patients with insomnia disorder and theoretical models of the development and maintenance of insomnia. 6. You will conduct semi-structured interviews with a sample of practice nurses, trial participants and practice managers or GPs (page 12, rows 21-26). How will you choose the participants? 7. Interviews with participants will take place after the intervention phase (page 12, rows 36-38). I interpret this as meaning that they will occur after the intervention but before the assessments. If that is the case, have you considered that it may bias your results, as taking part in an interview may itself comprise an intervention that could affect outcomes. 8. The estimate of sample size is based on a study by Fallon et al. Your study is therefore powered for a moderate effect size (page 13). Please consider that Fallon et al. employed a simplified algorithm for sleep restriction that probably resulted under-dosed treatment (total time in bed allowed at baseline was equal to the

	average total sleep duration plus 50% of the total time spent awake in bed). Because you plan to use standard sleep restriction, I suggest that you may have overestimated the sample size required.

REVIEWER	Judith R. Davidson Queen's University Department of Psychology Kingston, Ontario Canada
REVIEW RETURNED	26-Dec-2019

GENERAL COMMENTS	This is a very well conceptualized, designed and planned randomized controlled trial of nurse-delivered sleep restriction therapy in primary care. The study is powered to detect a small difference (1.35 points) on the ISI. I realize that the literature is scant, and agree with basing the same size calculations on the sole study that reported ISI data from sleep restriction therapy (Falloon et al., 2015) but I wonder whether you will find large differences between the groups before you get to 588 participants. I wonder this because of the large effect sizes on sleep diary variables of sleep restriction and stimulus control therapy in similar format to yours (4 sessions; 2 in person, 2 by phone) seen by Buysse et al., 2011 and McCrae et al., 2007. You might consider pre-planning an interim analysis of your primary outcome (and adverse events) at a specified point in the recruitment e.g., halfway. This would be done by a data monitoring committee. You would then stop the study early if you find a large, clinically significant benefit of the intervention (or if you find unlikely detrimental events). A few typos in references can be easily fixed (e.g., #21: systematic; #50: Schultz). Overall, this is an excellent protocol; the study will provide useful, important and scientifically sound data. Buysse et al., Arch Intern Med. 2011; 171(10):887-95. McCrae et al., Am J Geriatr Soc. 2007; 15(11):979-82.

REVIEWER	John Cape University College London, Clinical, Educational and Health Psychology
REVIEW RETURNED	31-Dec-2019

GENERAL COMMENTS	This protocol paper describes the design of a sizeable (planned N = 588) RCT of sleep restriction that commenced recruitment in August 2018 and is due to complete in March 2020. The rationale of the study is well set out in terms of the potential population benefits if sleep restriction (SRT) can be delivered effectively by practice nurses within primary care at scale. However, the supplementary table notes that the intervention will be delivered by research nurses from clinical research networks as well as practice nurses. While I can see the logic of this in terms of ensuring primary care buy in to the study and better fidelity implementation of the intervention, it does mean the results will not be generalisable to routine primary care. The authors might wish to consider explorative analyses of both outcomes and

	implementation of interventions separately for practice nurses and research nurses. And that both types of nurses will deliver the intervention needs to be in the body of the paper not just in a supplementary table. The planned study is well described and there are just a few points where additional clarification is needed: 1. Who is conducting the randomisation and what is the process and who is involved from baseline assessment to randomisation to informing participants (and nurses for those randomised to SRT) of their allocation? 2. Are all measures at baseline prior to randomisation, including exclusion criteria, from patient self-report or are some obtained from general practice records or contact with the general practice? 3. How will the baseline sleep diaries and actigraphs be distributed to both groups, with what instructions and when (specifically whether (1) before or after randomisation/allocation (2) before or after distribution of the sleep hygiene booklets (3) before or after contact with the nurse for the SRT group)? And (1) how and when will the baseline data from these be reported back to the researchers (2) will the SRT group be informed that the baseline diary data they are collecting will be used not just for the research but for their first treatment session)? 4. Is the “list of sleep hygiene guidelines” described as being part of the booklet provided to SRT participants a duplicate of the sleep hygiene guidelines they will have previously been sent by the research team or different; if different in what way different? In effect is the written information on sleep hygiene and lifestyle behaviours the same in both groups? 5. Is there an established rating scale to assess SRT intervention fidelity that will be used or will the clinical psychologist assessing fidelity construct an ad hoc scale for this? A few aspects the authors may wish to consider, but may or may not chose to include in a revision 6. Reading the paper title, I assumed the control condition was nurse-delivered sleep hygiene advice. While the abstract makes clear this is not the case, the authors might wish to consider whether a minor change to the title would be helpful to make this clear 7. Inclusion of the mediation analyses measures in Table 1. This table was very helpful in keeping track of the different measures related to the different study hypotheses, but omits the mediation analyses measures 8. I am assuming the ISI difference of 1.35 points was chosen for the sample size calculation not because this is considered a clinically significant difference but because this equates to a SMD effect size of 0.30 as set out in the following paragraph, but this was not entirely clear Finally, a couple of typos/minor errors to check 9. Page 7, first line after Trial Design: should be “individually randomised” (no comma) 10. Page 12, final paragraph: Reference no 43 looks incorrect 11. Top of page 14: CBT-I used as an acronym for the first time

