**RESEARCH PROTOCOL FOR OBSTRUCTIVE SLEEP APNOEA TREATMENT IN PEOPLE WITH PSYCHOSIS - CLINICAL TRIALS**

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| **1. Trial Details** |

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| **Protocol/Clinical Trial Title:** | Exploring treatment options for Obstructive Sleep Apnoea in People with Psychosis |
| **Protocol Number (Version and Date):** | V1 16/08/18 |
| **Amendment** **(Number and Date):** |  |
| **Trial Start Date:** | 1st January 2019 | **Trial Finish Date:** | 31st December 2021 |
| **Coordinating Principal Investigator Name:** | Jamilla Giles  |
| **Coordinating Principal Investigator Contact Details:** | Jamilla.giles@research.uwa.edu.au |

* 1. **Trial Summary (less than 300 words) including background, objectives and trial plan.**

Research suggests that Obstructive Sleep Apnoea (OSA) is highly prevalent in people diagnosed with a psychotic disorder such as schizophrenia, because of the high rates of obesity and metabolic syndrome. Despite the severe, negative consequences of OSA on cognition and daytime functions, research into treatments has been neglected in this group. While Continuous Positive Airway Pressure (CPAP) is the ‘gold standard’ in the general population, it is not well tolerated by people with severe mental illness, and CPAP adherence which is low in the general population, is lower still in those with mental illness (Lin & Winkelman, 2012; Parker, Johnston, Lane, Dark, & Siskind, 2017; Seeman, 2014). The overall aim of this research is to explore alternative treatment options for OSA in psychotic disorders. Specifically, the aims are to 1) qualitatively explore attitudes and preferences for CPAP and non-CPAP treatments (e.g. oropharyngeal exercises, positional therapy and dental appliances), and 2) to test the efficacy and tolerability of three previously unexplored treatment options for Obstructive Sleep Apnoea (OSA) and previously tested Continuous Positive Airway pressure (CPAP) in people with psychosis. The trial will run as 13 single case-experimental designs (SCED) using a bi-phasic A-B-A design or multiple baseline A-B design over 16 weeks. SCEDs operate by participants acting as their own baseline in non-treatment phases (A), and then comparison in treatment phases (B), based on predetermined measures. This study will use mixed-methods of qualitative and quantitative data to ascertain tolerance and efficacy of treatment devices. The outcome measures in this study will look at 1) OSA severity, 2) Quality of life, 3) Cognitive Functioning and 4) Severity of Psychosis Symptoms. All conditions have shown a reduction of OSA severity in the general population with mixed results for reducing clinical symptoms, improving quality of life and cognitive functioning.

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| **2. Rationale / Background** |

* 1. **Summary of findings from previous clinical and non-clinical projects, relevant to this proposed trial.**

Obstructive Sleep Apnoea (OSA) is a chronic sleep disorder that affects anywhere between 9-38% of the general population with prevalence rising in males and as age increases (Senaratna et al., 2016, 2017). It is caused by the repetitive narrowing or collapse of the upper airway during sleep, which results in cessation (apnoeas) or reduction (hypopnoeas) of airflow. Apnoeas and hypopnoeas result in oxygen desaturation, arousals from sleep and sleep fragmentation. There are severe, consequential effects of OSA on health (increased mortality and morbidity), quality of life (excessive daytime sleepiness, fatigue) (Flemons & Tsai, 1997), mental health (depression) (Ejaz, Khawaja, Bhatia, & Hurwitz, 2011; Guilleminault et al., 1988), and cognition (Olaithe, Bucks, Hillman, & Eastwood, 2018)*.* Additionally, the indirect and long-term effects of the disorder are extensive. People with OSA are estimated to consume 70% more healthcare resources than matched controls (Tarasiuk et al., 2005) and, if left untreated, have reduced life expectancy (Punjabi et al., 2009).

Approximately 20% to 40% of people with psychosis have OSA, which is twice general population rates (Myles et al., 2018; Stubbs et al., 2016). Precise prevalence figures are difficult to obtain, because few people with a psychotic illness complete an overnight sleep polysomnography (PSG) assessment to obtain a formal diagnosis (Parker et al., 2017). Contributing factors include fear about hospitals and being physically restrained, paranoia about laboratory equipment, and anxieties about being physically examined (Iwata, Strydom, & Osborn, 2011).

OSA is most commonly, and effectively, treated with adherent use of Continuous Positive Airway Pressure (CPAP). CPAP devices apply air pressure via the nose and/or mouth to prevent the pharyngeal airway from narrowing or collapsing (Sullivan, Berthon-Jones, Issa, & Eves, 1981). CPAP treatment improves functional outcomes and quality of life (Campos-Rodriguez et al., 2016; Weaver et al., 2012). However, despite being the ‘gold standard’, adherence is low in the general population (34.1%;Rotenberg, Murariu, & Pang, 2016). In people with psychosis, issues impacting on CPAP usage include financial hardships, as well as adherence. Anecdotally, compliance in people with schizophrenia is thought to be very low (Lin & Winkelman, 2012). Despite best efforts in helping patients adjust to CPAP, people report difficulties adjusting to the CPAP mask and needing intensive support from clinical teams (Seeman, 2014).

Only a handful of case studies exist of CPAP in psychosis. These show benefits of CPAP include: reduced frequency of psychotic symptoms (Karanti & Landen, 2007; Lee, Chiu, & Chen, 1989) and negative symptoms, improvements in sleep (Sugishita, Yamasue, & Kasai, 2010), and improvement in attention and executive functions (Boufidis et al., 2003). By contrast, another case study documented an acute relapse induced by CPAP therapy (Chiner, Arriero, Signes-Costa, & Marco, 2001). The paucity of large-scale trials of OSA treatment in psychosis, in particular with CPAP, is suggestive of the difficulties faced in this area of research.

