Clinical Trial Protocol

Physiological, Psychological, Psychiatric, Surgical or Health Interventions

UNSW HREC Title: Improving childhood sleep: the bedrock of depression prevention

January 2023, Version 1

Dr Sophie Li

Contents

1. General Information

Protocol Title				
Improving Childhood Sleep: The bedrock of depression prevention				
Protocol identifying number				
Version Number	**V1**	**Version date**	**19 January 2023**	
Amendment History				
Version Number		**Version date**		
Clinical Trial Sponsor				
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Type of Appointment with UNSW	☒ UNSW Employee ☐ UNSW Conjoint ☐ Other (Please describe)			
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Site	Black Dog Institute
Personnel authorised to sign the protocol and the protocol amendment(s) for the Sponsor (ICH GCP 6.1.3)	
Name	
Telephone	
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Address	

Human Research Ethics Committee	
Name	UNSW Sydney Human Research Ethics Committee
Status of ethical review	☐**Approved** ☒ **In progress** ☐ **To be submitted**
Trial Sites	**NA**
Funding for the Clinical Trial	
Funding Body Name	Australian Rotary
Amount of Funding	$210,000
Interests that the funding body has in the clinical trial	Nil
Insurance for Clinical Trial	
Insurer	UNSW insurance
Type of Insurance	Clinical trials are not automatically covered by UNSW insurance, and confirmation must be obtained by completing the Clinical Trials Spreadsheet and sending it to the UNSW Insurance manager (peter.mccarthy@unsw.edu.au). Once insurance has been confirmed, attach a copy of the insurance certificate to the trial protocol.
Confirmation of Insurance	☒**Attached** ☐ **In progress** ☐ **To be submitted**

2. Safety and Monitoring Contacts

Clinical Trials Involving Physiological, Psychological, Psychiatric or Surgical Interventions	
Qualified Physician/Medical Expert	
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Independent Safety Monitoring Board or Data Safety Monitoring Board Members

Internal members:

- Dr Sophie Li (Chief Investigator)
- Dr Gemma Sicouri (Co-investigator and clinical psychologist)
- Dr Mirjana Subotic-Kerry (Co-investigator and trial manager)

External members:

- Dr Joanne Crawford (clinical psychologist and Postdoctoral research fellow)
- Professor Phil Batterham

The current trial will utilise a Trial Management Group

Trial Management Group (TMG)

Overview

- The TMG will function in accordance with the principles of the following documents: Good Clinical Practice (GCP) Guidelines, Declaration of Helsinki 2000, NHMRC National Statement on Ethical Conduct in Human Research, NHMRC Guidance Safety and Monitoring of Clinical Trials involving a Therapeutic Good, and University of New South Wales HREC guidelines.
- Members will disclose conflicts of interest and will be cleared of significant conflicts of interest and potential conflicts of interest. No member should have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making by the TMG.
- Composition of membership will reflect expertise in clinical, statistics and the specific scientific expertise relevant to the study, in this case, severe mental health symptoms.
- A quorum group of two must be present..

Roles and responsibilities

The purpose of the Trial Management Group (TMG) is to supervise of the overall conduct and safety oversight of the trial, by safeguarding the interests of study participants and assessing the safety and efficacy of the trial protocol.

The TMG will provide:

- Oversight on the safety and monitoring procedures during the trial
- Provide recommendations to continue, modify, or terminate the trial
- Advice, guidance, and consultation on trial design and conduct
- Consultation on trial roadblocks and issues
- Oversight of trial processes
- Consultation on scientific quality and integrity
- Final sign-off on Trial Protocol
- Oversight of compliance with Good Clinical Practices

The investigators will:

- Assure the proper conduct of the study.
- Assure collection of accurate and timely data.
- Report relevant data to the TMG prior to scheduled meetings.
- Promptly report safety concerns to the TMG.
- Communicate with regulatory authorities (e.g., HREC) as necessary.

Meetings

Prior to recruitment commencing, the TMG members will form an understanding of the protocol and study endpoints. The TMG will be provided with a monthly report on safety events (see Reporting below), changes to protocol and recruitment updates, and will convene a meeting every 4-months, three times a year and additionally on an as-needed basis to review the UNSW Safety Monitoring Data, which includes the number of call backs that were triggered, and the follow-up that was carried out. Meetings will be held face-to-face if practicable, or otherwise by video conference. Prior to each meeting, a report will be sent to the TMG outlining any recommendations and rationales.

Reporting

For this current trial, an adverse event (AE) is defined as any untoward medical or clinical occurrence in a participant without regard to the possibility of a causal relationship. A register of these events and associated interactions will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.

A serious adverse event (SAE) for this trial is defined as any untoward occurrence that involves hospitalisation or death (suicide or otherwise). As per the NHMRC Safety Monitoring and Reporting Guidelines, any suspected unexpected SAEs or reactions will be reported to the TMG and the UNSW Human Research Ethics Committee within 48 hours of the research team becoming aware, using the Adverse Event Form provided by the UNSW HREC. All AEs, both solicited and spontaneous, will be reported to the TMG.

A breach of protocol is defined as something likely to affect the rights and safety of a trial participant (for example, the sharing of data to those outside those with approved access), or the reliability or robustness of the data is compromised. Any serious breaches of protocol will be reported to the TMG and UNSW HREC within 48 hours of the research team becoming aware, using the Suspected Serious Breach Report Form.

Confidentiality
All information and data provided to the TMG will be considered privileged and confidential. The TMG will agree to use these data to accomplish the responsibilities of the TMG and will not use it for any other purpose without written consent from the Chief Investigator or trial sponsor.

Stopping guidelines
The primary charge of the TMG is to monitor the study for participant safety. As such, the TMG may recommend pausing or terminating the trial if they have concerns for participant safety, based on (but not limited to) a higher than anticipated rate for one or more of the listed adverse events at the primary endpoint.

Sponsors Independent Physician/Medical Expert	
Name	
Telephone	
Email	
Address	
Pharmacy, Clinical Laboratory, Radiology, Pathology and other medical and/or technical departments involved in the trial	
Name	
Telephone	
Email	
Address	

3. Delegation of Clinical Trial Duties

Responsibilities for the conduct and oversight for the trial are delegated to you as the Coordinating Principal Investigator. You may delegate trial related responsibilities to the listed Principal Investigator(s) and any trial-related personnel. All trial-related duties delegated by the Coordinating Principal Investigator or Principal Investigator(s) and trial-related personnel must only be delegated to those that are qualified by experience and training. Delegated responsibilities must be retained in the UNSW Clinical Trial Delegation Log. The UNSW Sponsor's Delegate is to be notified of the following:

- Protocol deviation reports outlined in the UNSW Research Misconduct Procedure.
- Any serious breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Significant safety issues that are likely to (or have the potential to) affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Urgent safety measures implemented to remove or prevent a significant safety issue.
- Safety reports relating to the continuation, suspension, or discontinuation of the clinical trial for safety reasons.
- Non-compliance with the protocol, SOPs, GCP, and applicable regulatory requirement(s) significantly affects or can potentially affect human subject protection or reliability of trial results significantly.
- Participant complaints or concerns received concerning the conduct of the research.
- Significant modifications to the clinical trial are likely to affect a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial.
- Addition of participating trial sites, contractual arrangements at participating sites or modifications to legal agreements.
- The intention to conduct the trial in other countries.

