## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Open-label placebo for insomnia (OPIN): study protocol for a cohort multiple randomised controlled trial |
| **AUTHORS** | Colagiuri, Ben; Sharpe, Louise; Ambarchi, Zahava; Glozier, Nick; Bartlett, Delwyn; Costa, Daniel; Scott, Amelia |

## VERSION 1 – REVIEW

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| **REVIEWER** | Cun-Zhi Liu<br>Beijing University of Chineses Medicine, China |
| **REVIEW RETURNED** | 04-Oct-2020 |

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| **GENERAL COMMENTS** | The manuscript introduces a cohort multiple randomized controlled trial designed to explore the effect of open-label placebo in insomnia. It is interesting, innovative, and could be helpful to better understand the placebo effects in treating insomnia. The study design, to some extent, could improve the recruitment, ethics, and reduce bias from patients' preference. However, the following questions should be concerned.<br>1. The authors need to further explain the potential benefits of the study results for both clinical relevance and methodology. At this point, clinical significance values for outcomes should be mentioned in this protocol.<br>2. As a structural issue, there should be a section of "discussion" including the strengths and limitations of this study.<br>3. The effect size used for sample size calculation is generated through other conditions rather than insomnia. The authors may need to explain how much the effect sizes different from various disorders and if it is suitable for sample size calculations in this study based on limited data. |

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| **REVIEWER** | Prof. dr. Marike Lancel<br>University Groningen<br>Netherlands |
| **REVIEW RETURNED** | 15-Oct-2020 |

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| **GENERAL COMMENTS** | This paper describes an interesting randomised controlled trial to investigate the effects of open-label placebo treatment of insomnia in comparison to conventional placebo treatment and no treatment.<br>- Subject selection is based on an ISI score equal or larger than 10. As the ISI measures severity of insomnia symptoms during the last week, it does not detect chronic insomnia disorder (which additionally has the criteria that the insomnia symptoms occur at least 3 nights per week and are already present for at least 3 months). As a result a certain proportion of the recruted subjects may suffer from subacute or even acute insomnia and spontaneous improvements may therefore be more likely to occur. Furthermore, |

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| | subacute or acute insomniacs may be more sensitive to placebo treatment than chronic insomniacs. Why not diagnose insomnia disorder, either by interview or sleep disorder questionnaire? The results of a study based on the present protocol can not be extrapolated to people suffering from chronic insomnia.<br>- In my opinion the randomisation on a 2:2:1 ratio is unlogical, as (as explained above) spontaneous recovery is likely and all 3 parallel groups are analysed together.<br><br>- Figure 1 would be more informative when all outcome measures of visit 2 and 3 were mentioned in the flow chart. |

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| **REVIEWER** | Adam Bramoweth, PhD<br>VA Pittsburgh Healthcare System, USA |
| **REVIEW RETURNED** | 15-Oct-2020 |

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| **GENERAL COMMENTS** | This is an innovative and exciting study design to apply OLP and cmRCT methods to the treatment of insomnia and further elucidate the potential impact of placebo on insomnia. A few critiques/comments that may improve the protocol.<br><br>Further define OLP/CP in the abstract.<br><br>In the introduction, consider including estimates of insomnia symptoms, such as in Primary Care settings, as this may help to accurately reflect who is getting treated for insomnia, especially with sedative-hypnotics.<br><br>In the introduction, first paragraph, consider adding to the final sentence a statement about how pharmacological treatments, that complement behavioral treatments (CBT-I) especially when hard to access, need to be identified to "combat the burden of insomnia."<br><br>In the participants section or procedure section, if relevant, discuss methods to adapt the protocol to account for COVID-19 (e.g., telehealth options).<br><br>Is steady night shift allowed or is any shift-work exclusionary?<br><br>For the primary outcome, the ISI, 8 is reported as the clinically meaningful cutoff. However, 8-14 is subthreshold in the original scoring and >14 is often necessary for entrance to clinical trials. Morin et al. updated cutoffs to >10 as optimal for detecting cases in community samples. Please correct and cite appropriately.<br><br>For sample size calculation, is a 10% expected attrition in line with other medication and/or placebo RCTs? If attrition is higher than expected will you adjust recruitment efforts?<br><br>Consider formally defining cmRCT in the randomization section or elsewhere in the protocol.<br><br>If predictors of response is a secondary outcome, please define your treatment outcome. Are you using Morin et al.'s suggested >8 point reduction on the ISI?<br><br>It is unclear if those participants who are invited to OLP/CP but decline are asked to continue to participate and complete sleep diary/actigraphy/follow-up measures? Or are they withdrawn from the study? Based on the flow chart, it looks like they continue to |

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| | provide data. If so, please clarify this in the text. |