It is, therefore, important to explore alternative treatments for OSA for people with psychosis, in whom efficacy has not yet been reported. Alternative treatment options are as follows:

Mandibular advancement splints (MAS) are currently regarded as a second-line therapy for OSA, because they completely alleviate OSA in approximately 40% of patients (Sutherland & Cistulli, 2011). They are similar to a mouthguard. When fitted to the teeth, a MAS pulls the lower jaw forward. This increases the breathing area and supports the upper airway (Lim, Lasserson, Fleetham, & Wright, 2006). MAS are often recommended to patients with mild-to-moderate OSA or for patients with severe OSA who cannot tolerate CPAP (Kushida et al., 2006). Short-term, randomised control trials have shown that patients comply with MAS therapy better than CPAP and that patients generally report preferring MAS (Gagnadoux et al., 2009; Phillips et al., 2013). MAS therapy improves quality of life, somatic and cognitive symptoms and reduces excessive daytime sleepiness (Nordin, Stenberg, & Tegelberg, 2016). Thus, MAS is a treatment option with few adverse effects, and much higher compliance rates than CPAP**.**

Positional therapy is based on the observation that apnoeas and hypopnoeas are often more prevalent when the person is sleeping lying on their back (‘supine position’). It is estimated that this affects approximately 56% of people with OSA (Levendowski, Seagraves, Popovic, & Westbrook, 2014; Mador et al., 2005). This phenomenon is diagnosed by PSG and is termed Positional OSA. Current treatments range from simplistic tennis balls taped to the inside of a pyjama shirt to prevent the OSA patient from lying on their back, to high tech devices which gently alert the patient when they are lying supine, using vibrations. There is some evidence that positional therapy restricts supine sleep, reduces OSA symptoms, improves sleep architecture and continuity, and reduces depressive symptoms (Levendowski et al., 2014). The therapy is recommended for positional OSA in people who cannot tolerate CPAP (Booth, Djavadkhani, & Marshall, 2018). Devices which address positional therapy include the Night Shift sleep positioner (Levendowski et al., 2014).

Lastly, there is mixed evidence in the field of oropharyngealexercises as a treatment for OSA, which claim the exercises help to strengthen the upper airway muscles, and prevent the collapse of the airway during sleep (Kandasamy & Dharamsi, 2013; Puhan et al., 2006). Frequent practice of oropharyngeal exercises reduces snoring (Ieto et al., 2015), significantly decrease neck circumference, number of apnoeas, and daytime sleepiness (Mohamed, Sharshar, Elkolaly, & Serageldin, 2017) and increase sleep quality (Guimarães, Drager, Genta, Marcondes, & Lorenzi-Filho, 2009). Oropharyngeal exercises are best recommended for mild to moderate OSA. One emerging area of research suggests the didgeridoo instrument as a potential useful tool for incorporating oropharyngeal exercises. It is hypothesised that the circular breathing required to play the instrument leads to the strengthening of airway muscles. OSA trials involving didgeridoos show decreased daytime sleepiness and reduction of apnoea-hypopnoea arousals but no difference in sleep quality or quality of life outcomes compared to controls who were put on a waiting list for lessons (Puhan et al., 2006). It could be that oropharyngeal exercises simply reduce symptoms of OSA rather than controlling the sleep disorder, however evidence is limited and the treatment has only been trialled in general population samples.

None of the three treatment categories mentioned above has been trialled in people with psychosis. Thus, the variety of treatment options available is severely lacking, with no research being conducted on tolerance and efficacy of non-CPAP treatments in this population.

* 1. **Name and description of the intervention or product(s) used in this trial, including investigational product(s) and comparator product/s (if applicable). Include status of product registration (i.e. registration on Australian Therapeutic Goods Registry, or equivalent).**

Mandibular Advancement Splint (MAS) – for this trial we will be using the BluePro MAS which has shown comparable efficacy in reducing OSA severity to custom-made MAS (Gagnadoux et al., 2017). The reason for using a mid-level device is due to the cost of the custom-made MAS (often provided by Somnodent) being almost double the cost of the BluePro, which was out of the studies’ budget. It is expected that participant’s will not be significantly disadvantaged by using a middle range version of the MAS. Blue Pro is not listed on the ATG registry.

For positional therapy, the Night Shift TM device will be used. Night Shift is the most advanced technology available for positional therapy and can be used on its own or in conjunction with CPAP and MAS. This device is not listed on the ATG registry.

For the CPAP condition, the exact CPAP device used will be the one that is prescribed by the sleep technician/doctor to the participant for the duration of their treatment trial. The participant will simply be completing the outcome measures for the study and will not have their treatment provided for them for free unlike the other conditions.

For those in the didgeridoo condition, participants will have custom-made PVC didgeridoos according to participant’s height, weight and mouth shape. These will be made by the director of Creative Native – Jilan. PVC or plastic didgeridoos are often recommended as the starting place for beginner students to learn the techniques of playing the didgeridoo as they are more cost effective and easier for students to use. Similarly, in the only trial of didgeridoos as therapy for OSA to date, plastic didgeridoos were constructed for participants (Puhan et al., 2006). Didgeridoos are not yet a formally recognised treatment option for OSA however, many didgeridoo shops and teachers are aware of students learning the instrument to manage OSA severity.

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| **3. Trial Aims / Objectives / Hypotheses** |

* 1. **Detailed description of the specific primary and secondary objectives and the purpose of the trial. Describe any hypotheses that will be tested.**

The broad aim of my research will be to explore the feasibility, tolerability, and preferences of different treatment options for OSA in people diagnosed with a psychotic disorder. Specifically, I will:

1. conduct a qualitative study to better understand people with psychotic illness’ experience of OSA, their perspective about the diagnosis process and any treatments which had been sought, and their views about different treatment options (Study 2)
2. conduct a series of single-case example design studies of different treatment approaches - Didgeridoo playing (Puhan et al., 2006), NightShift Positional Therapy (Levendowski et al., 2014), Mandibular Advancement Splints (MAS), as well as CPAP (Study 3).

Study 2: Due to its qualitative research design, there are no hypotheses for this study. However the study will be broken into two research questions; 1) what is their personal experience of OSA diagnosis (polysomnography) and CPAP treatment, and 2) to what extent are participants interested in engaging in alternative therapies to CPAP (e.g. Mandibular splints, Positional Therapy, or oropharyngeal exercises)? Discussions will centre on what are the perceived advantages and drawbacks of each treatment? What are the potential barriers to taking up these treatment options (financial, psychological, personal, physical, etc.)? What would help or assist them in engaging with these treatment options?

Study 3: This trial has two aims, primarily to test the efficacy and tolerability of OSA treatment devices in people with psychosis and secondly, to show a difference on outcome measures such as OSA severity, psychosis severity, cognitive functioning and quality of life.

For the primary aim, it’s hypothesised that CPAP may show the most efficacy in reducing OSA severity and symptoms, however, the other conditions will yield greater tolerance and adherence from participants. For the secondary aim, it’s expected that participants in each treatment phase (B) should show a difference on outcome measures such as reduced OSA severity, improved clinical symptoms, cognitive functioning or quality of life compared to non-treatment phases (A) if the treatment is working.