4. Trial Objectives and Purpose

This clinical trial aims to investigate the effectiveness of a Cognitive Behavioural Therapy for Insomnia (CBT-I) program delivered via a smartphone application (called Sleep Ninja®) for improving sleep and mental health outcomes in Australian children (aged 10 to 12 years, and not yet in high school) with disrupted sleep relative to an attention matched control.

The primary outcome is insomnia symptoms, measured by a change in child- reported symptoms between baseline and 6-weeks post-baseline (primary endpoint). Secondary outcomes include improvements in depression and anxiety symptoms between baseline and 6-weeks post-baseline as measured by validated self-report scales. The emergence of new cases of Major Depressive Disorder at 9-months (tertiary endpoint) post-baseline as measured by diagnostic assessment will be explored. Insomnia and mental health outcomes will be evaluated at 3- and 9-months post-baseline using the same self-report scales to determine whether effects are sustained in the mid-term and whether the interventions are associated with any delayed benefits or harms.

The primary research questions this trial aims to address are:

- Does Sleep Ninja reduce insomnia symptoms at post-intervention compared to an attention-matched control?

Secondary research questions include:

- What is the effect of the Sleep Ninja on depression and anxiety?

Subsidiary and exploratory research questions include:

- Is the reduction in depressive symptoms mediated by changes in sleep and cognitive processes including repetitive negative thinking, dysfunctional beliefs about sleep and pre-sleep arousal?
- What is the effect of the Sleep Ninja on the emergence of new cases of Major Depressive Disorder over 9 months?

Primary and secondary hypotheses:

This trial will determine whether Sleep Ninja is effective in lowering insomnia symptoms when compared to an active attention-matched control in 10-12 year olds, not yet in high school with sleep difficulties. It is hypothesised that:

H1 = Participants allocated to the Sleep Ninja condition will have improved insomnia symptoms and sleep quality compared to control participants.

H2 = Participants allocated to the Sleep Ninja app will have improved depression and anxiety at post-intervention

H3 = Reductions in depression will be mediated by improvements in sleep and reductions in repetitive negative thinking, dysfunctional beliefs about sleep and pre-sleep arousal.

5. Background Information

It is estimated that 2% of children will develop Major Depressive Disorder by the age of 11, rapidly accelerating to 9% by the age of 14. Prodromal depression, that is subthreshold symptoms that signal the impending onset of diagnostically specific depression, typically emerge

in childhood (Tannous, 2018). Since Covid-19, rates of elevated depressive symptoms in children has doubled from 15% to 30% (Racine et al., 2021). Childhood depression is associated with a more chronic course of depression across the lifespan, including a greater risk recurrence, heightened comorbidity with other disorders, greater risk of suicidality and lifelong functional impairment (Lewinsohn et al., 2000). With a mental health system under pressure and limited access to care (Ebert, 2018), inoculating children against depression is critical.

Prevention programs aim to intervene before the disorder has emerged, or early in the course of illness (Ebert, 2018). Meta-analytic reviews in children and adolescents show prevention strategies significantly reduce the risk for future depression onset compared to control conditions (van Zoonen et al., 2014). However, universal preventive programs for depression have significant limitations, including low uptake, poor engagement and high cost (Spence & Shortt, 2007). Engaging people who are asymptomatic or experiencing mild, subthreshold symptoms and are therefore unlikely to experience immediate benefit, is challenging. Furthermore, they need to be delivered by specially trained experts in child mental health, which is a problem given the already over-extended mental health workforce (Headspace, 2019). Therefore, the ideal prevention program is one that: (i) targets children with elevated risk factors for depression and is non-stigmatising; (ii) can be flexibly delivered; (iii) engages the individual and addresses their needs; and iv) is inexpensive to deliver and scale.

Sleep problems are an important risk factor for depression onset. It is becoming increasingly clear that sleep problems precede depression, and explicitly contribute to depression onset. Many children (>30%) do not get the recommended 9-11 hours of sleep each night, and 40% will experience significant sleep problems by adolescence. Fortunately, sleep problems in children are treatable. As in adolescents and adults, cognitive behavioural sleep interventions (collectively termed cognitive behavioural therapy for insomnia; CBT-I) are effective at improving sleep in children (Blake et al., 2017). Yet, despite high rates of sleep problems in children, and increasing evidence that sleep problems cause depression (Gradisar et al., 2010), we are unaware of any published studies investigating the treatment or prevention of depression in children via improved sleep.

6. Statement of Compliance

The clinical trial will be conducted in compliance with the following guidelines and documentation:

- ICH Guidelines for Good Clinical Practice (GCP)
- National Statement on Ethical Conduct in Human Research (National Statement)
- As approved by the Human Research Ethics Committee (HREC), the clinical trial protocol is responsible for monitoring the trial's conduct.
- The responsibilities set out by the UNSW Sponsors Delegate.
  The onsite or remote monitoring standard operating procedures as put in place by the clinical trial sponsor.

7. Trial Design

This study will use a two-arm randomised controlled trial, conducted entirely online via the Qualtrics Survey Platform. Outcomes will be assessed as baseline, primary endpoint (6-weeks post-baseline), secondary endpoint (3-months post-baseline) and tertiary endpoint (9-months post-baseline). This methodology is appropriate to meet the research aims because RCTs are considered to provide the most reliable evidence on the effectiveness of interventions because the processes used during the conduct of this type of trial minimise the risk of confounding

factors influencing the results. Because of this, the findings generated by RCTs are likely to be closer to the true effect than the findings generated by other research methods (Akobeng, 2005).

Randomisation will be carried out according to the International Council for Harmonisation (ICH) guidelines. Randomisation to one of the two trial arms will be conducted immediately after completion of the baseline survey using a computerised randomisation procedure within the Qualtrics Survey Platform. Randomisation will be stratified according to gender (male/female/other), with 'other' including participants that select Non-binary or Different identity as their gender identity. Allocation will be fully automated, with no interference from the research team.

Blinding - Participants: All study materials will refer to the interventions being examined as "activities to improve sleep" to conceal Sleep Ninja being the smartphone app used in the trial. This is to prevent participants allocated to the control condition from accessing the Sleep Ninja smartphone app, which is publicly and freely available for download, during their participation in the trial. While participants will be aware of which activity or information they will be required to use (due to the PICF and instructions for use provided), they will not be directly informed of their condition allocation (i.e., intervention vs. control) to prevent biases in reporting related to expectancies. We are not aware of any known or likely reason that participants would not consent to participate if they were aware the intervention was the Sleep Ninja app.

Blinding – Statistician: The statistician involved in examining the effects of the conditions of primary and secondary outcomes will not be informed of participants' specific intervention allocation. Condition allocated will be marked as "Condition A, Condition B" to ensure the statistician remains blinded to participants' intervention upon primary and secondary analysis of the results. All other potential markers of allocation will be removed from the data analysis file. Upon completion of these analyses, the statistician will be become unblinded when examining mediators and moderators as well as intervention completion rates. This data will only be reviewed by the trial statistician upon completion of the primary and secondary outcomes.

Blinding – Chief Investigators, Trial Managers, Data Analyst and Research Officers/Assistants: The chief investigators, trial manager and research assistants will be unblinded to participants' allocation as they will have access to the Qualtrics data to contact participants if they experience adverse events. They will also be responsible for downloading and cleaning the data extract. The Chief Investigators, Trial Managers, Data Analyst and Research Officers/Assistants will not be involved in data analysis of the primary and secondary outcomes.

For the study outputs, a CONSORT flow diagram will be provided outlining study recruitment, including n for each stage.

