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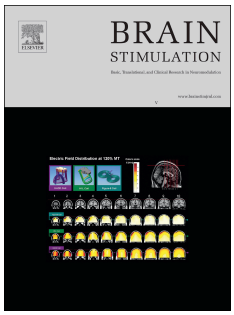

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Grace Curry, Teris Cheung, Shu-Dong Zhang, Susan Logue, Liadhan McAnena, Ruth Price, Julie J. Sittlington

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[Title page]

Repeated electrical vestibular nerve stimulation (VeNS) reduces severity in moderate to severe insomnia; a randomized, sham-controlled trial; The Modius Sleep Study

Author names and affiliations: Grace Curry[a] (g.curry@ulster.ac.uk), Teris Cheung[b,c] (teris.cheung@polyu.edu.hk), Shu-Dong Zhang[d] (sd.zhang@ulster.ac.uk), Susan Logue[a] (s.logue@ulster.ac.uk), Liadhan McAnena[a] (l.mcanena@ulster.ac.uk), Ruth Price[a] (rk.price@ulster.ac.uk), Julie J Sittlington[a] (jj.sittlington@ulster.ac.uk)

[a] School of Biomedical Sciences, Ulster University, Cromore Road, Coleraine, BT52 1SA, United Kingdom

[b] School of Nursing, The Hong Kong Polytechnic University, Hong Kong SAR, China

[c] The Mental Health Research Centre, The Hong Kong Polytechnic University, Hong Kong SAR, China

[d] School of Medicine, Ulster University, Londonderry, BT48 7JL, United Kingdom

Corresponding author: Julie Sittlington (jj.sittlington@ulster.ac.uk)

Conflicts of interest and funding

Neurovalens Limited (Belfast, UK), a medical device company, was sponsor of this study. They were involved in conceptualisation, study design, provision and postage of devices at no cost, and the decision to submit the article for publication. Devices were returned to Neurovalens at the end of the intervention period. The authors declare no conflicts of interest.

ABSTRACT

Background: Insomnia is a prevalent health concern in the general population associated with a range of adverse health effects. New, effective, safe and low-cost treatments, suitable for long-term use, are urgently required. Previous studies have shown the potential of electrical vestibular nerve stimulation (VeNS) in improving insomnia symptoms, however only one sham-controlled trial has been conducted on people with chronic insomnia.

Objectives/Hypothesis: Repeated VeNS delivered by the Modius Sleep device prior to sleep onset will show superior improvement in Insomnia Severity Index (ISI) scores over a 4-week period compared to sham stimulation.

Methods: In this double-blinded, multi-site, randomised, sham-controlled study, 147 participants with moderate to severe insomnia (ISI≥15) were recruited and allocated a VeNS or a sham device (1:1 ratio) which they were asked to use at home for 30 minutes daily (minimum 5 days per week) for 4 weeks.

Results: After 4 weeks, mean ISI score reduction was 2.26 greater in the VeNS treatment group than the sham group (p=0.002). In the per protocol analysis, the treatment group had a mean ISI score decrease of 5.8 (95% CI [-6.8, -4.81], approaching the clinically meaningful threshold of a 6-point reduction, with over half achieving a clinically significant decrease. Furthermore, the treatment group showed superior improvement to the sham group in the SF-36 (Quality of Life) energy/fatigue component (PP p=0.004, effect size 0.26; ITT p=0.006, effect size 0.22).

Conclusions: Modius sleep has the potential to provide a viable, non-invasive and safe clinically meaningful alternative treatment option for insomnia.

Keywords: insomnia, vestibular stimulation, sleep, brain, quality of life, RCT

Abbreviations: CBT-I (cognitive behavioural therapy for the treatment of insomnia), VeNS (electrical vestibular nerve stimulation), ISI (Insomnia Severity Index), PSQI (Pittsburgh Sleep Quality Index), SF-36 (RAND 36-Item Short Form Survey, Quality of Life), UK (Ulster University site consisting of participants resident in the UK and Ireland), HK (Hong Kong site consisting of participants resident in Hong Kong), AE

(adverse event), ITT (intention to treat analysis using last observation carried forward), PP (per protocol analysis), Wk0 (Week 0), Wk2 (Week 2), Wk4 (Week 4), Wk8 (Week 8), Wk16 (Week 16).

INTRODUCTION

Insomnia is a prevalent health concern; approximately one in three adults in the United Kingdom (UK), Hong Kong (HK) and other countries report symptoms of insomnia [1-4]. The clinical definition of insomnia varies, and so, therefore, do estimates of prevalence. The American Psychiatric Association estimates that approximately 10% of individuals meet their criteria for insomnia disorder, characterised by difficulty initiating or maintaining sleep and dissatisfaction with sleep quantity or quality [3]. Lack of sleep is associated with multiple adverse health effects including lower quality of life [5, 6], increased risk of accidents [7-9], depression [10-13], cardiovascular diseases [14-17] and impaired immune function [18, 19].

