PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cannabidiol (CBD) and □9-tetrahydrocannabinol (THC) for chronic insomnia disorder ('CANSLEEP' trial): protocol for a randomised, placebo-controlled, double-blinded, proof of concept trial
AUTHORS	Suraev, Anastasia; Grunstein, R; Marshall, Nathaniel; D'Rozario, Angela L; Gordon, Christopher J.; Bartlett, Delwyn; Wong, Keith; Yee, Brendon; Vandrey, Ryan; Irwin, Chris; Arnold, Jonathon C; McGregor, Iain; Hoyos, C. M.

VERSION 1 – REVIEW

REVIEWER	Jerome Sarris NICM Health Research Institute, Western Sydney University None directly. I am a colleague with some of the group, however I have not published or collaborated directly with them
REVIEW RETURNED	15-Oct-2019

GENERAL COMMENTS	This is a very interesting study which is of great value to the field. Very well-designed and communicated. I have some suggestions below to consider to strengthen your study design and protocol communication: 1) Abstract- Need according to BMJ to detail the dates of the planned recruitment (also in the body of paper). MRI not mentioned in the abstract- please mention if room. Some basic inclusion criteria and primary outcome is also of benefit to be mentioned 2) Main Methods- *Clarify why MRI structural scan needed and how this is important to improve EEG scans *Pharmacokinetics- ideally can be mentioned to justify 1 week between treatments washout * Blinding- great innovation re methol, however I would also have administering RA and participant to have their nose pinched with a device (or at least the menthol for the RA for extra blinding) * Randomisation process needs more detail- e.g. block randomisation 2x2 or latin squares * What is the actual Primary Outcome? Need to chose one and be clear * More detail as to what the actual outcome is from EEG in terms of the data (e.g. changes in EEG power in X area measured on a continuous variable looking at difference between X groups/times) * More detail needed on the Stats section- how data is handled, stats methods used for different types of data, drop outs etc. * Power calculation still of benefit to tell us what effect size may be expected based on a sample size crossed-over of 20 people

	* Strongly consider the PK in terms of using an oral form of cannabis. How long will this take to have a soporific effect?? I would say at least 45 min and potentially longer. So need to mention this and also consider your timeline. IF they fall asleep at midnight then according to your timeline they may only get 6.30 hours sleep. This by itself could provide a negative effect on their sleep pattern (if used to waking up later or needing longer sleep- I appreciate many will have poor sleep generally anyway as insomniacs). * Further to this point- will a post-30 min POMS be long enough to detect a change from the oral application of cannabis? * Would advise more precision regarding caffeine use- currently being based on investigator opinion is not ideal... Also, I advise a longer period of abstinence with alcohol. If they binged 2 days before it appears they can participate- but this would still be throwing out the sleep cycle. * Need to detail some perceived limitations in more detail Finally- I like the use of the word 'promiscuous' in this scientific context- very descriptive use of language for an academic paper!

REVIEWER	Dr. Benicio Frey McMaster University, Canada
REVIEW RETURNED	04-Dec-2019

GENERAL COMMENTS	This is a well written study protocol of a very interesting and much needed RCT. Here are suggestions to improve the description of the study protocol: Page 5 – INTRODUCTION Lines 17-29: o Some of these side effects, such as cognitive impairment and sedation, can also occur with cannabinoids and are well documented in scientific literature. It would be a more balanced manuscript if risks of cannabinoids are described the same way as risk of other sleep aids. o "…many of these medications disturb sleep architecture…": I strongly suggest citing the original studies that showed these effects in place of reference 23. Page 6 – INTRODUCTION Lines 12-17 – "Increasing endogenous anandamide… in individuals with disturbed sleep" o Authors should note that the study that demonstrated these results was conducted in men suffering from cannabis withdrawal and dependence o The referenced study also stated that a requirement of 40 patients in the treatment group was needed to detect group differences and only 36 patients completed the study o The referenced study has limitations that should be discussed if this point is to be used to justify cannabis use for sleep Page 7 – INTRODUCTION Line 33 – 200mg CBD o Please provide the justification of how this dose was determined Page 8 – RECRUITMENT AND ENROLMENT Study population: 35 to 60 years o Please explain why 35 was chosen as the youngest age for this study