8. Sample Size

The total baseline sample size for detecting change in the primary outcome is 200. This is based on calculations using α=.05, power=0.8 to detect a Cohen's d between-group effect of 0.30 on the primary outcome at post-intervention and a 20% attrition between baseline and primary end-point (N=200). An effect size of 0.3 is based on effect sizes from previous data (Werner-Seidler et al., 2019; 2023)

9. Selection and Withdrawal of Subjects

1. All inclusion and exclusion criteria will be assessed through a self-report screening assessment via a Qualtrics link on the study webpage. Excluded participants will be provided with a generic message providing information about where to seek help and self-care activities and instructions on accessing PDFs of information provided to the control group.

   To mitigate the potential of participants "gaming" the inclusion criteria (i.e., making multiple attempts to enter the study by various combinations of the inclusion/exclusion criteria), the Participant Information Statement and Consent Form (PISCF) will not stipulate the exact details of the inclusion and exclusion criteria for depressive scores, and will instead give generalised indications.

9.1 Inclusion Criteria

To participate in this trial, at the time of screening participants must:

- Aged 10 to 12 years, and not yet in high school (confirmed by self-report)
- Located in Australia (confirmed by self-report)
- Experiencing sleep disturbance (as determined by a score of 3 or more on any of items 1 to 5 on the Pediatric Insomnia Severity Index).
- Own or have access to a smartphone or mobile device (for receipt of the study interventions)
- Have access to the Internet, an active email address and mobile phone number (for receipt of study activities, invitations, reminders)
- Have a parent or guardian who can provide consent for participation.

9.2 Exclusion Criteria

At the time of screening, participants will be excluded if they:

- Meet criteria for current or previous diagnosis of MDD (determined by parent report; or found to meet current or past MDD criteria on K-SADS at baseline)
- Fail to satisfy any of the inclusion criteria

9.3 Recruitment Strategy

This study will use an online recruitment strategy targeting parents. Recruitment will take place until the desired sample size is achieved. It is estimated that the sample will be recruited within 12 months, between July 2023 to July 2024. All recruitment materials are outlined in Appendix B.

A webpage for the study will be established and the URL will be included in all study materials. All study adverts will direct participants to the study webpage, where they will access study information, provide consent and undertake screening via a Qualtrics link on the study webpage.

Study advertisements will be published on the Black Dog Institute website and social media channels including Facebook, Twitter, and Instagram. Study advertisements will also be included in Black Dog Institute internal and external communications, via established professional newsletters to agreed subscribers.

The research team will also contact relevant mental health organisations and services (e.g., psychology clinics), parent and youth groups independent of the research team to recruit participants to take part in the study. These organisations will be asked to share the study advertisements on their organisation's communication channels (e.g., website, social media, newsletters, mailing list, in-person clinics) using the same adverts outlined in Appendix B. Support to assist with recruitment will be assumed by the organisation's agreement to post or disseminate recruitment materials. No organisations will know whether a person agrees to participate or not as

the recruitment materials will direct potential participants to the study webpage, which includes further instructions on how to participate, screening, and consent via a Qualtrics link on the study webpage.

The research team will also send two email invitations via electronic direct mailout (sent one month apart) to the Black Dog Institute research database, which consists of individuals who have consented to being contacted about future research studies being conducted by the Institute. The email invitation is included in Appendix B.

The study will also utilise a paid advertising campaign on social media platforms (e.g., Snapchat, Twitter, Facebook, Instagram) and Google, for the duration of recruitment. This campaign will use the same adverts outlined in Appendix B and predominantly target parents.

The study will also contact independent primary schools via email to invite them to share study information with their school community (e.g., via newsletters or appropriate mailing lists). Any interested participants will be directed to the study webpage, which includes further instructions on how to participate, including completing screening and consent via a Qualtrics link on the study webpage. Schools will not be involved in the study or be required to facilitate any study activities. A staff contact at the school (e.g., school counsellor) will be sent an initial email inviting them to read more about the study via the study webpage and to get in touch with the research team if they are interested in sharing the study information with their school community. Following the school contact's expression of interest to share information about the study, the research team will provide relevant recruitment materials (see Appendix B – Recruitment materials) depending on the method of communication they wish to use. Non-independent (I.e., government) schools will not be contacted, therefore State Education research Approval Process applications are not required.

9.4 Screening

Screening will take place via a Qualtrics link on the study webpage. The homepage of study webpage will contain a brief version of the PISCF form (see Appendix H) so that parents of potential participants are aware of key study requirements prior to completing the screening questions. To determine whether a participant is eligible to take part in the study, interested participants will complete a self-report screener hosted via Qualtrics accessible via the study webpage (see Appendix H for the screening questionnaire). Participants will be informed that the responses to the screening assessment will be stored for reporting purposes. Consent to undergo the screening procedure will be implied based on individuals' completion of the questions. Parents will complete the screening questions on behalf of the child participant.

Ineligible participants will receive a short thank you message advising them that the study is not the right fit for them at this time. The message will also contain information on where to seek help and self-care activities and instructions accessing tips and information on healthy sleep.

9.5 Consent

Once screening is completed, parents of all eligible participants will be invited to review the full PISCF (Appendix C) and provide their parental consent. As this study is targeted at children, parents will provide consent on behalf of the child participant. However, following parental consent, children will be presented with a simplified PISCF (Appendix C.2), with assent assumed if they are registered for the trial. To register, parents of participants are asked to provide their full name, email, mobile phone number on Qualtrics. After registering, the child's parent will be automatically sent a welcome email confirming their involvement in the study and containing a copy of the parental and child PICF using the parents email address provided.

If requested by the parent, the parental PISCF will also be downloadable as a pdf from the study webpage so that parents of potential participants can complete the form as a hard-copy and scan or photograph the completed version to the study email address. As above, in the event of consent obtained this way, we will send a confirmation email to the parent's email address to safeguard against young people submitting on behalf of a parent.

Participants will have sufficient time to consider study participation because they have 7 days to complete their parent and child PICF.

Once registered, participants will automatically continue within the survey to complete the baseline assessment. The participants will be asked to complete their baseline assessment within 7 days, allowing participants further time to reconsider their consent after its initial provision. Participants can cease the baseline assessment at any time, which will result in their removal from the study. Participants will receive two reminders to return their consent form, sent on day 3 and day 5. Participants who fail to complete the child consent form will be withdrawn from the study.

The consent process used in the current study is appropriate for the study design and data collection method (i.e., online surveys) because participants are being recruited via online methods. Therefore, an online consent procedure aligns with their expectations of research participation. In addition, as this is an internet trial (i.e., all study procedures are conducted online) an online consent form is consistent with the study activities and description. Participants will not be reconsented at each timepoint to reduce participant burden.

9.6 Withdrawal of Consent or Participant

Participants will be able to withdraw from the study at any time by:

1. Emailing the research team: By emailing childsleep@blackdog.org.au and providing their full name, date of birth, mobile number with the subject line "withdraw" or equivalent.
2. Failure to complete the baseline assessment: Participants who fail to complete the baseline assessment will be automatically withdrawn from the study.

Once withdrawn from the research study, all of participants' personal identifiable data (e.g. name, email address, mobile phone number) will be removed and no further information will be collected from them. The research team will retain some information (e.g. age, gender, symptom severity) for trial reporting purposes. Withdrawn subjects will not be recontacted or followed up. However, to ensure participant safety, withdrawn subjects will be able to report whether their withdrawal from the study was associated with adverse events related or unrelated to the study activities. Participants who actively withdraw will be informed that they can, if they wish, provide feedback about any study activities but there is no obligation to do so.