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Dear Authors,

I have had the privilege of reviewing your manuscript, "Primary care treatment of insomnia: study protocol for a pragmatic, multicentre, randomised controlled trial comparing nurse-delivered sleep restriction therapy to sleep hygiene (the HABIT trial)" for BMJ Open.

Brief summary: The manuscript is a study protocol for a randomized controlled trial that aims to evaluate the effectiveness of nurse-delivered sleep restriction therapy in primary care. The main objective is to investigate whether nurse-delivered sleep restriction therapy and sleep hygiene advice reduce insomnia severity more than sleep hygiene advice alone. Other objectives are a cost-effectiveness evaluation and a process evaluation that includes but is not limited to qualitative analyses of participants' and nurses' experiences of sleep restriction therapy.

Overall impression: The manuscript outlines a well-thought-out, comprehensive project. The study plan is well-described and scientifically credible. There is sufficient detail to instil confidence that the study will be properly conducted and analysed.
==>Thank you for the positive comments.

However, I have some minor points that I think should be considered and some minor comments that I think should be addressed prior to publication in BMJ Open.

Comments

1. According to the methods section, you plan to identify potential participants in a variety of ways, including direct face-to-face GP referral (page 7, row 59). It may also be relevant to consider nurse referral. Nurses are often patients' first point of contact in primary care. Moreover, as you note (page 5, rows 46-51), practice nurses are increasingly involved in chronic disease management. They may therefore be well-placed to identify potential study participants.

==>The principal recruitment method is through letter invitation to potential participants who are identified through searches of practice lists. The reason we focus on GP referral as an additional strategy – which in effect means providing prospective participants with an information sheet – is that GPs are the primary point of contact for those with sleep problems in UK primary care and are best placed to assess general study suitability in relation to previous/current medical history.

2. The plan is for the research team to screen participants for eligibility (page 8, row 11). This seems out of keeping with the goal of assessing effectiveness in routine primary care. The research team includes insomnia experts, but in routine care, the patient's health care provider must be able to assess whether the patient is a candidate for sleep restriction or not. Have you considered letting the nurses perform the screening?

==>Screening is completed via questionnaire (self-completed or administered over the phone by members of the research team who are NOT experienced sleep researchers). We believe this approach could be readily translated to the primary care environment.

I would also like more information about the reasoning behind the decision to screen through an online questionnaire. Was the decision made for practical reasons, or was there additional motivation? I ask because this decision also seems out of keeping with the assessment of effectiveness in routine care, where insomnia assessment is performed clinically, with questionnaires as a complement.

==>Please see above response. We opted for this approach to ensure standardisation of screening across sites and because it does not require specialist training or expertise (and therefore could be a viable approach in primary care).

3. Ability and willingness to give informed consent is an inclusion criteria (page 8, row 16). How and by whom will informed consent be obtained? Will consent be verbal or written?

==>Written informed consent will be obtained by a member of the research team. We now clarify this (page 8).

4. There is a discrepancy between the exclusion criteria presented in the ISRCTN registry (updated 17 September 2019) and in the manuscript: “Trans-meridian travel planned during the baseline assessments or for > 3 nights during treatment phase” is missing from the manuscript. I suggest adding this criterion to the study protocol, as it is a relevant reason for exclusion, both in the study and clinically.

==>We initially listed this criterion when preparing the trial but prior to study enrolment we dropped it from the protocol and registry. We did so because we consider it to be a logistical/scheduling factor: intervention appointments are scheduled when participants are in the country. We have checked with the registry and they have acknowledged that this is an error on their part – they have now rectified it (you will see trans-meridian travel is now correctly listed as a previous exclusion criterion).

5. Nurse training will include information about insomnia (page 9, row 50). Please consider adding a brief description of whether the information includes how to identify patients with insomnia disorder and theoretical models of the development and maintenance of insomnia.
==>The training covers the definition of insomnia as well as Spielman’s model of insomnia development and maintenance, in keeping with the SRT approach. This information is contained within Supplementary Table 1.