Pharmaceutical treatments are widely used in the treatment of insomnia. Although effective short-term, their associated side-effects (e.g., daytime fatigue, impaired cognition, impaired driving, dependence, withdrawal, and abuse [20-24]) limit their use and long-term use is not recommended [23-27]. Cognitive behavioural therapy for insomnia (CBT-I) is the first approach in most western countries as it is effective with minimal side-effects [1, 20, 22-24, 28, 29], but traditional Chinese medicine remains the preferred option in HK [30]. However, limitations of CBT-I include time, costs, and a shortage of trained clinicians [28]. Alternative treatment approaches, that are more clinically and economically feasible, are urgently needed.

The vestibular system detects changes in both head motion and position and is critical for balance and spatial orientation. The vestibular system is known to affect sleep, but the mechanism of action is unclear. Some hypotheses propose that the daily movement information provided by the vestibular system affect the suprachiasmatic nucleus and therefore circadian rhythm [31-33] or influence the orexinergic neurons in the hypothalamus, impacting sleep regulation, potentially by the build-up of adenosine [34-36]. Previous studies induced vestibular activation mechanically, with rocking resulting in accelerated sleep onset and increased duration of non-rapid-eye-movement sleep [37-39]. Electrical vestibular nerve stimulation (VeNS), a safe and potentially effective treatment for insomnia [40-44]; is achieved by delivering current to the skin over the mastoid process [45]; however, the only sham-controlled study evaluating the effectiveness of VeNS delivered prior to sleep was on younger adults with chronic insomnia and was performed in an artificial lab setting [44]. The present study aimed to explore the effect of repeated VeNS applied at home,

on adults experiencing insomnia symptoms. We hypothesised that repeated use of a VeNS device will show superior improvement in Insomnia Severity Index (ISI) scores over a 4-week period compared to sham stimulation.

METHODS

Study design

This randomised, double-blinded, sham-controlled trial was conducted at two sites: Ulster University, UK, and Hong Kong Polytechnic University, HK. Participants were asked to use their allocated VeNS device at home for 30 minutes daily over 4 weeks (UK 28 consecutive days; HK 5 days/week, 20 days total). Questionnaires; ISI [46], Pittsburgh Sleep Quality Index (PSQI) [47] and SF-36 (RAND 36-Item Short Form Survey, Quality of Life [QoL]) [48] were completed as indicated in Figure 1. The primary outcome was change in ISI score over 4 weeks (Wk0-Wk4). Data were collected via video call (UK); and face-to-face (HK). The trial commenced June 2022 and concluded January 2023.

[Insert Figure 1 here – black and white online and print]

Recruitment and participants

Individuals suffering from chronic, moderate to severe insomnia (as defined by ISI≥15) were recruited via social media advertisement, email circulations, and on-campus posters/flyers. Eligibility (see Table 1) was confirmed via an in-depth screening telephone call.

[Insert Table 1 here]

Randomisation and blinding

Double-blinded randomisation was completed post-enrolment using a block method (1:1 allocation; block size: 2 [UK] or 10 [HK]). UK participants were stratified by sex and randomised using an independently provided sealed-envelope system. For HK participants, an independent statistician used a computer-generated list of random numbers (www.random.org, accessed on 1 June 2022) using a stochastic minimization programme to balance participants' sex, age, and ISI scores. At Week 4 (Wk4), participants (and [UK] researchers) indicated whether they believed they were in the treatment or sham group or were unsure.

Intervention and sham control

The Modius Sleep (MS1000), a portable, battery-operated vestibular nerve stimulator, and a visually similar sham devices were provided by Neurovalens Ltd. (Belfast, UK) (Figure 2). Table 2 displays the active and sham stimulation applied. Participants were trained at Week 0 (Wk0, Baseline) on how to operate the device and position the electrode pads.

[Insert Figure 2 here – colour online, black and white print]

[Insert Table 2 here]

Study outcomes

Insomnia Severity Index

The ISI is a validated 7-item self-report questionnaire that measures participants' perception of their insomnia over the previous two-weeks [46]. The total ISI score is categorised as not clinically significant (0-7), subthreshold (8-14), moderate (15-21), or severe (22-28) insomnia. A decrease in score of ≥6 points is considered clinically meaningful [54]. Additional data were collected at Wk2 (UK), Wk8 and Wk16 (HK).