Failure to complete the primary, secondary or tertiary endpoint assessments will be considered lost to follow-up for that timepoint but will not withdraw participants from the study. Participants who fail to download or access the study interventions during the study period will not be withdrawn from the study. Withdrawn subjects will not be replaced as the sample size calculations accounts for study attrition.

10. Treatment of Subjects

The study flow is outlined in Appendix A. Participants will be recruited through study advertisements containing links to the study webpage. Parents will complete an online screening questionnaire hosted on Qualtrics and accessed via the study webpage (Appendix H) and if eligible, parents will provide consent on behalf of their child using the online PISCF (Appendix

C) and children will be presented with the child PIS (Appendix C.2) and assent assumed if they are registered for the study. Ineligible participants will be excluded from the study and a generic message will provide appropriate referrals and instruction on accessing tips and information on health sleep (see Appendix H).

Following registration, participants will be automatically provided access to the baseline survey to complete with assistance from their parents. It will take approximately 30-mins to complete and can be completed on any Internet-enabled device. Participants will have 7 days to complete the baseline assessment (from the invitation date) and parents will receive two reminders for their child to complete the assessment (sent on day 3 and day 5). The outcome measures assessed at baseline are outlined in Appendix E. Parents and children will then be contacted to complete a diagnostic assessment using the K-SADS-COMP (Kaufman et al., 1997). The K-SADS-COMP will take approximately 30 minutes to complete (Depressive Disorders section only). Completion of the 7-day sleep diary is part of the baseline battery but completion of days 2-7 is not mandatory for participation in the study. Participants who fail to complete the baseline assessment will be withdrawn from the study.

Participants will be randomised to the intervention or control condition following the K-SADS COMP. Upon finalising the sleep diary, participants will be presented with information on the screen (also emailed to parents) that provides instructions on the requirements for their trial arm. The parents of participants allocated to the intervention condition who fail to download Sleep Ninja within 7 days will be sent an email and SMS reminder to download the app on their own or parents' device. Participants will then receive 6 weeks access to Sleep Ninja, or 6-weekly sleep psychoeducation flyers.

Participants will be reimbursed for the time taken to complete the study surveys and diagnostic assessments. The standard reimbursement rate to ensure financial incentives do not produce coercive effects is AUD$20/hour. This is also aligned with the best-practice wage-payment model (Dickert & Grady 1999), using the current minimum wage of $19.84p/hr. As each assessment will take approximately 30 minutes and each assessment approximately 30 minutes, reimbursement will be disseminated as $10 e-gift vouchers (Giftpay) at the completion of each assessment and on the completion of each diagnostic assessment. E-vouchers will be emailed to the parent email address provided at registration. We do not anticipate that this study will incur any out-of-pocket expenses as the Sleep Ninja app uses very minimal data and is programmed to send data back to Black Dog Institute servers only when the mobile device is connected to Wi-Fi.

Because of this incentive, data integrity checks will be embedded into the online assessments to check for duplicate users at baseline (e.g., emails, and mobile number checks) thereby ensuring that standards of internet studies are met (Reips, 2002). Data is collected electronically via the Qualtrics Survey Platform and the Sleep Ninja app. All data is stored on the UNSW OneDrive and supported by 128-bit encryption (the equivalent of that for internet banking services).

At the initiation of the study, participants will be allocated ID codes, which their survey responses and app usage data will be recorded against. This data is kept securely on the UNSW OneDrive, only accessible to authorized personnel using password protected accounts. At the data-analysis stage, participants will be identifiable only by their unique ID code, to protect their

privacy. All data will be destroyed 15 years after the completion of the study by the Chief Investigator.

For analyses, all study assessment data will be exported, via a Microsoft Excel file, from Qualtrics to SPSS-Version 26 for analysis by the trial statistician and research team. These files will be stored on UNSW OneDrive and only accessible to personnel listed on the project. The dataset will be de-identified (i.e., remove name, mobile phone number, email addresses, IP addresses, and free response data) and prepared (i.e., cleaning and ensuring blinding) for the trial statistician to conduct the primary and secondary analyses. The de-identified and blinded file will then be transferred to the trial statistician for analyses using a password protected OneDrive file. Aggregate deidentified data in a password protected OneDrive file will be retained for future evidence synthesis.

A separate spreadsheet consisting of participants' contact details (email addresses and mobile phone numbers) alongside their name and completion of the assessment dates, will also be stored in a password protected file in a private folder on One Drive to enable the GiftPay vouchers to be sent to participants and for the risk management protocol. This file will only be accessible to the personnel listed on the project.

As this study is collecting personal information (e.g., mobile phone numbers and email addresses), this information is protected in accordance with the Australian Privacy Act 1988. Participants have the right to access and destroy any personal information collected by this study. If participants have concerns about the way their data has been handled, they are encouraged to notify the Chief Investigator and the UNSW HREC. This information is outlined for participants in the PISCF.

Analyses will be conducted to determine the effect of the intervention on depressive and insomnia symptoms at the primary, secondary and tertiary end-points. Analyses will be undertaken on an intent-to-treat basis, including all randomised participants, regardless of intervention received. For scaled outcomes, mixed-model repeated measures (MMRM) analyses will be used because of the ability of this approach to include participants with missing data. The primary hypothesis will be evaluated by a contrast evaluating change from baseline to the post-intervention assessment point in the Sleep Ninja arm compared to that in the control arm for depression symptoms. The difference in relative risk for depressive episode onset will be calculated, its significance assessed, and number needed to treat to avoid caseness will be estimated. Secondary outcomes will be analysed with the same MRMM approach, using all timepoints. Mediation analyses addressing whether improvements in depression are mediated by changes in sleep, and the potential contribution of cognitive processes will be carried out using multilevel regression analyses to test criteria for mediation (Hayes & Rockwood, 2017). Other outcomes (i.e, adherence and acceptability) will be described.

10.1 Trial Intervention

Trial Arm 1. Intervention group: Sleep Ninja is an automated smartphone app co-designed with 12-16-year-olds and parents to deliver CBT-I. Given its gamified features and content reading level (Years 5-6), Sleep Ninja is suitable for 10–12-year-olds. Pilot data (N=5) showed 10-year-olds found it fun and easy to use, and easy to understand. However, to further adapt Sleep Ninja to a younger age group, parent training materials have been co-created with parents of 10-12 year olds to allow and encourage the involvement of parents in the intervention. These materials

aim to improve parents' knowledge of child sleep health, provide critical information on Sleep Ninja, including how to use it with their child and support the implementation of the sleep strategies.

The Sleep Ninja program includes 6 modules (referred to as 'training sessions'), a sleep tracking function, sleep scheduling based on required wake time, personalised wind-down routine and reminders, a series of sleep tips, and general information about sleep. The app uses gaming elements to enhance engagement, based on a Ninja analogy. Users complete training sessions to increase their sleep skills, allowing them to "level up" (move to the next level), and finish the program with a black belt in sleep. Each training session covers a core CBT-I strategy delivered through an automated chat-bot where the Ninja acts as a sleep coach. Components include sleep scheduling and circadian rhythms (training 1), stimulus control (training 2), daytime functioning and the pre-bed routine (training 3), cognitive therapy to address worries at night (training 4), planning for high-risk situations (training 5), and a final review session (training 6). Users progress through the app by completing each training session and tracking their sleep for 3 nights (out of a 7-night period). Sleep Ninja cannot be used within one hour of bedtime to prevent screen time and blue light interference with sleep. For the proposed study Sleep Ninja has been adapted for 10-12 year olds. It will include a parent's training module. Based on consultation with parents to improve acceptability and uptake, this module will consist of a short video providing information on children's sleep health, on the Sleep Ninja app, including its effectiveness, its various components, and how it has been designed to be used, and how to use Sleep Ninja with their child and support healthy sleep behaviours.