	Page 9 – STUDY INTERVENTION o Authors mention CBD might reduce adverse effects of THC. The adverse effects of THC were not previously mentioned in the protocol. Risks/benefits of cannabis should be discussed Page 9 – RANDOMISATION AND ALLOCATION CONCEALMENT Blinded study doctor will enrol and randomise o If the study doctor is enrolling and randomising participants, how are they blinded to the treatment? Could use more clarity. Page 12 – SCREENING Line 11 – “Participants testing positive for any drug…” o Does this include prescription medication? What about prescribed amphetamines/stimulants? Lines 50-52 – “Actigraphy for one week prior to…” o Are they wearing actigraphs during the study visits too? Or just in-between? Page 13 – STUDY DRUG ADMINISTRATION Line 45 – “The study’s medical doctor will prepare the study drug…” o Is this the same doctor that is enrolling and randomising? Again, how is this medical doctor blinded? Pages 18-19 – DATA COLLECTION AND MANAGEMENT o Is there a data safety monitoring board? Page 19 – STATISTICAL ANALYSIS o Please describe how missing data will be dealt with Pages 21-22 – TABLE 1: INCLUSION & EXCLUSION CRITERIA Exclusion o Please clarify if chronic pain is an exclusion criterion or not, given the major impact of chronic pain of sleep o Required to complete mandatory drug testing for any reason If this is listed as an exclusion criterion, it may be worded “refusal to complete mandatory drug testing” Pages 23-24 – TABLE 2: SCHEDULE OF STUDY VISITS AND PROCEDURES Saliva collection (Quantisal) o There is no indication in this table as to when this saliva collection will happen. Page 26 – FUNDING o Please add the role of Linnea in this study

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Jerome Sarris
Institution and Country: NICM Health Research Institute, Western Sydney University
Please state any competing interests or state ‘None declared’: None directly. I am a colleague with some of the group, however I have not published or collaborated directly with them

Please leave your comments for the authors below

This is a very interesting study which is of great value to the field. Very well-designed and communicated. I have some suggestions below to consider to strengthen your study design and protocol communication:

1) Abstract- Need according to BMJ to detail the dates of the planned recruitment (also in the body of paper). MRI not mentioned in the abstract- please mention if room. Some basic inclusion criteria and primary outcome is also of benefit to be mentioned

Thank you for taking the time to consider and review our manuscript for publication in BMJ Open.

We have now amended the abstract to include the dates of the planned recruitment, the use of structural MRI, and some basic inclusion criteria. Please note the primary endpoints (total sleep time and wake after sleep onset) are currently described in the abstract. See excerpt from the manuscript below:

Page 2/38: “In addition, 256-channel high-density electroencephalography and source modelling using structural magnetic resonance imaging will be used to comprehensively examine brain activation during sleep and wake periods on ETC120 versus placebo.”

Page 2 & 8/38: “Participants aged 35 to 60 years will be recruited over an 18-month period commencing August 2019.”

Main Methods:

1) *Clarify why MRI structural scan needed and how this is important to improve EEG scans

We have now provided clarification around why the structural brain MRI is needed and why it is important for our current study. Please see excerpt below:

Page 14538: “The GeoScan device will be used to measure, identify, and create a 3-dimensional coordinate file of the 256 electrode locations on the high-density EEG sensor cap. This will be combined with each individual participant’s structural brain MRI scan to localise the source of brain activity to specific brain regions.”

2) *Pharmacokinetics- ideally can be mentioned to justify 1 week between treatments washout

Thank you for this suggestion. For a single oral dose of 10 mg THC and 200 mg CBD, a minimum of 1-week between study assessment visit was chosen as the washout period. This was informed by previous studies of this nature (Arkell et al., 2019; Vandrey et al., 2017). Blood plasma THC after an oral dose of 10 mg THC tends to return to baseline within 24 hours post-exposure of a single dose (Vandrey et al., 2017). We expect the same timeframe following a single dose of CBD.