Secondary Outcomes

Pittsburgh Sleep Quality Index

The PSQI (completed at Wk0 and Wk4) is a validated self-report questionnaire which assesses sleep quality over one month [47]. It includes 19 items which generate 7 component scores: subjective sleep quality, latency, duration, efficiency, and disturbances, use of sleeping medication, and daytime dysfunction. Component scores are totalled to give a global score where a score >5 indicates a 'poor sleeper' vs a 'good sleeper' (diagnostic sensitivity 89.6%, specificity 86.5%) [47].

Health related Quality of Life (SF-36)

The RAND SF-36 (completed at Wk0 and Wk4) is a self-report QoL assessment tool. The 36 items generate 8 separately-assessed component scores: physical functioning, role limitations due to physical health, role

limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health.

Caffeine Diaries

Participants (UK) completed caffeine diaries (type, amount and time consumed) for one week prior to Wk0 and Wk4 appointments. Participants were asked not to change their caffeine intake during the study.

Compliance and Adverse Events

Compliance was monitored using the Modius Sleep iOS app. Data logs (usage, average current and electrical impedance) were reviewed by the clinical team. Duration (minutes) and number of sessions were used to calculate participants' mean number of weekly sessions; participants using the device <5 days per week were contacted by the study team to encourage increased usage.

Anticipated side effects of VeNS included discomfort/irritation behind the ears, vertigo/dizziness, mild-moderate nausea and headaches. Participants reported non-anticipated adverse events (AEs) and serious AE's as they occurred, and at Wk4. Reporting in UK was researcher-led, participants completed a questionnaire listing potential AEs; in HK, reporting was participant-led, only participants reporting AEs, completed this questionnaire.

Statistical analysis

Sample size was based on a pilot study [55] where baseline ISI score SD was 4.7 rounded to 5.0 as an estimate of SD for within-group ISI score change. Anticipating that the sham may have some placebo effect in reducing ISI score, our trial was powered to detect a difference of 3 points between the treatment and sham groups. Based on these parameters, n=60 per group was required to provide 90% power to detect the stated effect size, significance level of 0.05, using two-tailed two sample T test. Allowing for 15-20% dropout, target recruitment was n=144.

Data were analysed using SPSS 29.0, except for general linear hypotheses testing for which R (V4.1) was used. A per protocol analysis (PP) was carried out on participants who completed the study to Wk4. Intention-to-treat (ITT) analysis using last observation carried forward was used to address missing data for all participants with baseline-only data. Both analyses are presented throughout. For comparison, sensitivity analysis using multiple imputation was also performed for missing values which did not change study outcomes. Exploratory data collected at Wk8 and Wk16 was not statistically analysed due to the volume of missing data. Data are presented as mean$\pm$SD. A probability value of ≤ 0.05 was considered statistically significant, except where Bonferroni corrections were applied for multiple comparisons.

Internal consistency for the PSQI and SF-36 was determined using Cronbach's alpha.

Normality testing per intervention group was conducted for continuous variables using histograms and Q-Q plots. ISI scores were normally distributed, however change in ISI score, PSQI global scores, age, usage (average sessions per week), stimulation level and caffeine intake were not normally distributed therefore non-parametric tests were used.

Baseline between-group differences were determined using independent t-tests for ISI scores; Mann-Whitney U tests for age, caffeine intake, PSQI scores, and SF-36 scores; and X^2 tests for sex and ethnicity.

Associations between change in ISI score and usage and age were checked using Pearson Correlation, and between change in ISI score and sex using independent t-test.

Linear mixed modelling was used to compare between-group difference in ISI score over time (Wk0, Wk2 and Wk4). Age, sex, ethnicity, site and total usage were included as covariates; however, only age had a significant effect and therefore remained in the final model. General linear hypotheses testing was completed for between-group difference in ISI score from Wk0 to Wk4, in an age-adjusted model.

Independent t-tests were used to compare change in ISI scores between sites and to characterise those who were most likely to achieve a clinically significant reduction in ISI score (≥ 6) in the treatment group.

Between-group difference in the number of participants who achieved clinically significant reduction in ISI score was analysed using logistic regression.

For ISI, PSQI and SF-36 scores, Mann-Whitney U tests were conducted for between-group differences in the change from Wk0 to Wk4. Wilcoxon signed rank tests were used for within-group differences from Wk0 to Wk4 for PSQI, SF-36 and caffeine intake. Application of Bonferroni corrections gave a significance threshold of $p \leq 0.007$ for PSQI components, and $p \leq 0.006$ for SF-36 components.

Effect sizes were determined using $r = Z/\sqrt{n}$.

Between-site differences in usage and stimulation level were analysed using Mann-Whitney U tests.