Participant instructions for use: In this trial, participants are provided with access to Sleep Ninja for 6-weeks. Participants are instructed to complete the app content by undertaking one 'training session' and tracking their sleep for three nights each week (approximately 10 minutes) for the intervention period. To further ensure compliance, all participants in this intervention arm will be sent in-app notifications (reminders) to complete the training sessions and sleep tracking.

Trial Arm 2. Attention-matched control: This study will utilise an active attention matched control condition. Participants allocated to this condition will receive 6 weekly psychoeducation flyers, optimised for viewing on their mobile device. The psychoeducation flyers are matched for visual appeal and engagement duration, taking 5- to 10-mins to complete. They consist of 6 topics: 1) Why do we sleep?; 2) Fun facts about sleep; 3) Tips to help you sleep – part 1; 4) Tips to help you sleep – part 2; 5)Stress and sleep and 6) Where to go for more help. A full overview of the psychoeducation content is provided in Appendix G. Participants in this condition will receive the Sleep Ninja app after the tertiary end-point at 9-months post-baseline.

Participant instructions for use: In this trial, participants are provided with access to the digital psychoeducation e-flyers for the 6-week intervention period. Participants will be instructed to complete the content by undertaking one e-flyer per week (approximately 10 minutes) for the intervention period.

11. Safety and Monitoring

11.1 Assessment of Safety Event Report Forms

Safety reports will be assessed on the seriousness, causality, and expectedness of the event to the trial treatment(s), intervention(s), investigational medical product(s), investigational medical

device(s). The following are known and expected adverse effects, harms, risks or discomforts associated with trial procedures, treatments or interventions.

a) Known Adverse Effects

There are no known or expected adverse effects associated with the trial procedures, however, the following have the potential to occur:

Effect/Event	**Criteria**
Severe insomnia symptoms detected at final study assessment (i.e., tertiary endpoint: 9-months post-baseline)	A score of 5 on item 6 of the PISI (i.e., less than 5 hours of sleep most nights).
Action	
The following actions will occur when a participant satisfies the above criteria: a) This questionnaire is completed by parents. A pop-up message in the questionnaire will be displayed on participants' device. This message will provide individuals with immediate recognition of their response and recommend they seek support from a health professional for their child. This message will read: *"Your responses have indicated that your child is sleeping less than 5 hours most nights. We recommend seeking advice from a medical professional, such as a GP. If you would like to be contacted by the research team psychologist to discuss health support options, please contact us on childsleep@blackdog.org.au."* If a call is requested, the Trial Manager will arrange for the Clinical Psychologist to attempt contact with the participant within two working days. The Clinical Psychologist will conduct a brief risk assessment over the phone to determine the level of sleep problems and encourage the parent make an appointment with their GP. The research team's qualified psychologists have significant experience in working with distressed youth and families both in research and clinical settings. The clinical supervisor is well equipped to oversee and manage any issues that may arise. In all instances, if a participant is unable to be contacted by phone after two attempts, they will be sent an email from the study email address informing them of the attempt to make contact. This email will also contain mental health information and support services. b) A register of these events and associated interactions (i.e., telephone call attempts, times, dates, outcomes) will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.	
Effect/Event	**Criteria**
Severe depressive symptoms detected at final study assessment (i.e., tertiary endpoint: 9-months post-baseline) through the self-report RCADS depression subscale.	A participant reports a total t-score ≥ 70 on the RCADS (child or adult version) at tertiary endpoint assessment (i.e., 9-months post-baseline).
Action	
The following actions will occur when a participant satisfies the above criteria: a) A pop-up message in the questionnaire will be displayed on participants' device. This message will provide individuals with immediate recognition of their response and recommend they tell someone they trust about how they are currently feeling. This message will read: "*Your responses have indicated that you may not be doing so well right now. Thanks for letting us know. We think it'd be great if you could tell a trusted*	

adult about how you're feeling. We recommend seeking advice from a medical professional, such as a GP. If you're not up to talking to someone you know, try Kids Helpline on 1800 55 1800."

b) An email will be sent to the parent's email address informing them of their child's response or recognising their response and inviting them to request a call back from the research team's psychologist. This message will read: "*Responses have indicated that your child may not be doing so well right now. Because your child is coming to the end of the study, we'd like to offer you the opportunity to talk to a mental health professional from the Black Dog Institute about how to access mental health support. Please reply to this email if you would like to receive a confidential call from the research team psychologist."* The email will also contain support services and referral information (Appendix D).

   If a call is requested, the Trial Manager will arrange for the Psychologist to attempt contact with the participant within two working days. The Psychologist will conduct a brief risk assessment over the phone to determine the level of depressive symptoms and if necessary, the presence of suicidality. If determined to be at risk, the participant will be advised to contact an appropriate service (e.g., a GP, the BDI Psychology Clinic, Mental Health Line). The research team's qualified Psychologists have significant experience in working with distressed youth and families both in research and clinical settings. The clinical supervisor is well equipped to oversee and manage any issues that may arise. All participants who receive a call back will be offered an additional follow-up call, scheduled 7 days after the initial call, to check-in about the agreed safety plan. In all instances, if a participant is unable to be contacted by phone after two attempts, they will be sent an email from the study email address informing them of the attempt to make contact. This email will also contain mental health information and support services.

c) A register of these events and associated interactions (i.e., telephone call attempts, times, dates, outcomes) will be recorded in a separate risk management spreadsheet managed by the Trial Manager. These events will also be recorded in the UNSW Safety Monitoring Template.

b) Known Harms, Risks or Discomforts

The interventions evaluated in this trial have been designed and reviewed by mental health professionals to support children improve sleep with support from their parents. The intervention has been evaluated in an adolescent cohort and found not to produce harmful effects. As such, the researchers do not anticipate significant harm or distress related to use of the interventions in the current trial, however, the following harms, risks or discomforts may occur:

a) While CBT is the gold-standard treatment for depression and anxiety, CBT-based activities undertaken in the trial interventions may require emotional effort to complete and have the potential to cause a transient increase in symptoms as well as psychological distress (e.g., cognitive restructuring).

b) Some of the self-report questionnaires refer to sensitive personal experiences, including symptoms of depression and anxiety (although it is noted that those meeting criteria for past or current depression are not eligible to participate). That said,research shows that these

questionnaires are unlikely to bring about new episodes of psychological distress, some participants may experience some emotional discomfort related to being asked about their mental health during study assessments.

To minimise the potential known harms, risks or discomforts, various safety procedures will be implemented throughout the trial:

a) All participants not meeting inclusion criteria at screening will be provided with a list of referral services and information on how to access mental health crisis services. This information is provided in Appendix D.
b) To mitigate potential discomfort or distress associated with the study assessments, brief youth-friendly versions have been used.
c) At the beginning of the study, participants will be advised that the trial interventions are not intended to replace professional medical advice, or to provide crisis support. Participants are also able to seek unlimited mental health treatment and support throughout the study period.
d) A list of mental health support services will be provided to participants when completing each of the study assessments (see Appendix D).
e) Information regarding how participants can contact the research team, how often the trial email is checked, and response time will also be provided in the study welcome email.
f) Sleep Ninja contains a 'Get Help Now' feature which directs users to appropriate services, including Kids Helpline at any time during the intervention period.
g) In addition to external support resources, participants will be informed in the PICF that they can contact the research team if they become upset or distressed because of their participation in the study. If a parent or child contacts the research team, a psychologist from the research team will arrange follow-up contact to assess the level of distress and direct the family to the appropriate services. This will be provided free of charge.