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| **4. Trial Design** |

* 1. **Primary endpoints and the secondary endpoints, if any, to be measured during the trial and how they will be measured. *For further information refer to the TGA*** [**“Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)” 2000.**](http://www.tga.gov.au/industry/clinical-trials-note-ich13595.htm)

Baseline data will include a telephone call or text with a link to a mobile/web version of the Health Status questionnaire (using REDCap) on 3 occasions spread over 7 days, asking about ‘Health Status’. The health status questionnaire comprises seven brief questions about sleep quality, function and symptomology rated on a 5-point Likert scale. The phone calls/texts will happen once every 2-3 days. The same questions will be asked during the treatment phase (every two weeks during check-up), and once at follow up (1 month after the end of the treatment trial). It’s expected that participants in each treatment phase (B) should show a difference on outcome measures such as lower OSA severity, improved clinical symptoms, cognitive functioning or quality of life compared to non-treatment phases (A).

Check-up points: In addition to a health status questionnaire, every 2 weeks during treatment, questions will be asked about ‘Treatment status’. Seven questions will ask about the participant’s usage and tolerance of their treatment, including one open-ended question.

Follow up: Each condition has two follow ups, one at the end of the initial eight-week treatment trial and a one month follow up post-treatment, to reassess outcome measures and receive post-intervention questionnaire data.

Pre-and Post-Treatment measures will be collected face-to-face pre-treatment, post-treatment and at follow up four weeks after treatment has concluded. Measures include questionnaires about sleep such as the Berlin Questionnaire (BQ; Netzer, Stoohs, Netzer, Clark, & Strohl, 1999) for overall OSA symptoms, the Epworth Sleepiness Scale (ESS; Johns, 1991) for daytime symptoms of OSA and the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989) for night-time symptoms and functional consequences of OSA. Cognitive functioning will be assessed for changes in verbal fluency, memory and attention using Category Fluency (E. Strauss, 2006), verbal paired association (Wechsler, 1997) and trail making (Reitan, 1955) tasks respectively. Clinical symptoms will be measured using the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) and quality of life will be measured using the 12-item short form of the Health Survey (SF - 12; Ware, Kosinski, & Keller, 1996).

OSA severity will be measured using ApneaLink™ devices at pre- and post-treatment assessment and follow-up. The ApneaLink device measures nasal airflow, oxygen saturation, snoring, and pulse, and derives an apnoea-hypopnoea index (AHI).

Post-treatment: All participants will take part in a post-intervention feedback interview (based on the Change Interview; Elliot, Slatick, & Urman, 2001) to determine what they liked and disliked about the treatment to inform future clinical trials. Should a participant wish to cancel their participation in the study before the end of the trial, they will be asked if they would like to complete the post-intervention interview and outcome measures.

* 1. **Type and design of the trial to be conducted and a schematic diagram of the trial design, procedures and stages**

Study 2 (qualitative study): The first contact on the telephone will determine whether participants meet inclusion criteria (section 4.3). A mutually agreeable time will be made at a NMHS MH Community Clinic service location that suits them. At this appointment, the PI will seek signed informed consent. A brief questionnaires will ask background questions (e.g., age, gender, level of education, key dates of sleep/psychiatric diagnoses, previous treatments undertaken), before the qualitative interview. Together, the informed consent, questionnaire and the interview are expected to take approximately 1.5 hours. Interviews will be audio-recorded with participants’ permission. Participants will be offered breaks when needed.

Study 3 will conduct a series of single case example designs with participants acting as their own baseline for comparison of treatment effects (Smith, 2012), using a bi-phasic A-B-A design for the Mandibular Advancement Splints, Night Shift and CPAP conditions (with B condition reflecting a treatment condition). It is expected that participants in each treatment phase (B) should show a difference on outcome measures such as lower OSA severity, improved clinical symptoms, cognitive functioning or quality of life compared to non-treatment phases (A).

For the oropharyngeal (didgeridoo) condition, a multiple baseline A-B design will be used, as the physiological effects of didgeridoo playing on throat muscles cannot be withdrawn fully after exercise cessation, unlike the other three conditions (where physiological effects are directly and temporarily linked to the usage of the device). As such, this would skew the baseline measurements of those in the didgeridoo condition at the one month follow up. A multiple baseline design means that participants will have differing amounts of time for collecting baseline data, before the treatment begins (e.g. three baseline data collection for Participant A, four baseline collections for Participant B etc.), whereas, a classic A-B-A design collects the same amount of baseline data from each participant. A comparison of the two designs is shown in the graphs below, with a standard A-B-A design on the left and multiple baseline A-B design on the right.



Study 3 will comprise of one of the treatment conditions, as well as four face-to-face appointments (baseline, pre- and post-treatment assessment and follow-up at the sixteenth-week time point), and seven short ‘check-up’ points (three times before treatment to establish a solid baseline, and every two weeks during treatment). The ‘check-up’ points will be conducted either via phone call or a text (according to the person’s preference), and will work to determine that participants are well, to help troubleshoot and answer any questions they might have, to check that participants are adhering to their treatment options, and to monitor changes in key symptom dimension across baseline and treatment phases (in addition to monitoring change more comprehensively during face-to-face appointments). At the check-up points, change in key symptom dimension will be assessed with questions about Health Status (7 questions), and questions about treatment acceptability and side effects with Treatment Status (6 questions). The check-up will be conducted with phone call or with text with link to an online survey (through secure REDCap server and comprising no personal identifying information).

After an initial telephone call verifying the screening and eligibility criteria (see section 5.2) participant and PI will mutually agree on an available time for Session One (baseline) at a mental health service location that suits them.

SESSION 1 (BASELINE) at the first face-to-face appointment (lasting about 1.5 hrs), the session will include history taking (sleep problems and psychiatric issues) and questions about demographic info using a Clinical Sleep Interview.

A brief psychoeducation session ≈30 minutes about OSA will also be delivered (see Appendix A). Brief psychoeducation is necessary so as to ensure that all participants have the same basic level knowledge about OSA. The contents will be derived from the Australasian Sleep Association and Sleep Health Australia, and resources and flyers will be especially adapted for consumers, with consumer input and co-production. While psychoeducation may be argued to provide some active treatment component properties, psychoeducation in itself is not sufficient as an intervention for OSA and is therefore not expected to be a determining influence in the device’s outcome. Furthermore, psychoeducation is a core and basic foundation of all treatment approaches and it would be unethical for us to trial a new intervention approach without providing basic and minimum information about OSA.

Psychoeducation about OSA will comprise of: **1. OSA: What is it?** Aim: to provide explanations about what is widely known about the sleep disorder within a normal continuum context. **2. What are the symptoms of OSA?** Aim: to explain the common symptoms of OSA to help participants identify symptoms within themselves and others around them with similar mental health conditions. **3. How is OSA diagnosed?** Aim: to explain the process of diagnosis for the sleep disorder using Polysomnography. **4. How is OSA treated?** Aim: To explain the many things one can do to treat or reduce severity of OSA e.g. weight loss, drinking less alcohol, minimising use of sleeping tablets etc.