Ethical consideration

Ethical approval for the UK was granted by Health and Care Research Wales and Wales Research Ethics Committee 7 (22/WA/0022, IRAS ID 301555) and for HK by the Human Subjects Ethics Sub-Committee, Hong Kong Polytechnic University (Ref: HSEARS20220320001). The study was registered at https://clinicaltrials.gov (ClinicalTrials.gov Identifier: NCT04452981). The HK protocol has been published [56], and the UK protocol is available on request.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Participants who met the eligibility criteria provided written informed consent at enrolment.

RESULTS

Of the 149 participants who enrolled, 147 completed a baseline appointment and were included in the study analyses (Figure 3). A total of twenty-three participants withdrew before Wk4, meaning 84.6% completed the study to end of intervention. There was no between-group significant difference in the number of withdrawals during the intervention period (n=12 (16.4%) and n=9 (12.2%); treatment and sham group respectively; X^2 [1, n=147] = 0.549, p=0.459).

[Insert Figure 3 here – colour online, black and white print]

Participants were mostly female (66.7%) and of Asian ethnicity (68.0%); age 40.8±13.5 years (range 19-72 years). At baseline, there were no significant differences between intervention groups (Table 3); for both cohorts, the mean ISI score category indicated 'moderate' insomnia, and the mean PSQI score indicated a 'poor sleeper'.

[Insert Table 3 here]

Caffeine intake did not change between pre-Wk0 and pre-Wk4 (ITT p=0.725; PP p=0.587) and therefore was not included as a covariate in analyses.

Compliance

For the 126 participants who completed the intervention (PP cohort), the mean number of weekly sessions completed was 5.8±1.73 (sham group: 5.8±1.48 and treatment group: 5.8±1.97; no significant between-group difference, p=0.393). Almost three quarters (71.4%) achieved a mean of ≥5 sessions/week (80.0%, 62.3%; sham and treatment groups respectively), and 7.14% (6.15%, 8.20%) had a mean of <4 sessions/week (sham and treatment groups respectively). There was no significant difference in usage between sites (5.7±1.88 [HK] and 6.0±1.42 [UK]; p=0.071). The mean stimulation level was 4.0±2.5, equating to 0.4mA (sham group: 3.9±2.6 and treatment group:4.2±2.5; no significant between-group difference, p=0.351).

Adverse events (AEs)

Twenty-two non-anticipated AEs (n=20 in UK) were reported during the intervention period, and one additional serious AE (minor cerebral vascular accident) that was not device related. Most (n=16) AEs were reported by the treatment group and were infrequent headaches/migraines (Table 4). One participant (treatment group) withdrew due to experiencing nausea and headaches after wearing the device.

[Insert Table 4 here]

ISI score

In both groups, ISI score decreased during the intervention (primary outcome: 3.14 [17.1%] vs -4.85 [24.5%] [ITT], -3.52 [19.2%] vs -5.80 [29.4%] [PP]; sham and treatment groups respectively; p<0.001 for both groups) (Figure 4). However, this improvement was significantly greater in the treatment group (p=0.010), with age having a significant overall effect on the model (p=0.004). General linear hypotheses testing also showed a significant between-group difference in change in ISI score from Wk0 to Wk4 (p=0.002) and estimated a participant in the treatment group to have a decrease in ISI score of 2.26 more than a sham group participant. Mann Whitney U test also showed significant between-group difference in change in ISI score from Wk0 to Wk4 (PP p=0.019, effect size 0.21; ITT p=0.047, effect size 0.16). In both intervention groups, ISI score decreased most from Wk0 (18.4, 19.8) to Wk2 (15.6, 15.2) then further to Wk4 (14.8, 13.9); at Wk8 (14.1, 13.9) and Wk16, scores remained low (14.2, 13.9) (sham and treatment group respectively) (Figure 4).

Half of the participants in the treatment group (31/61, PP cohort) achieved a clinically significant decrease in ISI score. Those who did were more likely than those who did not to have a higher ISI baseline score (21.4±3.90 vs 18.0±3.49 respectively, t[59]=-3.50, p=0.001) and be defined as having severe insomnia (n=14 vs n=4), have a higher baseline PSQI score (13.8±3.10 vs 11.8±3.48, t[59]=-2.38, p=0.021) and see the greatest improvements, over the intervention, in global PSQI score (-4.61±3.29 vs -2.07±2.78, t[59]=3.26, p=0.002), sleep quality (PSQI Component 1; -1.06±0.57 vs -0.50±0.63, t[58]=3.66, p=0.001), latency (PSQI Component 2; -0.81±0.87 vs -0.23±0.73, t[58]=2.79, p=0.007) and duration (PSQI Component 3; -0.81±0.70 vs -0.37±0.89,

t[59]=2.15, p=0.036), energy/fatigue (SF-36 Component 4; 17.3±13.9 vs 9.33±10.4, t[59]=-2.52, p=0.015) and emotional well-being (SF-36 Component 5; 16.90±14.2 vs 5.60±12.2, t[59]=-3.33, p=0.002).