How benefits outweigh potential risks of discomfort/harms:

- CBT-I is the gold-standard, first line treatment for sleep difficulties in children. Psychoeducation is also an evidence-based approach to alleviate symptoms. Therefore, all participants in the current trial will receive access to trusted information and activities to improve sleep developed by a reputable Australian mental health organization (The Black Dog Institute). We expect therefore, that the benefits of interventions outweigh any potential risks of discomfort or harm associated with completing the study activities.
- The interventions in this study may also lead to increased help-seeking and greater engagement with other mental health services and support among participants/parents.
- Participants' involvement in the trial and engagement with the program has the potential to increase their mental health literacy and self-awareness, which is important to maintain psychological wellbeing across the lifespan.

11.2 Adverse Events or Adverse Reactions

Adverse events (AE) are considered any untoward medical occurrence in a patient or clinical trial participant administered the intervention, which does not necessarily have a causal relationship with this treatment.
Adverse Reactions (AR) are considered untoward and unintended responses to the trial intervention related to any intervention procedures.

Aes and Ars are assessed using the safety monitoring flow chart. Those classified as "not serious" are assessed by the qualified physician/medical expert specified in section 2 of the protocol. The Qualified Physician cannot delegate this responsibility to other research personnel.

Adverse event reports must be reported to the Coordinating Principal Investigator within 48 hours of being made aware of the event. All adverse event reports must be recorded in the UNSW Safety Monitoring Register Template.

11.3 Serious Adverse Events

Serious Adverse Events(SAEs) that result in or lead to one or more of the following and the event is **not related** to the trial intervention:

- The death of a trial participant.
- A life-threatening illness or injury involving a trial participant.
- A participant's permanent impairment of body structure or body function.
- In-patient or prolonged hospitalisation (not for a pre-existing condition or an elective surgery) of a trial participant.
- Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or function of a trial participant.
- Fetal distress, fetal death or congenital abnormality or birth defect.

SAE reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel. SAE reports are reported to the Coordinating Principal Investigator within 48 hours of being made aware of the event occurring. SAR reports must be recorded in the UNSW Safety Monitoring Register Template.

11.4 Serious Adverse Reactions

A Serious Adverse Reactions (SAR) is an SAE that is **related** to the trial intervention. SAR reports are classified following the safety assessment flowchart and are assessed by Sponsors Independent Medical specified in section 2 of the protocol. The sponsors independent medical expert must determine whether the SAR was expected or unexpected. The Sponsors Independent Medical cannot delegate this responsibility to other research personnel.

a) Expected Serious Adverse Reaction

A serious adverse reaction by its nature, incidence, severity, or outcome is anticipated and identified in the current version of the intervention safety information are classified as a SAR report. SAR reports are reported to the Coordinating Principal Investigator within 48 hours of being made aware of the event occurring. Serious Adverse Reaction reports must be recorded in the UNSW Safety Monitoring Register Template.

b) Suspected Unexpected Serious Adverse Reaction (SUSAR)

A serious adverse reaction by its nature, incidence, severity, or outcome is unanticipated and not identified in the interventions instructions for use or safety information are classified as a SUSAR.

Fatal or life-threatening Australian SUSAR reports are reported to the Coordinating Principal Investigator, the sponsor's delegate and the approving HREC within 7 calendar days after being made aware of the case follow up information reported within a further 8 calendar days.

All other Australian SUSAR reports are to be reported to the Coordinating Principal Investigator, the sponsor's delegate and the approving HREC within 15 calendar days after

being made aware of the case follow up information reported within a further 8 calendar days. SUSAR reports must be recorded in the UNSW Safety Monitoring Register Template.

11.5 Significant Safety Issue (SSI)

A safety issue that could adversely affect participants' safety or materially impact the trial's continued ethical acceptability or conduct. The Human Research Ethics Committee and Sponsor's Delegate must be notified of all significant safety issues within 15 calendar days of the sponsor instigating or being made aware of the issue**.** SSI reports must be recorded in the UNSW Safety Monitoring Register Template.

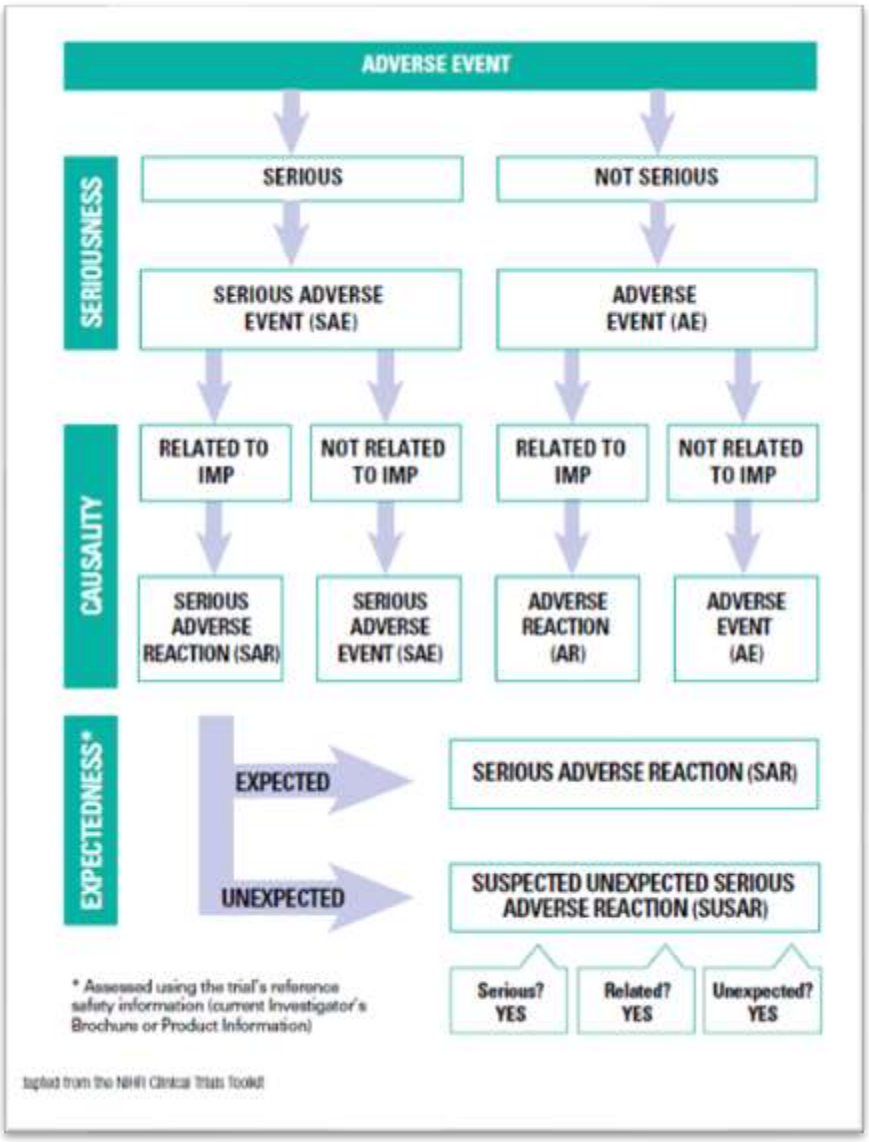
11.6 Urgent Safety Measure (USM)

A measure that is taken to eliminate an immediate hazard to a participant's health or safety. Significant safety issues where an urgent safety measure is required to be taken to eliminate an immediate hazard must be classified as a significant safety issue requiring an urgent safety measure. The Human Research Ethics Committee and the Sponsor's Delegate must be notified of any significant safety issues that meet the definition of an urgent safety measure should be notified within 72 hours. Examples include:

- a serious adverse event that could be associated with the trial procedures and that requires modification of the conduct of the trial
- a patient population hazard, such as lack of efficacy of an intervention used for the treatment of a life-threatening disease.