6. You will conduct semi-structured interviews with a sample of practice nurses, trial participants and practice managers or GPs (page 12, rows 21-26). How will you choose the participants?
==>Interview participants will be invited from 5 practices from each of the three trial recruitment centres. The practices will be selected to reflect a range of practice types (e.g., based on practice size, or membership of a consortium). One practice nurse, one trial participant and one practice manager or GP will be interviewed from each selected practice. We have added further information to clarify (page 12).

7. Interviews with participants will take place after the intervention phase (page 12, rows 36-38). I interpret this as meaning that they will occur after the intervention but before the assessments. If that is the case, have you considered that it may bias your results, as taking part in an interview may itself comprise an intervention that could affect outcomes.

==>In principle this is a possibility but we consider it important to sample views of the treatment proximal to completion, to ensure experiences are salient. Interviews are conducted by members of the research team and not therapists or sleep experts. Moreover only a small sample of participants

from the SRT arm [15/294 (5%)] will be interviewed; and therefore we consider any potential influence to be trivial.

8. The estimate of sample size is based on a study by Fallon et al. Your study is therefore powered for a moderate effect size (page 13). Please consider that Fallon et al. employed a simplified algorithm for sleep restriction that probably resulted under-dosed treatment (total time in bed allowed at baseline was equal to the average total sleep duration plus 50% of the total time spent awake in bed). Because you plan to use standard sleep restriction, I suggest that you may have overestimated the sample size required.

==>We consider that an effect size of 0.3 is appropriate for a pragmatic trial that 1) utilises broad eligibility criteria and 2) tests nurse-delivered therapy across multiple practices. This is in contrast to Falloon et al where the intervention was delivered by a single GP expert, across two sites, and included patients with primary insomnia free from comorbidity or sedative medication.

Reviewer: 2

Please leave your comments for the authors below
This is a very well conceptualized, designed and planned randomized controlled trial of nurse-delivered sleep restriction therapy in primary care.
==>Thank you for the positive comments.

The study is powered to detect a small difference (1.35 points) on the ISI. I realize that the literature is scant, and agree with basing the same size calculations on the sole study that reported ISI data from sleep restriction therapy (Falloon et al., 2015) but I wonder whether you will find large differences between the groups before you get to 588 participants. I wonder this because of the large effect sizes on sleep diary variables of sleep restriction and stimulus control therapy in similar format to yours (4 sessions; 2 in person, 2 by phone) seen by Buysse et al., 2011 and McCrae et al., 2007. You might consider pre-planning an interim analysis of your primary outcome (and adverse events) at a specified point in the recruitment e.g., halfway. This would be done by a data monitoring committee. You would then stop the study early if you find a large, clinically significant benefit of the intervention (or if you find unlikely detrimental events).

==>We thank the reviewer for this suggestion. While the mode of delivery may seem similar to other studies there are multiple design factors, such as NHS setting in the UK and nurse delivery of monotherapy across multiple primary care practices, which may affect the proposed effect size (and hence sample size). We believe we have appropriately powered the study based on the pragmatic trial design (see response to reviewer 1).
Our DMEC members review all efficacy and safety data but recommendation to stop the trial is based only on safety data. To avoid inflation of type 1 error rate we did not consider an interim analysis of efficacy data.

A few typos in references can be easily fixed (e.g., #21: systematic; #50: Schultz).
==>Now fixed.

Overall, this is an excellent protocol; the study will provide useful, important and scientifically sound data.
==>Many thanks for your comments.

Buysse et al., Arch Intern Med. 2011; 171(10):887-95.
McCrae et al., Am J Geriatr Soc. 2007; 15(11):979-82.

Reviewer: 3

Please leave your comments for the authors below
This protocol paper describes the design of a sizeable (planned N = 588) RCT of sleep restriction that commenced recruitment in August 2018 and is due to complete in March 2020. The rationale of the study is well set out in terms of the potential population benefits if sleep restriction (SRT) can be delivered effectively by practice nurses within primary care at scale.
==>Thank you for the positive comments.

However, the supplementary table notes that the intervention will be delivered by research nurses from clinical research networks as well as practice nurses. While I can see the logic of this in terms of ensuring primary care buy in to the study and better fidelity implementation of the intervention, it does mean the results will not be generalisable to routine primary care. The authors might wish to consider explorative analyses of both outcomes and implementation of interventions separately for practice nurses and research nurses. And that both types of nurses will deliver the intervention needs to be in the body of the paper not just in a supplementary table.