There was no significant between group difference in the number who achieved a clinically significant decrease; p=0.164.

There were also improvements in the ISI categories for both intervention groups (Figure 5) with an increase in the number of participants in the "none" (+n9 and +n4) and "sub-threshold" (+n9 and +n27) insomnia categories, and a decrease in the "moderate" (-n12 and –n16) and "severe" (-n6 and –n15) insomnia categories (sham and treatment group respectively).

Change in ISI score (Wk0 to Wk4) was not significantly associated with age (ITT sham R=0.185, p=0.114; treatment R=-0.28, p=0.815; PP sham R=0.195, p=0.119; treatment R=0.062, p=0.635), sex (ITT sham male -3.42±5.15, female -2.96±4.64, p=0.703; treatment male -4.92±4.30, female -4.81±4.12, p=0.917; PP sham male -3.90±5.34, female -3.34±4.77, p=0.669; treatment male -5.86±4.05, female -5.78±3.85, p=0.938) or usage (PP sham R=0.124, p=0.327; treatment R=0.054, p=0.678). ISI response did not differ significantly between sites (ITT sham t[61]=0.475, p=0.637, treatment t[41]=-0.13 p=0.990; PP sham t[51]=0.433, p=0.667, treatment t[32]=-0.055, p=0.957).

[Insert Figure 4 here – colour online, colour print]

[Insert Figure 5 here – colour online, black and white print]

PSQI

Cronbach's alpha was 0.515 and 0.663 (PP) (ITT 0.541 and 0.690) at Wk0 and Wk4 respectively. The number of poor sleepers decreased, and the number of good sleepers increased, from WK0 to Wk4 for both intervention groups (Table 5).

[Insert Table 5 here]

The change in global score from Wk0 to Wk4 was -1.82 (14.6%) and -2.81 (21.7%) (ITT), or -2.08 (16.9%) and -3.36 (26.1%) (PP) (sham and treatment respectively). Change in PSQI global score did not differ significantly between groups in the ITT (p=0.118) or PP cohort (p=0.068).

An improvement in sleep efficiency was reported in the treatment group (ITT p=0.040, PP p=0.027), but after Bonferroni corrections were applied no significant between-group differences in change in PSQI component scores from Wk0 to Wk4 remained (all p>0.007) (Figure 6, Table 6).

Within-group analysis showed improvements in all PSQI components for the treatment group ($p \leq 0.003$), except medication, and improvements in sleep quality, latency, duration and disturbance ($p \leq 0.002$) in the sham group (Table 6).

[Insert Figure 6 here – colour online, colour print]

[Insert Table 6 here]

Health related Quality of Life

Cronbach's alpha was 0.861 and 0.854 (PP) (ITT 0.859 and 0.859) at Wk0 and Wk4 respectively. Improvements were observed for several items in the QoL (SF-36); after Bonferroni corrections were applied, the change in energy/fatigue remained significantly different between groups (ITT p=0.006; PP p=0.004) (Table 7, Figure 7).

Within-group analysis showed improvements in limitation due to physical health, energy/fatigue, emotional well-being and social functioning (p<0.001) in the treatment group, and improvements in physical functioning, energy/fatigue, social functioning, pain and general health ($p \leq 0.005$) in the sham group (Table 7).

[Insert Table 7 here]

[Insert Figure 7 here – colour online, colour print]

Blinding assessment

Almost two-thirds of participants (56.9% vs 60.7%; sham and treatment group respectively) correctly guessed their intervention group. Researchers (UK) were only able to correctly determine allocation for participants in the treatment group (21.7% vs 57.4%; sham and treatment group respectively).

DISCUSSION

After the 4-week intervention, VeNS using the Modius Sleep device significantly improved insomnia severity compared to a sham device, with the most benefit seen in those with severe insomnia. Participants in the treatment group showed a decrease in ISI scores of 24.5% (4.85) and 29.4% (5.80) in the ITT and PP cohorts respectively, compared to 17.1% (3.14) and 19.2% (3.52) in the sham group. The 5.80 decrease in the PP cohort approaches the 6-point reduction that indicates clinically meaningful improvement [49]. Additionally, improvements in energy/fatigue were observed in the treatment group compared to the sham group, with increases in score of 37.2% (11.2) and 15.4% (5.81) respectively (ITT cohort). Though they failed to reach significance after Bonferroni corrections, there were slight improvements in sleep efficiency (PSQI) and emotional well-being (SF-36) in the treatment group compared to the sham group. Improvements seen in the sham group may have been due to the routine of sitting for 30 minutes before sleep. This adds to pilot work where Modius Sleep reduced ISI scores by 48.1% (7.55) over a 14-day period, and a randomised sham-controlled trial where ISI score in the Modius Sleep group was reduced by 42.1% (7.23) over 28 days with significant between-group difference ($p<0.001$). Additionally, that same RCT observed a significant between-group difference for improvement in all aspects of QoL ($p<0.001$), not seen in the current trial [44, 55].