Furthermore, to ensure prior use of cannabis is excluded, each participant must complete a urinary drug screen prior to each study assessment visit. Any individuals who have used cannabis in the past 3 months (self-report and confirmed positive by urinary drug screen) will be excluded from trial participation at screening (see Table 1 – Inclusion and exclusion criteria).

Please see excerpt below:

Page 8/38: “Each study assessment visit will be scheduled at least one week apart to avoid any carryover effects, as informed by previous studies of this nature.67,82”

3) Blinding- great innovation re menthol, however I would also have administering RA and participant to have their nose pinched with a device (or at least the menthol for the RA for extra blinding)

Thank you for this suggestion. The use of disposable nose pegs for additional blinding is a great idea! We will certainly consider this next time as we have already received ethics approval for the current study protocol and have since commenced participant recruitment.

4) Randomisation process needs more detail- e.g. block randomisation 2x2 or Latin squares

Thank you for this suggestion. We have now amended the manuscript to include more information about the randomisation process. See excerpt below:

Page 10/38: “The sequence will be computer-generated using a simple 1:1 randomisation ratio by the trial statistician, and by the order of participant enrolment.”

5) What is the actual Primary Outcome? Need to choose one and be clear

We selected the two primary endpoints based on the recent FDA registration for the novel hypnotic, suvorexant – an orexin receptor antagonist (Herring et al., 2016).

We have provided more clarification of the analyses of the endpoints (see excerpt below). We will interpret either outcome as having been affected if either are significant at 0.05, keeping in mind both total sleep time (TST) and wake after sleep onset (WASO) are highly correlated variables. We realise that using two primary endpoints will inflate chances of type I statistical error, however, this is a proof of concept and the decision to proceed to Phase II trial will not solely driven by statistical significance.

Page 21/38: “Primary outcomes will be interpreted as affected if either are significant at 0.05.”

Herring, W. J., Connor, K. M., Snyder, E., Snavely, D. B., Zhang, Y., Hutzelmann, J., ... & Lines, C. (2016). Suvorexant in patients with insomnia: pooled analyses of three-month data from phase-3 randomized controlled clinical trials. Journal of Clinical Sleep Medicine, 12(09), 1215-1225.

6) More detail as to what the actual outcome is from EEG in terms of the data (e.g. changes in EEG power in X area measured on a continuous variable looking at difference between X groups/times)

This information is listed on our ANZCTR clinical trial registration (ACTRN12619000714189). Due to the limited manuscript space we provided the hyperlink in the manuscript on page 11 of 38 under the section, Study objectives. This includes a comprehensive list of the trial’s primary and secondary outcomes and measures under the Outcomes section.

7) More detail needed on the Stats section- how data is handled, stats methods used for different types of data, drop outs etc.

Thank you for this suggestion. We have now amended the statistical section to include more information about how data will be handled (e.g. missing data) and the statistical methods for data collected. Please see excerpt below:

Page 20-21/38: “Data will be analysed using mixed-model analyses of variance in SAS (SAS Institute, Version 9.4) to test whether either of the treatments are different from the other. Order and treatment

will be fixed effects and the patient code will be used as a random effect.88 Treatment by order effect will not be tested. All of our variables are suitable for mixed model analyses except for the adverse event profile which will be tabulated but not statistically tested. The least-squares means procedure will be used in the mixed-model analyses to handle missing data. All participants will be analysed in the groups they have been randomised to.
Primary outcomes will be interpreted as affected if either are significant at 0.05."

8) Power calculation still of benefit to tell us what effect size may be expected based on a sample size crossed-over of 20 people

We agree this is useful information to know. For a crossover study of 20 participants, using a simple paired t-test as there is no commercially available power calculation tool for mixed-model analyses at present, we are adequately powered to detect an effect size of 0.67 with 80% power at an alpha of 0.05 (two-tailed).