Participants will then be booked in for their next face-to-face visit (pre-treatment outcomes assessment) and will be told they will be contacted three times (by phone and texts) over the next week to collect baseline measures of ‘health status’.

CHECK-UP POINTS (pre-treatment): During the next week, The Principal Investigator will contact participants every 2 or 3 days (depending on participant or PI availability) by phone or texts to ask seven short questions (‘Health Status’ questions) using a 5-point Likert scale about the participant’s quality of sleep the night before, their impact of sleep on daily functioning and about night and daytime symptoms of OSA. These results will form a solid baseline measurement of OSA symptoms and severity pre-treatment. The same questions (Health Status) will be asked every two weeks during treatment phase, again at post-treatment assessment (week 9) and at the one month follow up (week 12) (with additional questions asking about treatment adherence and any issues with the devices).

CHECK-UP POINTS (during-treatment): In addition to a (7 question) Health Status questionnaire (as above), every 2 weeks during treatment, questions will be asked about ‘Treatment status’ at check-up points. Six 5-point Likert scale questions and one open-ended question will ask about the participant’s acceptability, usage, tolerance of their treatment as well as any issues encountered.

SESSION 2 (PRE-TREATMENT). At the second face-to-face session, participants will complete their pre-treatment outcome measures assessment.

The same measures will also be collected face-to-face at post-treatment assessment and follow-up. Questionnaires and tasks include:

* The Epworth Sleepiness Scale (ESS)- assesses sleepiness
* The Berlin Questionnaire (BQ)- assess risk for OSA
* The Pittsburgh Sleep Quality Index (PSQI) – assesses sleep and impact of sleep problems
* The Brief Psychiatric Rating Scale (BPRS) – assesses severity of psychotic symptoms
* The Short-Form Health Survey (SF-12) – assesses everyday functions
* Digit Span (forward/background) – assesses attention
* Trail Making Task (Reitan, 1955) – assesses attention, speed, and executive functions
* Memory passage learning – with 1 and 5 minute recall, and recognition – assesses memory
* Verbal Paired Association Learning Test (Weschler, 1997) – assesses memory and fluency
* Category Fluency (Strauss, 2006) – assesses executive functions and fluency
* Symbol Digit Modality Test (Smith, 1999) – assesses speed of responding

The cognitive tasks are needed because OSA causes severe cognitive deficits, in the area of attention, memory, and executive functions. These measures have been carefully selected because they are brief (less than 20 minutes total), well tolerated in this clinical group, are sensitive to change, and likely to be impacted by OSA.

In addition, all participants will be asked to undergo three optional overnight sleep studies with an ambulatory (portable) home based device (ApneaLinkTM). ApneaLink is a simple, light weight device, which is worn as a chest belt while the person is asleep in the person’s own home/bed. The ApneaLink device measures nasal airflow (with nasal cannula), oxygen saturation, snoring, and pulse (finger oximeter), and chest breathing effort (with chest belt), from which it derives an apnoea-hypopnoea index (AHI). This is comparable to the AHI that is derived from participant’s initial diagnosis mechanism: Polysomnography. The device will be given to them during the first session, with explanations on how to fit it before bed time. It is easily explained and demonstrated, and clinical participants are often able to manage themselves. This will provide an important measure of OSA physiological change in treatment. ApneaLinkTM data will only be recorded at pre- and post-treatment outcome assessment (weeks 31, and 9 and respectively). The ApneaLink devices will need to be picked up from participant’s the day after they have been used so that the Principal Investigator can download the sleep study data. The Principal Investigator (PI) will follow strict safety protocols when visiting participant’s homes for collection of ApneaLink devices, and will always have a second person accompany the PI. In the event that the PI cannot get a second person to attend, the participant will be asked to drop off the ApneaLink device to their closest NMHS Mental Health Community Centre for collection by the PI. In addition, the PI will adhere to the following safety protocol for home visits, which is in compliance with the NMHS MH Community Visiting Policy.

1. The PI must have telephoned in advance to check the participant is happy for them to turn up and agree to a time. At the same time they can ask about any risks such as dogs, other people at the property.

2. The PI will check with the treating mental health team that there are no identified risk issues to going to the participant’s home.

3. Visits must always be in pairs.

4. The PI will tell a designated person (CPI: Flavie Waters) where and when they are going and confirm when they return.

5. The PI and accompanying persons will have charged mobile phones and the number for the police on speed dial.

6. If the PI has any concerns about risk they will not go to the home and they will ask the participant to drop off the ApneaLink at their local community mental health clinic.

These devices have been used in this clinical population before, as a part of a Graylands audit by Prof Flavie Waters, and are safe and relatively well tolerated by some (although not all) participants. Accordingly, some participants may wish to opt out of the ApneaLink overnight study should they feel uncomfortable or unsafe.

It is possible that a participant may want to switch to a different treatment group or try a different treatment after completion of their allocated treatment. This will be supported in principle, and unlikely to affect results given that the current methodological design ensures that each condition has own baseline, but subject to the following conditions: (i) Participants should complete the treatment arm they are currently enrolled in if at all possible, (ii) baseline measurement will need to be collected again, and (iii) if budget and resources are available.

Participants undertaking CPAP and Night Shift also have their own objective measures built into each device. Measures included for CPAP are: hours device is used throughout the night, number of nights where hours used is >4hrs, pressure and leak of the mask, and an Apnoea-Hypopnoea Index (AHI). For Night Shift positional therapy, objective measures are broken into three categories: sleep quality, positional feedback and snoring. The measures are further broken down into: number of supine (lying on back) attempts, sleep movement and intensity, sleep position (supine, upright, left, right or prone) and snoring intensity (decibels) and frequency.

TREATMENT DETAILS:

All participants will be given their respective treatment device in week one although each condition will require different time commitments (see below), and measurements:

**Mandibular advancement splints**: Require one consultation prior study by a dentist including an X-Ray, and mold fitting of the splint (occurring around 2-3 days before pre-treatment assessment). A second consult for appliance adjustment will be needed by a Dentist two weeks after receiving the device.