USM reports must be recorded in the UNSW Safety Monitoring Register Template.

11.7 Safety Assessment Flow Chart Investigational Medical Product Trials



11.8 Register of Clinical Trial Safety Monitoring Reports

A register of all event reports assessed and classified is to be retained by the Coordinating Principal Investigator and reported to the trial sponsor annually and the HREC if required.

11.9 Reporting of Clinical Trial Safety Monitoring Reports

Single case reports of Adverse Events Adverse Reactions, Serious Adverse Events (SAEs), Serious Adverse Reactions (SARs), reports do not need to be reported to the UNSW Sponsor's Delegate or the HREC. All single case reports must be recorded in a safety monitoring register and are reported to the UNSW Sponsor's Delegate annually.

a) Emerging Safety Issues

The Trial Management Group, Trial Safety Committee or the Data Safety Monitoring Board is responsible for reviewing the safety information to identify any serious emerging safety concerns. If safety concerns are identified, this body will establish a plan to minimise the time participants may be placed at excess risk of harm. Before implementing the plan, the Trial Management Group, Trial Safety Committee or the Data Safety Monitoring Board must seek the advice of the human research ethics committee and sponsor's delegate.

b) Annual assessment of safety

The following information must be provided in a report to the sponsors delegate annually:

- Documented evidence that the Trial Management Group, Trial Safety Committee, or the Data Safety Monitoring Board (e.g. meeting minutes) confirmed that regular safety reviews occurred.
- Analysis of the trial intervention(s) and its implications for participants considering all available safety data and relevant clinical or non-clinical studies results.
- Any reports of emerging safety issues and a description of any measures taken or proposed to minimise risks.
- A copy of the safety monitoring register.

12. Non-compliance, Protocol Deviation and Serious Breaches of Good Clinical Practice

12.1 Protocol Deviation

A protocol deviation is defined as any breach, divergence or departure from the requirements of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that does not have a significant impact on the continued safety or rights of participants or the reliability and robustness of the data generated in the research or clinical trial. Protocol deviations are events that do not occur persistently or systematically and do not potentially result in participant harms. Examples of protocol deviations include but are not limited to:

- Deviations because of participant adherence to the protocol, including rescheduled study visits, participants refusal to complete scheduled research activities or failure to complete self-report questionnaires required by the study protocol.
- Blood samples obtained or clinical trial testing occurring at times close to, but not precisely at the time points specified in the protocol.
- The completion of consent forms, safety monitoring report, case report forms or data collection tools in a manner that is not consistent with the protocol instructions or failure to make reports within the required reporting timeframes.
- Administration of the clinical trial investigational medical product or device in a manner that is not consistent with the manufacturer's instructions for use.
- Use of an unapproved version of the participant information statement or recruitment of participants using unapproved recruitment procedures.
- Inclusion of a participant that does not meet the inclusion criteria.
- An urgent safety measure must be taken to eliminate an immediate hazard to a participant's health or safety.

12.2 Serious Breach of Good Clinical Practice

A serious breach is defined as a breach of Good Clinical Practice, the clinical trial protocol, the clinical trial standard operating procedures, or the human ethics approval that is likely to affect to a significant degree the safety or rights of participants or the reliability and robustness of the data generated in the clinical trial. Examples of serious breaches include but are not limited to:

- Persistent or systematic non-compliance with the instructions for completing consent forms, safety monitoring forms, case report forms or data collection tools that result in continued missed or incomplete data collection.
- Failure to record or report adverse events, serious adverse events, suspected unexpected serious adverse reactions, significant safety issues where urgent safety measures were implemented.
- Failure to conduct clinical trial procedures following the clinical trial delegation log.
- Widespread and uncontrolled use of protocol waivers affecting eligibility criteria, which leads to harm to trial subjects.
- Failure to report investigational medical product or device defects to the clinical trial sponsor or any relevant regulatory body.
- Failure to conduct research following the issued approvals, permits or licences by required laws, regulations, disciplinary standards, and UNSW policies relating to the responsible or safe conduct of research.
- Concealing or facilitating breaches (or potential breaches) of the Research Code by others.
- Researching without the requisite approvals, permits or licences required by laws, regulations, disciplinary standards, and UNSW policies related to the responsible or safe conduct of research.
- Failure to conduct research as approved by an ethics review body where that conduct leads to (or has the potential to) results in participant harms.
- Researching without ethics approval as required by the National Statement on Ethical Conduct in Human Research where that conduct leads to (or has the potential to) result in participant harms.
- Any breaches as outlined in the UNSW Research Misconduct Procedure or the Australian Code for responsible conduct of research that leads to (or can potentially) result in participant harms.

12.3 Reporting Protocol Deviations

- Protocol deviations occurring at a site must be documented in site files and reported by the principal site investigator to the Coordinating Principal Investigator.
- The Coordinating Principal Investigator must review the protocol deviation and the clinical trial protocol to establish the corrective actions and preventative steps to prevent the deviation from reoccurring.
- The protocol deviation and corrective action plan must be reported to the UNSW Sponsor's Delegate by the Coordinating Principal Investigator or Coordinating Research Team using the protocol deviation report form.

12.4 Reporting of a Serious Breach

- The Principal Investigator must report a serious breach occurring at a participating site to the Coordinating Principal Investigator within a specified timeframe.
- The Coordinating Principal Investigator must review the serious breach, along with the clinical trial protocol, to develop a Corrective and Preventive Action (CAPA) that defines the steps to prevent the serious breach from reoccurring.
- The serious breach report and the CAPA must be provided to the approving HREC, and the UNSW sponsors delegate for review and approval.

12.5 Reporting of Serious Breaches by Third Parties

- A Suspected Breach is a report judged by the reporter as a possible serious breach but has yet to be formally confirmed as a serious breach by the sponsor.

- A Suspected Breach form must be completed when a third party (e.g., individual/institution) wishes to report a suspected breach of Good Clinical Practice or the protocol and should be reported directly to the reviewing HREC without reporting through the sponsor.
- Recording of Protocol Deviation and Serious Breach Reports
- A register of protocol deviation and serious breach reports must be recorded. Written records and copies of documentation sent to the sponsor must be retained in the Investigator Site File.
- Copies of protocol deviation and serious breach reports must be recorded, written records and copies of documentation sent to the sponsor, referrals made to the HREC or establishing whether a breach of the Australian Code for Responsible conduct of research must be retained in the Master Site File.