We have now amended the statistical section of the manuscript to include this power calculation. Please see excerpt below:

Page 20/38: "As there is no commercially available power calculation software for mixed-model analyses available at present, using a simple paired t-test, a crossover trial of 20 participants is adequately powered to detect an effect size of 0.67 with 80% power at an alpha level of 0.05 (two-tailed). Data obtained will guide future studies by providing 95% confidence limits for sensitivity analyses for power calculations of a larger trial if warranted."

9) Strongly consider the PK in terms of using an oral form of cannabis. How long will this take to have a soporific effect?? I would say at least 45 min and potentially longer. So, need to mention this and also consider your timeline. IF they fall asleep at midnight then according to your timeline they may only get 6.30 hours sleep. This by itself could provide a negative effect on their sleep pattern (if used to waking up later or needing longer sleep- I appreciate many will have poor sleep generally anyway as insomniacs).

A recent study showed that a single 10 mg oral dose of THC resulted in a Cmax of 1 ng/mL (0 – 3 ng/mL) and a Tmax of 50 minutes (0 – 2 hours). We chose to administer drug one hour prior to the participant's typical bedtime. The participant's typical bedtime will be determined by the sleep psychologist using the one-week of actigraphy and sleep diary data at baseline (during screening). The sleep-onset and wake-time is not fixed. It is specific to the individual participant and can shift across a 45-minute window. This is mainly for practical reasons as it will depend on the availability of research staff and sleep technicians in the late evening.

To ensure that all participants go to bed at roughly the same time (±45 minutes), we recently modified the study protocol to exclude participants with delayed and advanced sleep phase syndrome as determined by baseline actigraphy. This ethics modification was submitted and approved after we submitted this manuscript. Therefore, if the participant's habitual bedtime is at 22:30, drug administration will occur at 21:30, and they will be woken up 8 hours later at 06:30 (at roughly their wake-time).

We have now amended the manuscript to clarify timing of drug, sleep-onset and wake times. Please see excerpts below:

Page 14/37: "One hour prior to the participant's typical sleep-onset time, the study investigator will then instruct and directly observe the participant to orally ingest the fixed dose of the study drug. This timeframe was chosen to represent the THC Tmax following a single oral dose of 10 mg THC.67 All

participants will be given an 8-hour sleep opportunity. Time of drug administration is relative to the participant's typical sleep-onset time, which may vary up to 45 minutes."
Page 23/37: In Table 1: "Advanced or delayed sleep-wake phase disorder based on actigraphy"
10) Further to this point- will a post-30 min POMS be long enough to detect a change from the oral application of cannabis?

That is a good point. We have decided to shift the first administration of the POMS questionnaire to 1 h as opposed to 0.5 h. Based off of recent literature, a single 10 mg oral dose of THC starts to produce noticeable subjective drug effects (on a 100 mm VAS scale) at 0.5 h. This increases substantially by the 1 h mark i.e. just before bedtime. See reference 60 (Vandrey et al., 2017) in the main manuscript.

We have also decided to stop the subjective drug effects questionnaire after the 08:00 time point because we do not expect that such effects would persist beyond that time.

See excerpt below:

Page 15/37: "Mood will be assessed using the Profile of Mood States (POMS) abbreviated version79 at baseline, 60 minutes post-drug administration, and the next-day at approximately 08:00, 10:00, 12:00, 14:00, and 16:00 hours. Subjective drug effects will be assessed using a series of Visual Analog Scales (VAS) at baseline, 60 minutes post-drug administration and the next-day at approximately 08:00. Measurements will stop after the 08:00 timepoint because subjective drug effects following a single acute dose are not expected to persist beyond this time.

Figure 2 has been amended to reflect this change in number of VAS questionnaires administered to the participant.

11) Would advise more precision regarding caffeine use- currently being based on investigator opinion is not ideal... Also, I advise a longer period of abstinence with alcohol. If they binged 2 days before it appears they can participate- but this would still be throwing out the sleep cycle.