**Oropharyngeal exercise (Didgeridoo):** digeridoo lessons will be required, whereby participants will have to attend four lessons and practice at least five times a week in between lessons to build up their upper airway muscles (Puhan et al., 2006)

**Night shift Positional therapy device and CPAP**: Participants have the device available to them for the full 8 weeks of the study which they will be encouraged to use as much as they can (a minimum of 4 hours a night (e.g. half of the time based on an 8hr sleep cycle) in a 8 week period to determine that participants have used the devices and treatment was successfully implemented). CPAP has device check-up and adjustment points at week 2, 3 and 4 of the trial, whereas Night Shift has only one device review offered in week 2 of treatment.

SESSION 3 (POST-TREATMENT). At post-treatment assessment (week 9), participants will undergo questionnaires again as per pre-treatment, as well as an ApneaLink study. At this point all participant’s treatment trial has ended. The nature of the SCED’s is that they can be tailored to each participant and thus, the researcher can wait until the participant has finished their prescribed treatment trial to complete the post-treatment assessments.

They will also have the opportunity to provide feedback about any changes that they have noticed due to the intervention, what they attribute these changes to, helpful, unhelpful, and missing aspects of the intervention, feedback about their experience participating in the research study itself, and any suggestions for future research (based on the Change Interview; Elliot, Slatick, & Urman, 2001).

SESSION 4 (follow-up). For the final follow up (week 13) after participants have gone 4 weeks without using the treatment device, participants will be invited to complete the questionnaires and ApneaLink overnight sleep study again.

Projected timelines and activities are shown in the table below.

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|  | **A: Pre-Treatment Phase****(Baseline)** | **Pre-treatment Assessment** | **B: Treatment Phase** | **Post-Treatment Assessment** | **A: Follow-Up**  |
| **Week** | **-2** | **-1** | **0** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **12** |
| **Days** |  | 2-3 | 4-5 | 6-7 |  |  |  |  |  |  |  |  |  |  |  |
| **Activity timeline for all conditions** |
| Health Status |  | ✓ | ✓ | ✓ |  |  | ✓ |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ |
| Sleep Interview | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Info/Consent | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| OSA Psychoeducation | ✓ |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| Treatment Status |  |  |  |  |  |  | ✓ |  | ✓ |  | ✓ |  | ✓ | ✓ | ✓ |
| Epworth Sleepiness Scale |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| Berlin Questionnaire |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| PSQI |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| BPRS – Clinical Symptoms |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| SF-12 – Quality of Life |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| Cognitive Tasks |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ | ✓ |
| ApneaLink |  |  |  |  | ✓ |  |  |  |  |  |  |  |  | ✓ |  |
| Post-Intervention Interview + Side Effects |  |  |  |  |  |  |  |  |  |  |  |  |  | ✓ |  |
| **Condition-specific timelines** |
| CPAP device check-ups and adjustments |  |  |  |  |  |  | ✓ | ✓ | ✓ |  |  |  |  |  |  |
| Night Shift check-up |  |  |  |  |  |  | ✓ |  |  |  |  |  |  |  |  |
| Receive MAS |  |  |  |  |  | ✓ |  |  |  |  |  |  |  |  |  |
| MAS Dental Consults |  |  |  | ✓ |  |  |  | ✓ |  |  |  |  |  |  |  |
| Didgeridoo Lessons |  |  |  |  |  | ✓ |  | ✓ |  | ✓ |  | ✓ |  |  |  |

* 1. **Measures taken to minimise/avoid bias, including randomisation and blinding.**

Neither randomisation or blinding will be taking place in this study as it is a quasi-experimental design due to the pre-requisite that participant’s must be prescribed for CPAP/MAS/Night Shift treatment based on their sleep study diagnosis report. It is arguable that this is more reflective of real life where participants are limited in their choice of OSA treatment based on their diagnosis and treatment recommendation as a result of their polysomnography study. Similarly, it is important that participants in this population are willing, so that they will adhere to treatment.

* 1. **Maintenance of any blinding records or randomisation codes and procedures for breaking codes.**

For all participants, a unique identifier code will be assigned to participants and used to identify all digital and physical data. No names will ever be listed on participant data and the document containing the allocation of unique IDs to participant names will be stored in a password protected document on the chief investigator’s password protected computer.

Study 2: Audio-recordings of interviews with participants will be transcribed into NVivo software verbatim, and then destroyed after transcription. At transcription, the names of participants will be coded, so that no identifying information is included within the transcripts. Participant names and codes and the corresponding transcripts will never be stored together within the same location to prevent re-identification of the data.

Study 3: Outcome measures will be collected either face-to-face (pre and post-treatment assessment and follow up) or through RedCAPS (health and treatment status questionnaires asked at baseline and every two weeks during treatment phase). Because clinical participants will be pre-screened by telephone (see above), they will be given a unique ID code to enter into RedCAPS to assist with identification (reimbursement and linkage with data from the other studies). Qualitative interviews audio recordings will be transcribed and destroyed as per study 2.

Data collection using pen and paper will only show unique ID, and not the name of participants.

All data will be stored securely within password protected files and hard drives, and will only be accessible to the researchers on the project. Participants will remain de-identified within the resulting thesis, journal articles, conferences, and other public presentations utilising the data, including the use of pseudonyms within the qualitative studies.

* 1. **Accountability procedures for the investigational product(s) including the placebo(s) and comparator(s) (if applicable).**

For those in the CPAP, MAS and Night Shift condition, participants will be closely monitored by their respective treating physician who the CPI will contact regularly to ensure the participant is managing treatment. In the conditions mentioned above, the treating physician (either dentist Dr Christopher Pantin or a sleep physician) are accountable for the safety and well-being of the participant during treatment. However, for all conditions, the CPI of this study will be using health status and treatment status questionnaires at two-week intervals during treatment, to check on the participant and ensure they are not at risk of an adverse event. During didgeridoo lessons, the CPI will be present at each lesson along with the participant and instructor to ensure the safety of the participant. The study is supervised by an experienced sleep physician Dr Ivan Ling, who will be on call for any health-related issues related to the OSA treatment. Any issues reported as part of the response to the treatment status questionnaire will be reported and discussed with the Chief Principal Investigator Dr Flavie Waters and if relevant, to Dr Ivan Ling who can advise if treatment needs to be stopped, adjusted or if the participant requires medical attention.

* 1. **Criteria for the termination of the trial. Description of the discontinuation criteria for individual participants, parts of the trial and entire trial.**

In the event of an adverse event happening, the trial will be discontinued. NMHS HREC will be notified of the events and the cessation of the trial along with the corresponding supervisors of the trial (Dr Flavie Waters, Dr Ivan Ling, and Prof. Romola Bucks).