While research is limited, studies have shown that impaired vestibular function is associated with sleep problems [57-59], suggesting an association between sleep and the vestibular system. Vestibular stimulation is well-known to promote sleep in infants via rocking, and this effect can also be seen in adults [37, 38], as well as decreasing sleep latency in mice [39]. VeNS has been shown to decrease sleep latency in humans with one study showing a mean sleep latency reduction of 18.3 minutes after 30 days of 1-hour daily VeNS sessions [42, 43, 60]. In contrast, some studies which subjected participants to rotational movements in addition to the usual translational movements, did not show significant improvement in sleep [61, 62] perhaps due to the recruitment of ‘good sleepers’ [62] or, alternatively, to the inclusion of rotational movements [61], which may impair the beneficial effects of vestibular stimulation. Rotation is detected by the semi-circular canals [45], whereas the Modius Sleep delivers stimulation at low levels

(<3mA) intended to activate specifically the otolith organs of the vestibular apparatus, which sense gravity and linear acceleration.

The mechanism through which the vestibular system impacts sleep is unclear and may be multimodal. One hypothesis is that the vestibular system influences the suprachiasmatic nucleus, therefore affecting circadian rhythm, by providing information on activity and motion during the day [31-33]. Another potential mechanism is via the orexinergic neurons in the hypothalamus which affect sleep regulation by maintaining wakefulness and have been shown to project to the vestibular nuclei in rats [34-36]. It has been suggested that this pathway may be influenced by the vestibular system providing information about daily movement, possibly via the accumulation of adenosine [34]. One well-documented link is that stimulation of the vestibular system activates the hippocampus [63-65] which in turn influences rapid eye movement (REM) sleep [66-68], and stimulation of the vestibular system can influence REM sleep directly [69-71]. Some studies suggest a link between vestibular stimulation and an increase in the vividness of dreams, again indicating an effect on REM sleep [71-73]. This suggests that sleep quality, not only quantity, may be affected by vestibular stimulation. Although the data in this study are subjective, PSQI global score showed no significant between-group difference in sleep quality improvement over the intervention period.

The population recruited for this study was those for whom the device is intended, i.e., those with moderate or severe insomnia (ISI score ≥15), who had experienced symptoms for an extended period. The device does not have a sedative effect comparable to that of sleeping pills so it may not overcome external insomnia causes e.g. noise, light. Pharmaceutical treatments still have their place in short-term insomnia treatment, but for chronic insomnia, pharmaceuticals may not be an appropriate solution. The side effects of pharmaceutical sleep treatments are well-documented e.g. hypersomnia, reduced cognition, and addiction [21, 23, 25-27]. The Modius Sleep device was well-accepted by participants and has fewer reported side effects than pharmaceutical treatments. There were few AEs, the majority being mild or moderate, and infrequent. In the treatment group, completion to end of intervention was 80.8%, with 62.3% of these participants completing a mean of ≥5 sessions/week. Only one participant withdrew due to

a device-related AE. This device provides a lower-risk alternative for patients who cannot, or would prefer not to, rely on pharmaceuticals.

Due to factors including reduced productivity, inability to work and increased mortality, the estimated economic loss in the U.S. due to insomnia is $280-411 billion annually [74]. CBT-I is demonstrably a cost-effective treatment over the long-term [75] and is recommended ahead of pharmaceuticals due to its minimal side effects [1, 20, 22-24, 28, 29], however CBT-I requires time, money, and multiple sessions with trained professionals [28]. The NHS states that CBT-I usually lasts for 6 to 20 sessions [76] with most studies assessing effectivity providing 6-8 sessions [29]. Participants on this study successfully used the device after one training session, though they were given a contact number in case of technical issues. Device use could reduce healthcare and economic costs and increase accessibility.

Study strengths and limitations

There were small between-site protocol differences (Supplementary Table 1) but analyses suggest that this did not impact the study conclusions.

Participants successfully operated the device whether they received training face-to-face (HK) or by video call (UK), meaning that training can be provided off-site. An issue with CBT-I is that patients cannot always access a trained CBT-I professional [28]; the provision of online training for the Modius Sleep device removes this barrier.

The present study outcome measures are based on participant perceptions i.e., no laboratory-based sleep monitoring occurred. This, however, allowed participants to maintain their usual sleep environment, providing findings applicable to a real-life scenario where patients will use the device at home.