The study doctor (sleep physician) will rule out excessive caffeine use as a contributing reason for the individual's insomnia on clinical interview with the individual at the medical screen. We have now amended Table 1 to indicate that this will be determined by an expert (i.e. a sleep physician) as opposed to a trial coordinator or research assistant. Please see excerpt below:

Page 23/38 – Table 1: "Excessive caffeine use that in the opinion of the medical doctor contributes to the participant's insomnia, or is unable to abstain from caffeine use 24 hours prior to each overnight study sleep assessment"

To our knowledge, there are no commercially available point-of-collection testing devices for caffeine in oral fluid. Participants are given explicit instruction not to drink caffeinated substances at the outset of the study or this may result in their exclusion from the study, and those deemed dependent on caffeine (i.e. unable to abstain for at least 24 hours prior to each study assessment visit) will be excluded at screening.

A 24-hour period of alcohol abstinence is standard procedure for our previous studies of this nature. It is based on patient self-report on clinical interview with a sleep physician at the outset of the study. Individuals must give a negative result on urinary drug screening for alcohol before being enrolled into the study. This is checked again prior to each overnight study assessment visit. Individuals will not be randomised if they test positive for alcohol at the medical screen.

12) Need to detail some perceived limitations in more detail

We have now elaborated on some of the perceived limitations in the Significance section of the manuscript. Please see excerpt below:

Page 21/38: “Of note, this is a proof of concept trial that is limited by its’ small sample size and single-dose design, precluding examination of long-term effects of this cannabis-based in this clinical population. Moreover, the study cannot assess the individual contribution of THC and CBD.”

Finally- I like the use of the word 'promiscuous' in this scientific context- very descriptive use of language for an academic paper!

Thank you!

Reviewer: 2
Reviewer Name: Dr. Benicio Frey
Institution and Country: McMaster University, Canada
Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This is a well written study protocol of a very interesting and much needed RCT. Here are suggestions to improve the description of the study protocol:

1) Page 5 – INTRODUCTION Lines 17-29: Some of these side effects, such as cognitive impairment and sedation, can also occur with cannabinoids and are well documented in scientific literature. It would be a more balanced manuscript if risks of cannabinoids are described the same way as risk of other sleep aids.

Thank you for taking the time to consider and review our manuscript for publication in BMJ Open.

We agree that cannabinoids have similar documented side effects such as cognitive impairment and next-day sedation as other hypnotic medication.

Our aim was to utilise a pharmaceutical-grade formulation where the THC level is controlled. This was to avoid common adverse side-effects associated with THC such as intoxication and cognitive impairment. We have amended the manuscript to describe the possible risks of cannabinoids, in particular THC. Please see excerpt below:

Page 6/38: “Administration of THC alone (15 mg) in the evening was associated with next-day changes in mood, sleepiness, and memory in healthy adults,44 emphasising the need for careful consideration of dose and ratio of cannabinoids when administered in clinical insomnia populations.”

2) “…many of these medications disturb sleep architecture…”: I strongly suggest citing the original studies that showed these effects in place of reference 23.

Thank you for this suggestion. We have now cited an original study that described the effects of benzodiazepines on sleep architecture in place of reference 23.

Please see new reference 23: “Bastien, C. H., LeBlanc, M., Carrier, J., & Morin, C. M. (2003). Sleep EEG power spectra, insomnia, and chronic use of benzodiazepines. Sleep, 26(3), 313-317.”

3) Page 6 – INTRODUCTION Lines 12-17 – “Increasing endogenous anandamide… in individuals with disturbed sleep”. Authors should note that the study that demonstrated these results was conducted in men suffering from cannabis withdrawal and dependence. The referenced study also stated that a requirement of 40 patients in the treatment group was needed to detect group differences and only 36 patients completed the study. The referenced study has limitations that should be discussed if this point is to be used to justify cannabis use for sleep.

Thank you for this suggestion. We have edited this sentence to describe the patient population where these effects were described in: cannabis-dependent males experiencing withdrawal. We acknowledge that the link between endogenous anandamide and sleep is unclear, and that these effects may not be necessarily generalisable to other clinical populations such as those with insomnia disorder. Please see excerpt below:

Page 6/38: “Increasing endogenous anandamide via FAAH inhibition normalised deficits in stage N3 sleep in cannabis-dependent males experiencing withdrawal,34 consistent with preclinical data showing that anandamide promotes slow wave sleep, possibly through increases in extracellular adenosine concentrations.35-37”

4) Page 7 – INTRODUCTION Line 33 – 200mg CBD: Please provide the justification of how this dose was determined.