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| **5. Source and Selection of Participants** |

* 1. **Source of participants - research population, sample size, source, and sampling frame (if possible, split by site if multicentre trial).**

Consumers will make direct contact with the investigator because he/she has seen a flyer (posted at MH clinic, elsewhere in community, mental health hostels, mental health service, and drop-in centres across Perth) because he/she was made aware of the study taking place. Sleep clinics (Mental Health Sleep Clinic at Graylands, and the SCGH Sleep Clinic) also have a database of individuals who have received care or treatment at the sleep clinic, and who have agreed to be contacted of the purpose of research and provided consent to be contacted should a project require participants with sleep problems. The process will be as follows: (i) The researcher provides sleep clinic with a list of inclusion criteria (see 4.3), (ii) the sleep clinic will identify individuals, and will let them know about the research opportunity. If they are interested, potential participants will be invited to contact the researchers directly.

Posters and flyers will be distributed in the waiting areas of the sites, with contact details for the Principal Investigator (phone number and email address) for potential participants to contact if they are interested in finding out more about the study. Interested MH clinicians may also assist in showing flyers to potentially suitable participants e.g. if they have been referred for a sleep study through the Graylands Mental Health Sleep Clinic.

For clinical participants in Study 2 and 3, participants will contact the Principal Investigator (Jamilla Giles) through the contact details provided. At this point, their eligibility to participate in the research project will first be assessed with an informal telephone conversation, assessing whether the participant is over 18 years old, and whether they have a combination of; i) a current diagnosis of a psychotic disorder i.e. schizophrenia spectrum disorder or bipolar depression with psychosis symptoms, and ii) they have been referred for a sleep study because of suspected Obstructive Sleep Apnoea (Study 2), OR been formally diagnosed via Polysomnography (PSG) with either OSA or Positional OSA (Study 3), OR they have been prescribed CPAP or Mandibular Advancement Splint treatment as a result of OSA diagnosis PSG (Study 3). It is not necessary for participants to have completed treatment or to sleep study, as information about refusal is also worthwhile and interesting.

Only people who are capable of providing informed consent will be eligible to participate. After the potential participant has contacted the Principal Investigator and has met the initial screening criteria, they will be asked for the name and the contact details of their case manager or treating clinician to ensure that they agree with the person taking part. The case manager will then be asked to confirm the potential participant’s suitability for the study, and that the person is able to provide informed consent for the research.

For Study 2: Up to 20 people diagnosed with psychosis (schizophrenia-spectrum disorder, other psychosis, including anxiety or mood disorders with psychotic features, as diagnosed by their mental health worker) and a diagnosis of OSA will be required for this study. Qualitative study methods require that recruitment continues until a sufficient number has been achieved for data saturation. In line with previous studies, we expect this number to be no more than 20. As consumers may be difficult to recruit and retain, each participant will be offered to take part in study 3 as well, and may choose to participate in either/both studies.

For Study 3: 13 people who complete the intervention. This may mean initially recruiting more participants, to account for attrition.

* 1. **Participant inclusion and exclusion criteria. Describe appropriate criteria for special risk populations (e.g. women of reproductive age, participants with disease states or organ impairment).**

Inclusion criteria for participants of Study 2 will include:

* A current diagnosis of psychotic disorder (schizophrenia-spectrum disorder, other psychosis, including anxiety or mood disorders with psychotic features, as diagnosed by their mental health worker)
* Referral made for an overnight sleep study or CPAP (whether the overnight sleep study or CPAP was completed by the participant or not)
* Aged 18+

Exclusion criteria include:

* Inability to provide informed consent
* Inability to communicate adequately in English
* Currently experiencing crisis or clinical instability (as assessed by their case manager)
* Aggression, problematic drug/alcohol usage associated with behavioral or security issues

The same inclusion and exclusion criteria listed above apply to the participants of Study 3 however these participants, as they are receiving treatment for OSA, will need to have the following additional inclusion criteria:

* All participants must have a formal diagnosis of OSA confirmed by sleep study (PSG). We will ask them to sign a ‘consent to release’ document, seeking the results of the PSG detailing their sleep disorder diagnosis.
* Those in the Mandibular Advancement Splint and CPAP will need to have been prescribed those treatments prior to participating in the study (as evidenced in the sleep study results letter)
* Night Shift participants will need to have a diagnosis of Positional OSA as determined by their PSG data which will be obtained with participant’s consent from the provider of the diagnosis.
	1. **Participant withdrawal criteria (i.e. terminating investigational product/trial treatment) and procedures specifying:**

**(a) when and how to withdraw participants from the investigational product/trial treatment;**

**(b) the type and timing of the data to be collected for withdrawn participant(s);**

**(c) whether and how participants are to be replaced; and**

**(d) the follow-up for participants withdrawn from the investigational product/trial treatment.**

All participants are free to withdraw from the project at any stage and participation is voluntary. If participants decide to withdraw from the project, they must notify a member of the research team before they withdraw. If they withdraw consent during the research project, we will not collect additional personal information from them, although they will be made aware that data collected to the time they withdraw will form part of the research project results. If they do not want this, they must tell us before joining the research project.

In the event that participants withdraw from the study or stop treatment earlier than prescribed, they will be asked to voluntarily complete the outcome measures for a final time. If they do not wish to complete any or all of these measures, they must let us know and will be provided with a withdrawal of participation form.

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| **6. Treatment of Participants** |

* 1. **Description and justification for the treatments, interventions or methods to be utilised (including product name(s), dose(s), dosing schedule(s), route/mode(s) of administration and treatment period(s)) and the follow-up period(s) for participants for each investigational product/trial treatment group/arm of the trial.**

See section 4.2.

* 1. **The medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial.**

As the principal researcher is not administering the treatment, participants will be told by their sleep and/or health physician whom has prescribed treatment (for CPAP, NightShift and MAS conditions) what is to be permitted and not permitted during treatment. As part of screening for the study, participants will complete a clinical sleep interview to rule out any prevalence of a comorbid sleep disorder and if participants are on any medications which may affect their treatment experience.

* 1. **The procedures for monitoring participant compliance.**

Measures for compliance are inbuilt for the CPAP and Night Shift device however each participant will be asked as part of their treatment status questionnaires, how often they have used the treatment device within the last two weeks.

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| **7. Assessment of Efficacy** |

* 1. **Specification of the efficacy parameters**. Outcome measurements will include questionnaires about symptoms, cognitive change, functions, as well as physiological changes (as per 4.1).