The current eligibility criteria excluded participants with health concerns including inner ear disease, epilepsy, and migraines with aura. This may limit the generalisability of the results, as the device may be unsuitable for people with certain conditions. Additionally, the results are subject to the study conditions; without compliance monitoring, device usage may be lower, and effectiveness might be reduced.

Further research

The FDA have approved this device for medical treatment of chronic insomnia in the U.S. as an outcome of this study (K230826). Further research should focus on device effectivity with different types of insomnia (onset, middle or late insomnia). The trend in ISI score remaining lower than baseline up to 8 weeks post-intervention suggests that the device may have an extended effect. Further investigation could be made into the optimal usage requirements i.e., how long the effects last without usage, and the minimum regular usage required to give the desired result.

CONCLUSIONS

The Modius Sleep device improved insomnia severity and energy levels compared to a sham device, indicating an improvement in QoL for those who use Modius Sleep regularly for a 4-week period. This device could provide a low-risk, non-invasive alternative treatment for chronic insomnia sufferers. It can be administered at home, providing an option to those without access to CBT-I, or for whom pharmaceutical treatments are not suitable. The stimulation is well-tolerated, and intensity is adjustable by the user to allow optimal stimulation for the individual. It therefore provides a viable cost-effective alternative treatment for insomnia.

FIGURE CAPTIONS

Figure 1. Participant timeline. Heavier line indicates period where intervention is applied. UK – Ulster University site with participants resident in UK and Ireland; HK – Hong Kong site with participants resident in Hong Kong; appt – appointment; ISI – Insomnia Severity Index; PSQI – Pittsburgh Sleep Quality Index; SF-36 – RAND 36-Item Short Form Survey, Quality of Life.

Figure 2. The Modius Sleep device as intended to be worn, with electrode pads over the mastoid processes. Modius Sleep and sham devices had this identical appearance.

Figure 3. CONSORT flow diagram showing participant numbers at each stage of the study and details of withdrawals. UK – Ulster University site consisting of participants resident in the UK and Ireland; HK – Hong Kong site consisting of participants resident in Hong Kong; AE – adverse event; PP – per protocol cohort; ITT – intention to treat analysis using last observation carried forward cohort.

Figure 4. Change in mean Insomnia Severity Index (ISI) score from Week 0 by intervention group. Intention to treat not applied: Week 0 n=147, Week 2 n=46 (UK), Week 4 n=126, Week 8 n=80 (HK), Week 16 n=79 (HK). Error bars show 95% confidence intervals. *General linear hypotheses testing showed significant between-group difference in change from Week 0 to Week 4 in age-adjusted model; p=0.002.

Figure 5. Distribution of Insomnia Severity Index (ISI) scores in categories for sham and treatment group at Week 0 and Week 4 for the intention to treat analysis using last observation carried forward (ITT) cohort.

Figure 6. Mean PSQI component score decrease for the treatment and sham groups at Week 0 and Week 4 for the intention to treat analysis using last observation carried forward (ITT) cohort. Increased distance from centre of chart indicates a larger decrease and therefore more improvement in that component. Mann-Whitney U Tests; all p-values >0.007.

Figure 7. Mean SF-36 (RAND 36-Item Short Form Survey, Quality of Life) component score change for the treatment and sham groups at Week 0 and Week 4 for the intention to treat analysis using last observation carried forward (ITT) cohort. Increased distance from centre of chart indicates a larger change and therefore

394 more improvement in that component. *Significant between-group difference in Energy/Fatigue; Mann-

395 Whitney U test; ITT cohort p=0.006, PP cohort p=0.004.

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Table 1. Eligibility criteria.