==>Our initial plan was to use only practice nurses but to overcome scheduling challenges (e.g., practice nurses having limited capacity) we added research nurses to the protocol soon after the trial commenced in 2018. We agree this limits direct comparability with routine primary care but we note that the vast majority of our trained nurses to date (80%) are practice nurses, and none of the nurses in the trial have a background in sleep. We will report on this in the trial paper once the trial is complete. We will also consider a subgroup analysis to assess whether research nurses affect the treatment effect compared to practice nurses. This will be added to our Statistical Analysis Plan before the final data analysis.
We now make it clear in the text (in addition to the table) that research nurses will also be trained to deliver SRT. (page 10)

The planned study is well described and there are just a few points where additional clarification is needed:
1. Who is conducting the randomisation and what is the process and who is involved from baseline assessment to randomisation to informing participants (and nurses for those randomised to SRT) of their allocation?

==>Following completion of baselines assessments, randomisation is carried out by the research team using a web-based randomisation program. The research team inform participants of their allocation, and contact relevant nurses detailing those randomised to SRT. We have now added further text to help clarify (page 10-11)

2. Are all measures at baseline prior to randomisation, including exclusion criteria, from patient self-report or are some obtained from general practice records or contact with the general practice?

==>Yes all baseline measures are completed prior to randomisation. Study inclusion/exclusion is assessed through completion of the same questionnaire for each participant. Exclusionary diagnoses are applied when searching practice records prior to practice mailout (page 7-8).

3. How will the baseline sleep diaries and actigraphs be distributed to both groups, with what instructions and when (specifically whether (1) before or after randomisation/allocation (2) before or after distribution of the sleep hygiene booklets (3) before or after contact with the nurse for the SRT group)?

==>Diaries and actigraph watches form part of the baseline assessment and are therefore completed/returned prior to randomisation and prior to interventions (SRT+SH or SH only). Have added text to clarify (page 8-9).

And (1) how and when will the baseline data from these be reported back to the researchers (2) will the SRT group be informed that the baseline diary data they are collecting will be used not just for the research but for their first treatment session)?

==>See above. These are completed pre-randomisation and therefore before group allocation.

4. Is the “list of sleep hygiene guidelines” described as being part of the booklet provided to SRT participants a duplicate of the sleep hygiene guidelines they will have previously been sent by the research team or different; if different in what way different? In effect is the written information on sleep hygiene and lifestyle behaviours the same in both groups?

==>The research team send the control arm the booklet. The SRT arm receives their booklet as part of the SRT intervention material. The booklets are identical. We make this clearer in the manuscript. (Page 10)

5. Is there an established rating scale to assess SRT intervention fidelity that will be used or will the clinical psychologist assessing fidelity construct an ad hoc scale for this?

==>There is no established scale. Yes the CP will construct a measure for this purpose. We now make this clear in the manuscript (page 13)

A few aspects the authors may wish to consider, but may or may not chose to include in a revision
6. Reading the paper title, I assumed the control condition was nurse-delivered sleep hygiene advice. While the abstract makes clear this is not the case, the authors might wish to consider whether a minor change to the title would be helpful to make this clear.

==>Thank you for this suggestion – we feel that the abstract makes this point clear.

7. Inclusion of the mediation analyses measures in Table 1. This table was very helpful in keeping track of the different measures related to the different study hypotheses, but omits the mediation analyses measures

==>Thank you, have now added (page 25).

8. I am assuming the ISI difference of 1.35 points was chosen for the sample size calculation not because this is considered a clinically significant difference but because this equates to a SMD effect size of 0.30 as set out in the following paragraph, but this was not entirely clear.

==>Yes, that is correct. We now make this clear (page 13).

Finally, a couple of typos/minor errors to check
9. Page 7, first line after Trial Design: should be “individually randomised” (no comma)

==>Have modified.

10. Page 12, final paragraph: Reference no 43 looks incorrect

==>This reference is correct – the CSRI collects resource use data, including nurse contacts for sleep. We use this to guide contamination assessment in the control arm.

11. Top of page 14: CBT-I used as an acronym for the first time
==>Have modified.

VERSION 2 – REVIEW

REVIEWER	Christina Sandlund Karolinska Institutet, Stockholm Academic primary health care centre, Stockholm Region
REVIEW RETURNED	01-Feb-2020

GENERAL COMMENTS	Dear Authors, My comments have been considered and addressed when appropriate in the revised version of the manuscript. I have no further comments on the manuscript. I look forward to follow the project.

REVIEWER	John Cape University College London, UK
REVIEW RETURNED	03-Feb-2020

GENERAL COMMENTS	Thank you for your very clear and helpful additions in the revision which have addressed all my previous review queries