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| **8. Assessment of Safety** |

* 1. **Summary of known and potential risks and benefits, if any, to research participants.**

Benefits of CPAP include: reduced frequency of psychotic symptoms (Karanti & Landen, 2007; Lee, Chiu, & Chen, 1989) and negative symptoms, improvements in sleep (Sugishita, Yamasue, & Kasai, 2010), and improvement in attention and executive functions (Boufidis et al., 2003). MAS therapy improves quality of life, somatic and cognitive symptoms and reduces excessive daytime sleepiness (Nordin, Stenberg, & Tegelberg, 2016). There is some evidence that positional therapy restricts supine sleep, reduces OSA symptoms, improves sleep architecture and continuity, and reduces depressive symptoms (Levendowski et al., 2014). Lastly, there is evidence that oropharyngealexercises help to strengthen the upper airway muscles, and prevent the collapse of the airway during sleep (Kandasamy & Dharamsi, 2013; Puhan et al., 2006). Frequent practice of oropharyngeal exercises reduces snoring (Ieto et al., 2015), significantly decrease neck circumference, number of apnoeas, and daytime sleepiness (Mohamed, Sharshar, Elkolaly, & Serageldin, 2017) and increase sleep quality (Guimarães, Drager, Genta, Marcondes, & Lorenzi-Filho, 2009). OSA trials involving didgeridoos show decreased daytime sleepiness and reduction of apnoea-hypopnoea arousals but no difference in sleep quality or quality of life outcomes compared to controls who were put on a waiting list for lessons (Puhan et al., 2006). It could be that oropharyngeal exercises simply reduce symptoms of OSA rather than controlling the sleep disorder, however evidence is limited and the treatment has only been trialled in general population samples

For study 2, there is an unlikely but small risk that interview questions may lead to psychological distress. Because of this, participants will be interviewed at MH outpatient clinic, so that support is at hand if required. Participants will be made fully aware that they can stop the interview at any time. If they become distressed, the supervisor and the person’s case manager will be alerted.

For study 3, there is also a small risk that participants may experience physical discomfort or increased tiredness with one or more of the treatment options. However, there will be repeated and frequent contact by the Investigator (Jamilla Gilles) where any issues or problems can be discussed. Possible side-effects that can occur as a result of each treatment device include;

CPAP side-effects:

* Dry throat
* Blocked or runny nose,
* Irritated eyes,
* Feeling uncomfortable or uncomfortable pressure of mask,
* Anxiety during treatment and,
* Disturbing noise.

MAS side-effects:

* Aching teeth,
* Aching jaw,
* Splint falling out at night,
* Dry throat,
* Headaches,
* Nasal congestion,
* Ulcers

Night Shift and Didgeridoo side-effects:

* There are no known side-effects for either of these devices however, potential side-effects that could come up for NightShift are feeling uncomfortable, sore neck, feeling of choking or restricted breathing, and/or embarrassment from wearing device. Similarly, with didgeridoo practice, participants may get swollen lips, or, feel uncomfortable or embarrassed to practice the instrument.

There is small but potential risk that participants in the CPAP condition could have an induced psychosis, as seen in Chiner et al., (2001).

In order to mitigate the above risks, participants will have regular check-ins from the primary investigator to ask about the health status of the participant and of any negative symptoms/side-effects they are experiencing as a result of their treatment. Participants will fill out a treatment status questionnaire every two weeks during the eight week treatment trial, which contains side-effect specific closed-ended questions and one open-ended question for the participant to express anything else they have been experiencing. At the end of the treatment trial, participants will be asked a side-effect specific questionnaire according to their condition.This project is a part of a larger research program with people diagnosed with psychosis, where we monitor and support our participants very closely and regularly. Any adverse events will be immediately reported to the study’s supervisors, and to the NMHS MH HREC.

Additionally, all participants must be deemed clinically stable enough to participate (i.e., not currently experiencing a crisis or acute psychosis), and be able to provide signed informed consent. We will be working with the case managers closely throughout the study to ensure good communication about the process of the research and so that the consumers feel supported. At initial contact, the case manager will be liaised with to establish whether the consumer is able to provide informed consent, and to enquire whether there are any known reasons that would preclude the person from taking part (aggression, clinical stability, other issues).

The Student/Principal Investigator has a background in psychology, with a Bachelor of Science degree with honours in psychology. She will undertake NMHS MH First Aid, and Managing Aggression training, and will be fully supported as she starts her project with consumers. She will be trained in clinical and qualitative interviewing by her supervisor and will initially be working with consumers under supervision. The CPI and primary supervisor has been working with clinical populations including severe mental health issues for several years and has strong protocols to ensure risk management when working with these vulnerable populations. Any problems or queries will first be discussed with the supervisor. The consumer’s case manager will be alerted if concerning clinical issues arise during the sessions, and with consent from the consumer. Any emergencies will follow the NMHS emergency procedures.

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| **9. Data Management, Statistical Analysis and Record Keeping** |

* 1. **Description of the statistical methods to be employed, including timing of any planned interim analysis.**

Data will be downloaded to an SPSS database and de-identified at regular intervals and backed up to prevent loss of data. Statistical analyses will be conducted in SPSS, and will involve correlation, regression, and analyses of variance.

For Study 2, all qualitative interview data will be transcribed from audio-recordings into NVivo software verbatim and de-identified, and audio-recordings will be destroyed immediately after transcription. Interpretative phenomenological analysis and thematic analysis will be used to analyse the data in NVivo.

* 1. **The number of participants planned to be enrolled (if possible, include number at each site). Document the reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.**

Participants recruited from the aforementioned mental health services will be invited to take part in one or two of the studies being conducted, depending on their preference. The aim is to have approximately 20 and 13 sourced participants (studies 2 and 3 respectively). Qualitative study methods require that recruitment continues until a sufficient number has been achieved for data saturation. In line with previous studies, we expect this number to be no more than 20.

Participants will provide most of the data. Where data is missing (medications type/dose, diagnoses and dates), permission will be sought to access these participants’ medical records with a view to obtain details of diagnoses, medications, previous service utilization.

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| **Site** | **Number of Participants** |
| NMHS MENTAL HEALTH | 33 |

* 1. **The level of significance to be used**. P<0.05.
	2. **Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in the protocol and/or in the final report, as appropriate).**

No deviations from the original statistical plan are envisaged but if any arise, these will be updated in the protocol and will be described and justified in the following annual report and in the final report to the HREC.

Possible deviations from the statistical plan include: attrition, missing data or incomplete data.

* 1. **Information on how data will be managed, including coding for computer analysis and data handling (collection, storage, maintenance, security and archiving). Include details regarding these processes if the data is sent off-site (e.g. encryption). *Clinical trial records should be retained for a minimum of 15 years from the completion of the trial.***

For all participants, a unique identifier code will be assigned to participants and used to identify all digital and physical data. No names will ever be listed on participant data and the document containing the allocation of unique IDs to participant names will be stored in a password protected document on the chief investigator’s password protected computer.