## VERSION 1 – AUTHOR RESPONSE

**REVIEWER 1 COMMENTS**

*The manuscript introduces a cohort multiple randomized controlled trial designed to explore the effect of open-label placebo in insomnia. It is interesting, innovative, and could be helpful to better understand the placebo effects in treating insomnia. The study design, to some extent, could improve the recruitment, ethics, and reduce bias from patients' preference. However, the following questions should be concerned.*

*1. The authors need to further explain the potential benefits of the study results for both clinical relevance and methodology. At this point, clinical significance values for outcomes should be mentioned in this protocol.*

**Reply:**

The potential benefits of the study results from a methodological standpoint have been addressed in the introduction. Incorporating open-label placebo could harness the strength of placebo effects without ethical barriers involving patient trust and consent, provide greater evidence of the efficacy of open-label placebos in clinical practice, and evaluate the cost-benefit of open-label relative to conventional placebo and no treatment (addressed throughout pages 5-6).

Clinically, study results could provide further evidence for placebo effects for perceived insomnia symptoms and other related patient-reported outcomes while taking into account potentially differential effects of open-label and conventional placebo (addressed in paragraph 2 of the introduction, pages 4-5, and secondary outcomes). Study results could also provide evidence of the effectiveness of a low risk, cost-effective treatment harnessing individual preference for and willingness to persist with pharmacological-type interventions compared to behavioural interventions such as CBT-I, which face barriers to implementation such as access and clinical training (addressed in paragraph 1 under Introduction, page 4).

Study objectives have been amended to include the following secondary outcome to assesses responders with clinically significant reductions in ISI:

1. Determine whether OLP is associated with clinically significant improvements in insomnia (response rate), relative to CP and no treatment.

Response rate has been defined under *Secondary outcome measures* on page 12:

*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.

We have opted for a hybrid approach to address clinically significant response rates. A 6-point reduction has been recommended by Yang, Morin, Schaefer and Wallenstein (2009) to conservatively detect a Minimally Important Difference (MID) on the ISI. In addition, the rate of participants scoring less than the inclusion cut-off of 10 has been included as a secondary outcome as achieving a 6-point reduction in participants whose baseline ISI scores are in the lower range of inclusion (e.g. 10-12 points) would not capture potentially meaningful changes in participants' perceptions of their insomnia or other related symptoms (e.g. fatigue) associated with 2- or 4-point ISI reductions.

*2. As a structural issue, there should be a section of "discussion" including the strengths and limitations of this study."*

**Reply:** We thank the reviewer for their comments. We followed the BMJ Open Author Instructions for Protocols which does not include a discussion section.

*3. The effect size used for sample size calculation is generated through other conditions rather than insomnia. The authors may need to explain how much the effect sizes different from various disorders and if it is suitable for sample size calculations in this study based on limited data.*

**Reply:** We thank the reviewer for making this point. There are no prior OLP studies in insomnia on which we could base our power calculation and therefore we consider the Charlesworth meta-analysis of other conditions to be the best available estimate. Nonetheless, we have clarified in the manuscript that there are no OLP studies in insomnia and that we are assuming a similar effect size to Charlesworth as follows on page 17:

> "There have been no previous studies on OLP for insomnia. 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. 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."

**REVIEWER 2 COMMENTS**
*This paper describes an interesting randomised controlled trial to investigate the effects of open-label placebo treatment of insomnia in comparison to conventional placebo treatment and no treatment.*

*1. Subject selection is based on an ISI score equal or larger than 10. As the ISI measures severity of insomnia symptoms during the last week, it does not detect chronic insomnia disorder (which additionally has the criteria that the insomnia symptoms occur at least 3 nights per week and are already present for at least 3 months). As a result a certain proportion of the recruted subjects may suffer from subacute or even acute insomnia and spontaneous improvements may therefore be more likely to occur. Furthermore, subacute or acute insomniacs may be more sensitive to placebo treatment than chronic insomniacs. Why not diagnose insomnia disorder, either by interview or sleep disorder questionnaire? The results of a study based on the present protocol can not be extrapolated to people suffering from chronic insomnia.*

**Reply:** We wish to clarify that the ISI measures insomnia severity over the last 2 weeks, not 1 week. Bastien et al (2001; ref #37 in the manuscript) suggest <10 as indicating minimal or no sleep disturbance. Supporting this, Morin, Belleville, Belnager and Ivers (2011), suggest that an ISI cut-off score of 10 produces the optimal classifications of community samples as having insomnia symptoms versus having minimal/no sleep disturbance, with sensitivity 86.1% and sensitivity 87.7%. Further, both pharmacological (e.g. Herring et al., 2019) and non-pharmacological RCTs (e.g. Hartescu, Morgan & Stevinson, 2015) reference an ISI cut-off of 10 as optimal in terms of sensitivity to intervention.