13. Review of a Protocol Deviation and a Serious Breach

- The UNSW Sponsor's Delegate will review reports to establish whether the event meets the definition of a protocol deviation or serious breach, establish whether the proposed CAPA is appropriate and establish whether there is or will be ongoing impact reliability and robustness of the data generated.
- The UNSW Sponsor's Delegate will seek advice from the approving HREC on the corrective and preventive actions.
- Protocol deviation or serious breach reports where a UNSW researcher, staff or student is responsible for the protocol deviation or the serious breach will be reviewed as per the UNSW Research Misconduct Procedure to establish a breach of the UNSW Research Code of Conduct has occurred.
- Protocol deviation or serious breach reports where the UNSW Sponsor's Delegate determines that site personnel are responsible for a protocol deviation or the serious breach will be referred onto their responsible institution for review under their Research Misconduct procedures to establish whether a breach of the Australian Research Code for the Responsible Conduct of Research has occurred.

14. Statistics

- Primary analyses will be conducted to determine the effect of the intervention on depressive and insomnia symptoms at the primary, secondary and tertiary end-points. Analyses will be undertaken on an intent-to-treat basis, including all randomised participants, regardless of intervention received. For scaled outcomes, mixed-model repeated measures (MMRM) analyses will be used because of the ability of this approach to include participants with missing data. The primary hypothesis will be evaluated by a contrast evaluating change from baseline to the post-intervention assessment point in the Sleep Ninja arm compared to that in the control arm for depression symptoms. The difference in relative risk for depressive episode onset will be calculated, its significance assessed, and number needed to treat to avoid caseness will be estimated. Secondary outcomes will be analysed with the same MRMM approach, using all timepoints. Mediation analyses addressing whether improvements in depression are mediated by changes in sleep, and the potential contribution of cognitive processes will be carried out using multilevel regression analyses to test criteria for mediation (Hayes & Rockwood, 2017). Other outcomes (i.e, adherence and acceptability) will be described.

15. Data Ownership

All research data collected during this trial is governed and handled following the Research Data Governance and Materials Handling policy. UNSW, rather than any individual or Organisational Unit, is the Custodian of data and materials and any information derived from the data. Original

research data and primary materials generated in the research conducted at the University will be owned and retained by the University subject to any contractual, statutory, ethical, or funding body requirements.

16. Handling and Reporting Data

Principal Investigators are responsible for maintaining adequate and accurate source documents and trial records that include all pertinent observations on each site's trial subjects. Source data must be attributable, legible, contemporaneous, original, accurate, and complete.

Trial subjects will be assigned a participant ID, and data will be reported using the [case report form]. Data reported on the [case report form], derived from source documents, should be consistent with the source documents, or the discrepancies must be explained. Any change or correction to a [case report form] should be dated, initialled, and explained (if necessary) and should not obscure the original entry (i.e., an audit trail should be maintained); this applies to both written and electronic changes or corrections.

14.1 Direct Access to Source Data and Documents

Site principal investigator(s) and institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

17. Monitoring Quality Control and Quality Assurance

The Coordinating Principal Investigator and Principal Investigator(s) 'responsibility are to monitor the clinical trial. The Coordinating Principal Investigator and Principal Investigator(s) are responsible for undertaking or participating in site initiation or protocol-specific training before recruitment and data collection commences. A monitoring report demonstrating regular compliance monitoring with the clinical trial protocol, procedures, and HREC approval is provided to the UNSW Sponsor's Delegate annually.

Root, cause, analysis reports are to be completed by the Coordinating Principal Investigator for reports of non-compliance and serious breaches. A corrective and preventative action plan must be developed and actioned for any reports of non-compliance and serious breaches.

18. Clinical Trial Research Agreement

The Coordinating Principal investigators must ensure that agreements are executed at each of the following sites before site initiation, recruitment, and data collection commences.

19. Research Governance Site Authorisation

Site authorisation is to be obtained, or if a research site is added, a site authorisation letter from the delegated authority of an institution responsible for any participating site is obtained. It is to be stored as a GCP essential document before participants are recruited at a participating site.

20. Good Clinical Practice Requirements

It is recommended that the Coordinating and Principal Investigators' ensure that all investigators and trial-related staff have current Good Clinical Practice Training. Once completed, the evidence of training confirmation is to be stored as a GCP essential document.

It is the responsibility of the Coordinating and Principal Investigators to familiarise themselves with the requirements of the Guideline for Good Clinical Practice (E6, R2)

21. Essential Documents for the Conduct of a Clinical Trial

All essential documents referred to in section 8.2 of the Guideline for Good Clinical Practice (E6, R2) are to be retained by all trial investigators.

22. Clinical Trial Delegation and Responsibilities Log

Protocol / Study Number:		**Sponsor Name:**	
Principal Investigator Name:		**Site Number:**	
Site Name (if applicable)			

***THIS FORM IS TO BE COMPLETED BY ALL PERSONNEL INVOLVED IN THE STUDY AFTER RECEIVING PROPER STUDY TRAINING AND BEFORE TAKING PART IN ANY STUDY ACTIVITIES**

Principal Investigator (PI)

By signing, I confirm/acknowledge that the tasks listed below will only be delegated to appropriately trained, skilled and qualified staff. I will remain responsible for the overall study conduct and reported data, ensuring study oversight. All associates, colleagues, and employees assisting in the conduct of the study are informed about their obligations and have not performed any study tasks before appropriate delegation and completion of appropriate training. Mechanisms are in place to ensure that site staff receives the appropriate information and training throughout the study and that a 2-way communication channel exists between staff and self. Any changes in staff or delegation in staff will be recorded promptly.

Name	Principal Investigator's Signature	Initials	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)

Site Staff

Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
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Name	Signature	Initials	Study Role	Key Study Task(s) (choose from list below)	Start (dd/mmm/yyyy)	End (dd/mmm/yyyy) (complete only if prior to end of study)	PI Initials & Date (dd/mmm/yyyy)
							_____ __/___/____
							_____ __/___/____
							_____ __/___/____

Comments:

Electronic Signature Declaration for Principal Investigator and Site Staff

- My electronic signature as it applies to entering electronic data or signing records in sponsor-owned or sponsor -outsourced computer systems is the legally binding equivalent of my handwritten signature.
- I will not share password(s) assigned to me for this study with any other persons.

Principal Investigator's End of Study Declaration

I hereby confirm that the above information is accurate and complete, and that I authorised the delegation of study-related tasks to each individual as listed above.

Principal Investigator's Signature: _____ **Date:**

Task Key:

1. Obtain informed consent *
2. Subject selection/recruitment*
3. Confirm eligibility (review inclusion/exclusion criteria)*
4. Obtain medical history (source documents)
5. Perform physical exam*
6. Conduct study visit procedure as outlined in the protocol*
7. Make study-related medical decisions*
8. Assess AEs/SAEs*
9. Dispense study drug*
10. Perform drug accountability
11. Study drug storage and temperature monitoring
12. Sample collection
13. Sample processing and/or shipment
14. Evaluate study-related test results *
15. Use IWRS/IVRS
16. Make entries/corrections on (e)CRFs
17. Sign- off (e)CRFs*
18. Maintain essential documents
19. Perform study-related assessments as per protocol *
20. Complete company- specific log (if applicable)
21. Other (specify)_____
22. Other (specify) _____

*These tasks may only be performed by qualified individual as permitted by local law, medical or standard of care practices, or applicable required training as per job description or designation.

23. Safety Monitoring Register Template

- UNSW Safety Monitoring Register Template
- UNSW Adverse Event or Incident Event Case Report Form Example.