For the group discussions as part of Study 2, all participants will be asked to maintain group confidentiality by not discussing any group content with people outside of the group and after the group has finished. Additionally participants will be asked to sign a consent form acknowledging their understanding and responsibility to maintain group confidentiality.

Audio-recordings of interviews with participants will be transcribed into NVivo software verbatim, and then destroyed after transcription. At transcription, the names of participants will be coded, so that no identifying information is included within the transcripts. Participant names and codes and the corresponding transcripts will never be stored together within the same location to prevent re-identification of the data.

Study 3: Outcome measures will be collected either face-to-face (pre and post-treatment assessment and follow up) or through RedCAPS (health and treatment status questionnaires asked at baseline and every two weeks during treatment phase). Because clinical participants will be pre-screened by telephone, they will be given a unique ID code to enter into RedCAPS to assist with identification (reimbursement and linkage with data from the other studies). Qualitative interviews audio recordings will be transcribed and destroyed as per study 2.

Data collection using pen and paper will only show unique ID, and not the name of participants.

All data will be stored securely within password protected files and hard drives, and will only be accessible to the researchers on the project. Participants will remain deidentified within the resulting thesis, journal articles, conferences, and other public presentations utilising the data, including the use of pseudonyms within the qualitative studies.

Data and information will strictly be stored in a locked cabinet in a locked office if in hard copy form, or on a secure password protected hard drive if electronic. Research data will be kept in safe and secure storage on the NMHS MH server at Flavie Water’s password protected drive and computer in a locked room, and at the University of Western Australia after the research project has been completed

When the study is completed, data will be retained for up to 25 years, as per the University of Western Australia’s retention and disposal schedule, and in compliance with section 2.1.1 of the Australian Code for the Responsible Conduct of Research, and the Western Australian University Sector Disposal Authority’s (WAUSDA) retention of research data, analysis, and results involving research trials.

Any personal information will be safely discarded according to section 5.7 of the Western Australian University Sector Disposal Authority’s (WAUSDA) guidelines. After the retention period, digital data and records will be securely deleted (i.e. over-written) with software for that purpose. Paper consent forms will be shredded through the University of Western Australia’s sector disposal methods.

* 1. **Procedure for accounting for missing, unused, and spurious (*false*) data.**

Any unused data will be safely secured if physical copies or password-protected if electronic. Any missing questionnaire data will be checked on the day of collection and clarified by the principal investigator with the participant. All closed-ended questions disseminated via REDCaps will be marked as requiring an answer before the participant can complete the next question, to avoid the likeliness of missing data. All ratings from Brief Psychiatric Interviews will be discussed with the study supervisor Dr Flavie Waters, to ensure rating accuracy. In the event that an ApneaLink study does not record overnight, or records erroneously, participants will not be asked to complete the measure again and other measures can be used to account for the missing data, such as the Treatment status questionnaire.

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| **10. Monitoring / Audit** |

* 1. **Statement that the trial investigators/institutions will permit trial-related monitoring, audits, and regulatory inspections, providing direct access to source data/documents. This may include, but not limited to, review by external sponsors, Human Research Ethics Committees and institutional governance review bodies.**
	2. Description of the procedures for monitoring and auditing.

This clinical trial will be monitored by the Principal Supervisor of this study, Dr Flavie Waters who will be in regular contact with the coordinating investigator to monitor (a) the rights and well-being of human subjects are protected. (b) The reported trial data are accurate, complete, and verifiable from source documents. (c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s). Monitoring and auditing of the project will be conducted by the NMHS MH REGO during the life of the project.

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| **11. Quality Control and Quality Assurance** |

* 1. **Statement that the trial will be conducted in compliance with the protocol, Good Clinical Practice and the application regulatory requirements.**
	2. Quality control & quality assurance measures to ensure quality of data.

This clinical trial will be quality assured by the Principal Supervisor of this study, Dr Flavie Waters who will be in regular contact with the coordinating investigator to ensure that (a) trials are conducted and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements and (b) each stage of data handling are reliable and have been processed correctly.

The coordinating investigator is responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the Principal Supervisor, and inspection by regulatory authorities.

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| **12. Ethics** |

* 1. **Description of ethical considerations related to the trial with particular reference to participant consent (including Participant Information and Consent Forms).**

Only people who are capable of providing informed consent will be eligible to participate. After the potential participant has contacted the Principal Investigator and has met the initial screening criteria, they will be asked for the name and the contact details of their case manager or treating clinician to ensure that they agree with the person taking part. The case manager will then be asked to confirm the potential participant’s suitability for the study, and that the person is able to provide informed consent for the research.

For studies 2 and 3, the Principal Investigator will then send the Information Sheet and Consent Form to the potential participant (by mail/email) so that they can read it ahead of time and discuss the research with their family or carer and/or friends as needed. Then, at the organised (first) appointment, an explanation of the study will be provided so as to obtain informed consent. Written informed consent will be obtained from the participant at this stage.

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| **13. Budget, Financing, Indemnity and Insurance** |

* 1. Budget, financing, indemnity and insurance, if not addressed in a separate agreement.

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| Funder Organisation Type (For All Sites) | Funder Organisation Name | Esitmate $ Amount of Any Funding (For All Sites) | Estimate $ Amount of Any In-kind-support (For All Sites) | Funding is Confirmed/Received or Being Sought |
| Government - state (WA) | NMHS Mental Health | 0 | 0  | Confirmed |
| University | University of Western Australia | $4411 | 0 | Confirmed |
| Sub-total  |  | $4411 |  |  |

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| **14. Publication**  |

* 1. **Publication and dissemination of trial results (including any limitations), if not addressed in a separate agreement. *In accordance with the Declaration of Helsinki (2008) every clinical trial must be registered in a publicly accessible database before recruitment of the first participant.***

The results obtained from this research project will be used by the Principal Investigator (Jamilla Giles) to submit a thesis to the University of Western Australia, to obtain a Doctor of Philosophy (PhD) degree, under the School of Psychological Science. This is expected to occur in 2022. This thesis is expected to be formatted as a series of papers, with the intention of submitting articles to peer reviewed journals and publishing along the way. Results will also likely be presented at conferences and other public presentations.

The key findings will also be disseminated broadly in media, to consumer groups, university/health agencies, conferences and workshops, staff professional development sessions, and through organisations’ newsletters in lay language, and the results will also be feedback to the community organisations and health services where participants were recruited from.

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| **16. Appendices**  |

Appendix A – OSA Pyschoeducation