The chosen formulation was a 1:20 ratio of THC to CBD, with a 10 mg dose of THC chosen as the maximum dose that is likely to induce subjective drug effects of feeling ‘sleepy/tired’ without impairing cognitive performance or producing significant intoxication in naïve or occasional cannabis users (see Study intervention on page 9/38).

Our justification for choosing this ration is explained on page 10/38. Please see excerpt below:

“The 1:20 ratio of THC to CBD was chosen to harness the sedating properties of THC while including some of the potential anti-anxiety properties of CBD,65 given that anxiety is a very common comorbidity in people with insomnia disorder.66,67 As noted above, there is also possibility that this dose of CBD might reduce some of the possible adverse effects of THC (e.g. anxiety, memory impairment). The chosen ratio also mimics naturalistic findings in recent surveys where individuals reported using cannabis with higher CBD concentrations in addition to THC to effectively manage insomnia symptoms.68,69’

As such, the 200 mg CBD dose was determined based off of the maximum dose of THC and the chosen 1:20 ratio.

5) Page 8 – RECRUITMENT AND ENROLMENT Study population: 35 to 60 years: Please explain why 35 was chosen as the youngest age for this study

The cut-off of 35 years was chosen to limit age-related variability sleep architecture across the lifespan. We chose 35 years as the lower end of the age bracket due to the limited numbers of studies examining changes to sleep architecture in young adulthood. This cut-off was also chosen to represent the typical age range of clinical patients with chronic insomnia seeking treatment in the clinic.

We have now amended the ‘Recruitment and enrolment’ section to include this explanation. See excerpt below:

Page 8/36: “This age range was chosen to limit age-related variability in sleep architecture for better interpretation of EEG changes.64”

Page 35/38: See new reference 64: Sprecher, K. E., Riedner, B. A., Smith, R. F., Tononi, G., Davidson, R. J., & Benca, R. M. (2016). High resolution topography of age-related changes in non-rapid eye movement sleep electroencephalography. PLoS One, 11(2), e0149770.

6) Page 9 – STUDY INTERVENTION Authors mention CBD might reduce adverse effects of THC. The adverse effects of THC were not previously mentioned in the protocol. Risks/benefits of cannabis should be discussed

The adverse effects of THC were previously mentioned in the Introduction on Page 6 of the manuscript. See excerpt below:

Page 6/36: "CBD is also a negative allosteric modulator of CB1 receptor40 and may reduce the effects of THC and anandamide on the brain.41,42 Indeed, there is an emerging viewpoint that co-administration of CBD with THC may enhance therapeutic outcomes by attenuating the adverse effects of THC (e.g. on emotion recognition,43 next-day memory performance,44 appetitive effects,45 and acute psychotic symptoms46,47); however, findings are inconsistent with a recent study showing CBD exacerbating THC-induced impairment on driving and cognition, possibly via a pharmacokinetic interaction.48"

New sentence: "Administration of THC alone (15 mg) in the evening was associated with next-day changes in mood, sleepiness, and memory in healthy adults,44 emphasising the need for careful consideration of dose and ratio of cannabinoids when used in clinical insomnia populations."

We have now added some examples of the adverse effects of THC under the 'Study intervention' section. See excerpt below:

Page 9/36: "As noted above, there is also possibility that this dose of CBD might reduce some of the possible adverse effects of THC (e.g. anxiety, memory impairment)."

The risks/benefits of cannabis are important and are comprehensively outlined in the Participant Information Statement which is presented to participants at the outset of the study. Previous literature on risks of cannabis typically focused on recreational (non-medical) use which involved heavy use, over extended periods of time, often via smoked or vaporised routes which is associated with cognitive impairment, dependence, and psychotic symptoms in some individuals. This may not be relevant to the current protocol because we are utilising a pharmaceutical-grade extract where the THC is controlled (lower dose of 10 mg). Moreover, we are administering a single-dose to examine safety as well as what effects it has on the brain during sleep and wake.