We have clarified the text on pages 8-9 as follows:

> "To be eligible, participants must report an Insomnia Severity Index (ISI) ≥10, … . 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]".

The point regarding generalisation to those with chronic insomnia is an important one. We are not aware of data indicating that (deceptive) placebo effects are weaker in people with chronic insomnia, although we agree this is a possibility. As this is the first study of OLP in insomnia and we are recruiting from a community sample, we consider the ISI cut-off of 10 as the most appropriate inclusion criterion. Nonetheless, as part of our screening measures, are already collecting data on duration of sleep disturbances, including:

- "How long have your current sleeping difficulties been a problem?"
- "Have you experienced any other periods of sleeping difficulty before your current episode?"
- "How many periods of sleep difficulty would you guess you have experienced?"

These data will provide us with the opportunity to use chronicity (as measured by time) as a predictor of the placebo effect and will therefore provide some insight into whether effect sizes differ due to chronicity. We have updated the text on page 3 to indicate this:

> "Predictors of uptake and any resulting placebo effect will be explored, including expectancy and baseline insomnia severity."

In terms of the potential for greater spontaneous improvement in those with sub-acute/acute insomnia, we are not aware of data indicating this is the case – although agree that it is possibility. However, it is also conversely possible that greater regression to the mean would occur in those with higher ISI scores, or even some combination of the two. Irrespective of what eventuates, the fact that we have a no treatment group controls for both of these possibilities by providing a point of comparison among individuals who enter the study with exactly the same baseline criteria.

*2. In my opinion the randomisation on a 2:2:1 ratio is unlogical, as (as explained above) spontaneous recovery is likely and all 3 parallel groups are analysed together.*

**Reply:** As discussed in relation to the reviewer's first point above, we are not aware of evidence indicating that that greater spontaneous recovery occurs with an ISI cut off of 10 for study entry. Importantly, although less common, our 2:2:1 randomisation ratio allows us to maximise power to detect differences *both* between OLP and no treatment and between OLP and CP. Therefore, we cannot see a justification – scientific, ethical, or resource-related – for increasing the sample size in the control group, when the power analysis reveals that the 2:2:1 is optimal. We fear that increasing sample size on this basis would unnecessarily lead to greater inconvenience to the community than is necessary to rigorously conduct the trial.

*3. Figure 1 would be more informative when all outcome measures of visit 2 and 3 were mentioned in the flow chart.*

**Reply:** As requested, Figure 1 has been amended to include outcome measures.

**REVIEWER 3 COMMENTS**

*This is an innovative and exciting study design to apply OLP and cmRCT methods to the treatment of insomnia and further elucidate the potential impact of placebo on insomnia. A few critiques/comments that may improve the protocol.*

*1. Further define OLP/CP in the abstract.*

**Reply:** As requested, we have further defined OLP/CP in the abstract as follows:

> "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…"

2. *In the introduction, consider including estimates of insomnia symptoms, such as in Primary Care settings, as this may help to accurately reflect who is getting treated for insomnia, especially with sedative-hypnotics.*

**Reply:** In the first paragraph of the Introduction, recent estimates of diagnostic and symptom prevalence, including primacy care settings and pharmacological treatment estimates have been added:

> "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]."

*3. In the introduction, first paragraph, consider adding to the final sentence a statement about how pharmacological treatments, that complement behavioral treatments (CBT-I) especially when hard to access, need to be identified to "combat the burden of insomnia."*

**Reply:** As suggested, we have amended the 2nd paragraph of the Introduction on page 4 to read:

"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."

*4. In the participants section or procedure section, if relevant, discuss methods to adapt the protocol to account for COVID-19 (e.g., telehealth options).*

**Reply:** A sentence has been added at the end of the Procedures section on page 17 to indicate that video-link visits may replace on-site visits if social distancing requirements are enforced as follows:

"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."

*5. Is steady night shift allowed or is any shift-work exclusionary?*

**Reply:** The wording on pages 8-9 has been amended to specify that individuals who undertake shift work (fixed or rotating) that include regular night shifts will be exclude as follows:

"6) undertaking shift work (fixed or rotating, including regular night shifts),"

*6. For the primary outcome, the ISI, 8 is reported as the clinically meaningful cutoff. However, 8-14 is subthreshold in the original scoring and >14 is often necessary for entrance to clinical trials. Morin et al. updated cutoffs to >10 as optimal for detecting cases in community samples. Please correct and cite appropriately.*

**Reply:** The appropriate citation justifying an ISI of 10 as inclusion criteria cut-off has been added under the Participants section (pages 9-10), with the rationale explained under point 1 of Reviewer 2's comments.