7) Page 9 – RANDOMISATION AND ALLOCATION CONCEALMENT Blinded study doctor will enrol and randomise. If the study doctor is enrolling and randomising participants, how are they blinded to the treatment? Could use more clarity.

We have amended this section in the manuscript to provide more clarity around who enrols and randomises the participants. The blinded study doctor will enrol the participant (confirm eligibility and take informed consent) and assign them to a unique code (NOT randomising them to the treatment order). This unique code is linked to the order of treatment which is stored in a password-protected data management system and cannot be accessed by any study staff who have contact with participants.

The drug distributer will number identical containers according to the randomisation sequence that was prepared by the trial statistician using central randomisation by computer. Neither the drug

distributer or the trial statistician will meet any prospective or enrolled participants or be involved in any day-to-day trial process.

Please see excerpt below:

Page 10/36: “Each participant will be randomly allocated to one of two treatment sequences: (1) ETC120 – placebo, or (2) placebo – ETC120. As this is a blinded study, the participant, the study staff (including the study doctor), and the outcome assessors will not be aware of which treatment order participants have been allocated to. Method of allocation concealment will involve central randomisation by computer prepared by the trial statistician (NSM) and identical containers numbered according to the randomisation sequence prepared by the drug distributer. Neither the drug distributer or the trial statistician will meet any prospective or enrolled participants or be involved in any day-to-day trial process. The sequence will be computer-generated using a simple 1:1 randomisation ratio by the trial statistician, and by the order of participant enrolment. The sequence will be stored in a password-protected data management system and cannot be accessed by study staff who have contact with participants. The order of treatment will only be known by the drug distributer and the trial statistician. In the event of a serious adverse event (SAE) or reaction, the allocation list will be retrieved from the unblinded trial statistician or drug distributer to reveal the participant’s allocated treatment during the trial.”

8) Page 12 – SCREENING Line 11 – “Participants testing positive for any drug…” Does this include prescription medication? What about prescribed amphetamines/stimulants?

The urinary drug screen tests for illicit drugs including cannabis, cocaine, amphetamines, and methamphetamines, as well as prescribed medications including benzodiazepines and opiates but not prescribed amphetamines/stimulants. As is standard procedure for our previous studies of this nature, the study doctor will rule out any conditions that may warrant prescription amphetamine/stimulant use such as ADHD or narcolepsy on clinical interview at the medical screen.

9) Lines 50-52 – “Actigraphy for one week prior to…” Are they wearing actigraphs during the study visits too? Or just in-between?

Participants will only be asked to wear the Actiwatches 1-week prior to each treatment session to ensure that they have maintained consistent sleep- and wake-onset times (not during the study visits). Sleep will be monitored using polysomnography with high-density EEG during the overnight study assessment visits. Please see excerpts below referencing the actigraphy time periods:

Page 12/38: “Participants will then be instructed to maintain a sleep diary and wear a wrist-worn commercially available device (Actiwatch 2, Philips Respironics) to monitor sleep and wake periods for one week during screening. These data will allow the study team to estimate the participant’s individual typical sleep- and wake-onset times for the study assessment visits.”

Page 13/38: “Participants will then be asked to maintain consistent sleep- and wake-onset times, confirmed by at-home sleep diary and actigraphy for one week prior to each study assessment visit.”

10) Page 13 – STUDY DRUG ADMINISTRATION Line 45 – “The study’s medical doctor will prepare the study drug…” Is this the same doctor that is enrolling and randomising? Again, how is this medical doctor blinded?

This was incorrectly written in the manuscript. As per our response to your previous comment (number 7), the blinded study doctor will enrol the participant (confirm eligibility and take informed consent) and allocate them to a unique code (NOT randomise them to the treatment order). This

unique code is linked to the order of treatment which is kept hidden from the medical doctor and any blinded research staff via pre-allocated numbered containers prepared by the drug distributer.

11) Pages 18-19 – DATA COLLECTION AND MANAGEMENT Is there a data safety monitoring board?

This is a single-centre, proof of concept trial of 20 participants. As such, an internal Trial Management Group (TMG) consisting of the principal investigators (PIs), trial coordinator/research assistants, trial statistician, data manager, and sleep clinic manager will be used for monitoring trial conduct. The trial coordinator will check-in with the PI on a weekly basis (or as needed) to address any safety or efficacy issues related to the trial. Please see amended excerpt below:

Page 20/38: “Study progress and safety will be monitored and evaluated internally in an ongoing fashion by the Trial Management Group consisting of the principal investigator, trial coordinator, research assistants, trial statistician, data manager, and sleep clinic manager.”

12) Page 19 – STATISTICAL ANALYSIS Please describe how missing data will be dealt with

Thank you for this request. We will be using the least-squares means procedure in the mixed-model analyses to handle missing data. We have now amended the statistical section of the manuscript. See excerpt below:

Page 20-21/38: “Data obtained will guide future studies by providing 95% confidence limits for sensitivity analyses for power calculations of a larger trial if warranted. Data will be analysed using mixed-model analyses of variance in SAS (SAS Institute, Version 9.4) to test whether either of the treatments are different from the other. Order and treatment will be fixed effects and the patient code will be used as a random effect.88 Treatment by order effect will not be tested. All variables are suitable for mixed model analyses except for the adverse event profile which will be tabulated but not statistically tested. The least-squares means procedure will be used in the mixed-model analyses to handle missing data. All participants will be analysed in the groups they have been randomised to. Primary outcomes will be interpreted as affected if either are significant at 0.05.”

13) Pages 21-22 – TABLE 1: INCLUSION & EXCLUSION CRITERIA Please clarify if chronic pain is an exclusion criterion or not, given the major impact of chronic pain of sleep. Required to complete mandatory drug testing for any reason. If this is listed as an exclusion criterion, it may be worded “refusal to complete mandatory drug testing”

We can confirm that chronic pain is a definite exclusion criterion for this trial.

We have now included reference to this in Table 1, please see excerpt below: Page 23/38: “Medical condition (e.g. chronic pain) or medication that is the cause of the insomnia.”

The exclusion criterion regarding mandatory drug testing refers to any drug testing that individuals must undergo as part of their day-to-day life such as employment or court order. We have now rephrased this criterion in Table 1 to the following:

Page 23/36 – Table 1: “Required to undergo drug testing on a regular basis (e.g. employment, court order)”

14) Pages 23-24 – TABLE 2: SCHEDULE OF STUDY VISITS AND PROCEDURES
Saliva collection (Quantisal). There is no indication in this table as to when this saliva collection will happen.

Thank you for picking up on this error!

The saliva collection will occur in conjunction with the saliva drug tests in the evening and daytime at each study assessment visit. We have now indicated when these tests will occur in Table 2.

Page 26 – FUNDING. Please add the role of Linnea in this study.

Thank you. The custom-made investigational product was purchased from Linnea (Ticino, Switzerland) who were not involved in the conception or design of the study. As requested, we have now clarified this in the funding statement. Please see excerpt below:

Page 27/38: “The investigational product was purchased from Linnea (Ticino, Switzerland) who were not involved in the conception or design of this study.”

We have also amended the wording under the section Study intervention on page 9/38 from ‘supplied’ to ‘purchased’.

VERSION 2 – REVIEW

REVIEWER	Jerome Sarris NICM Health Research Institute; Australia I conduct cannabis research as university members of the Australia Medicinal Cannabis Research and Education Collaboration (www.AMCREC.org). I have received consultancy payment from a cannabis manufacturing company as an independent scientific advisor (Australian Natural Therapeutics Group)
REVIEW RETURNED	14-Jan-2020

GENERAL COMMENTS	All suggestions addressed and good for publication

REVIEWER	Dr. Benicio Frey McMaster University, Canada
REVIEW RETURNED	30-Jan-2020

GENERAL COMMENTS	All of my comments have been adequately answered.