*7. For sample size calculation, is a 10% expected attrition in line with other medication and/or placebo RCTs? If attrition is higher than expected will you adjust recruitment efforts?*
RCT's with 10% attrition rate: Ribeiro Pinto Jr et al., 2016 – will find others
Zhou 2017, Kallestaad 2018 – 50%

**Reply:** An attrition rate of 10% is common across pharmacological intervention trials in insomnia (e.g. Zhou et al., 2017; Ribeiro-Pinto Jr et al., 2016), although higher estimates have also reported (e.g. Azimaraghi et al., 2020; Herring et al., 2016). As this is the first-ever RCT implementing a placebo-only intervention in insomnia, more accurate estimates are difficult to make, hence the rate of uptake in each treatment arm is an important secondary objective. The protocol has been modified (page 8) to explain that the study Steering Committee will review retentiorates at 6-monthly meetings and if necessary revise the sample size if attrition rates are higher than estimated:

"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."

*8. Consider formally defining cmRCT in the randomization section or elsewhere in the protocol.*

**Reply:** cmRCT is formally defined on its first appearance on page 6, as follows:

"…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)."

*9. If predictors of response is a secondary outcome, please define your treatment outcome. Are you using Morin et al.'s suggested >8 point reduction on the ISI?*

**Reply:** When initially written, we were referring to predicting the placebo effect in terms of changes of the size of changes in ISI and related outcomes. However, as also suggested by Reviewer 1, we have now defined a secondary outcome as the rate of clinically significant responses. This classification will be based on the whether the participant demonstrates ≥ 6-point reduction from baseline to posttreatment (Yang et al.'s, 2009) and/or as posttreatment ISI score <10 (Morin et al., 2011). Similar to pharmacological intervention trials in insomnia (e.g. Herring et al., 2019), the primary outcome remains as a change from baseline in mean ISI scores, with secondary outcomes including rates of responders (defined as ≥ 6 point reduction) and rates of participants whose post-treatment ISI scores fall below the community-based clinical cut-off of 10. Therefore, we will investigate predictors of both continuous changes in ISI and the rate of responders.

We have clarified this on page 7:
"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."

And on page 19:
"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: responder rates) to open-label and conventional placebo."

*10. It is unclear if those participants who are invited to OLP/CP but decline are asked to continue to participate and complete sleep diary/actigraphy/follow-up measures? Or are they withdrawn from the study? Based on the flow chart, it looks like they continue to provide data. If so, please clarify this in the text.*

**Reply:** Yes, participants who are invited to OLP/CP but decline will be asked to continue to participate and complete sleep measures. This has been clarified on pages 16-17 as follows:

> "Participants who decline an invite to the OLP or CP arms will continue in the study, unless they choose to withdraw."

## VERSION 2 – REVIEW

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| **REVIEWER** | Cun-Zhi Liu<br>Beijing University of Chinese Medicine, China |
| **REVIEW RETURNED** | 02-Jan-2021 |

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| **GENERAL COMMENTS** | Thank you for addressing all the points highlighted in the previous review. |

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| **REVIEWER** | Marike Lancel<br>Sleep Center for Psychiatry, Mental Health Institute Drenthe, The Netherlands |
| **REVIEW RETURNED** | 13-Jan-2021 |

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| **GENERAL COMMENTS** | This paper describes an intersting randomised controlled trial to examine the effects of open-label placebo treatment of insomnia symptoms in comparison to conventional placebo treatment and no treatment.<br>Two minor comments:<br>- page 13, Potential predictors of uptake and the placebo effect: it not stated when these questionnaires are completed, neither are they mentioned in the flowchart.<br>- page 16, Sample Size, first paragraph "We hypothesise ... less effective CP .." The word than is missing. |

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| **REVIEWER** | Adam Bramoweth, PhD<br>VA Pittsburgh Healthcare System, USA |
| **REVIEW RETURNED** | 07-Jan-2021 |

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| **GENERAL COMMENTS** | The authors have thoroughly responded to all reviewer comments and have improved the manuscript with their edits. No further comments. |

## VERSION 2 – AUTHOR RESPONSE

REVIEWER 2 COMMENTS (Dr. Marike Lancel, University of Groningen)
1. page 13, Potential predictors of uptake and the placebo effect: it not stated when these questionnaires are completed, neither are they mentioned in the flowchart.

Reply: An additional sentence under the subheading Potential predictors of uptake and the placebo effect on page 14 has been added to clarify when these measures will be administered.

“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.”

The study flow chart (page 10) has also been updated to include greater detail on the measures administered during online screening including inclusion/exclusion screening, demographic and clinical insomnia history (including the insomnia treatment history measure), and personality measures (BFI, LOT-R).

2. page 16, Sample Size, first paragraph "We hypothesise ... less effective CP .." The word than is missing.

Reply: Thank you for informing us of this error which has now been corrected.

“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.”

As requested, marked and clean copies of the manuscript have been uploaded for review. The text remains within the 4,000 word limit.