Inclusion criteria	Exclusion criteria

• Insomnia Severity Index (ISI) score of 15 or greater
• Agreement not to do the following during the study:
  ○ undergo any extreme lifestyle changes during the study that could impact on sleep e.g., dietary or exercise changes
  ○ use sleep trackers for the duration of the study
  ○ travel to different time zones during the study
• Ability and willingness to engage with the monitoring company as required to discuss usage and technical issues
• Access to Wi-Fi
• Access to a mobile device with Bluetooth (HK only)
• Agreement not to use prescription or over the counter sleep medications for the duration of the trial, and haven't for 4 weeks before the trial
• Aged 18-80 years (UK); Aged 18-60 years (HK)
• Ability and willingness to complete all study visits and procedures; in particular, an agreement to engage with trying to use the device daily and attend study appointments remotely (UK) or in person (HK)
• Agreement to maintain a familiar sleeping environment/routine throughout the study and will not discontinue or begin treatment with new devices used while sleeping during the study
• Able to provide written informed consent
• Live in UK or Ireland and understand English (UK) or live in Hong Kong, be ethnic Chinese and understand Simplified and Traditional Chinese (Mandarin) (HK)
• Confirmation that insomnia was not related to recent lifestyle changes that may alter during trial
	• History of
	  ○ skin breakdown, eczema or other dermatological condition (e.g. psoriasis) affecting the skin behind the ears
	  ○ stroke or severe head injury (requiring intensive care or neurosurgery)
	  ○ active migraines with aura
	  ○ epilepsy
	  ○ diagnosed cognitive impairment such as Alzheimer's disease/dementia
	  ○ vestibular dysfunction or other inner ear disease
	  ○ major depressive disorder, psychotic disorder, bipolar affective disorder, substance use disorders, or clinical depression, or a current characterised depressive episode
	• Previous diagnosis of HIV infection or AIDS
	• Presence of permanently implanted battery powered medical device or stimulator (e.g., pacemaker, implanted defibrillator, deep brain stimulator, vagal nerve stimulator etc.).
	• A diagnosis of myelofibrosis or a myelodysplastic syndrome
	• Previous use of any VeNS device
	• Pregnancy or breast-feeding, or intends to become pregnant
	• Regular use (more than twice a month) of antihistamine medication within the last 6 months, excluding fexofenadine
	• History or presence of malignancy within the last year (except basal and squamous cell skin cancer and in-situ carcinomas)
	• Participation in other clinical trials sponsored by Neurovalens or other insomnia studies
	• Use of betablockers/antidepressants/any other medications that may affect the neurostimulation
	• Have a member of the same household who is currently participating in this study
	• Significant communicative impairments

Table 2. Stimulation and usage parameters for the Modius Sleep and sham devices.

	Modius Sleep Device	**Sham Device**
Stimulation frequency	0.25Hz	0.8Hz; reduces likelihood of meaningful vestibular stimulation [44, 45]
Stimulation current	0.1mA-1.0mA; participant to ↑ in 0.1mA increments until gentle swaying sensation felt indicating modulation of vestibular nerve	
Length of stimulation	30 minutes	Total 50 seconds: 30 seconds at selected current, ↓ to 0mA over next 20 seconds*
Placement	Bilateral (mastoid processes)	
Usage frequency	30 minutes daily for 28 days	
Usage pattern	While sitting; before sleep	
Post-session lockout period	16 hours	

* Due to user accommodation to the current, sensations of tingling/prickling typically subside after 30 seconds [46, 47]; participants are unable to distinguish between a device delivering 20 minutes of real stimulation, vs a sham device delivering 30 seconds of stimulation before switching off [48].

Table 3. Baseline (Week 0) characteristics for participants using an electrical vestibular stimulation device (treatment) compared to those using a sham control device split by analysis.

Analysis cohort		**ITT (n=147)**		**PP (n=126)**	
Intervention group		**Sham (n=74)**	**Treatment (n=73)**	**Sham (n=65)**	**Treatment (n=61)**
Sex, n (%)	**Male**	24 (32.4)	25 (34.2)	21 (32.3)	21 (34.4)
	Female	50 (67.6)	48 (65.8)	44 (67.7)	40 (65.6)
	df, X^2	**1, 0.054**		**1, 0.064**	
	***p*-value**	**0.816**		**0.801**	
Ethnicity, n (%)	**Caucasian**	23 (31.1)	23 (31.5)	19 (29.2)	20 (32.8)
	Asian	50 (67.6)	50 (68.5)	45 (69.2)	41 (67.2)
	Mixed	1 (1.35)	0 (0.00)	1 (1.54)	0 (0.00)
	df, X^2	**2, 0.993**		**1, 0.140**	
	p*-value	**1**		**0.709**	
Age in years, *mean (SD)*		42.0 (13.0)	39.6 (13.9)	41.9 (12.8)	40.5 (13.1)
	p-value	**0.313**		**0.667**	
ISI score, *mean (SD)*		18.4 (4.51)	19.8 (4.14)	18.3 (4.70)	19.7 (4.03)
	p-value	**0.051**		**0.078**	
PSQI global score, *mean (SD)*		12.5 (3.16)	13.0 (3.58)	12.3 (3.14)	12.9 (3.42)
	p-value	**0.388**		**0.381**	
Caffeine intake, *mean (SD)*		N/A	N/A	1.67 (1.14)	1.51 (1.32)
	p-value	**N/A**		**0.897**	

* Note that for ethnicity X^2, the data for 'Mixed' ethnicity had to be excluded due to low expected cell count therefore the Pearson X^2 values for ethnicity were performed with Caucasian and Asian data only. X^2 tests carried out for sex and ethnicity, Mann-Whitney U test for age, PSQI global score and caffeine intake, and independent t-tests for ISI score,. Caffeine intake was calculated in units where one unit is equal to 90mg of caffeine. Significant at $p \leq 0.05$. A per protocol analysis (PP) was carried out on participants who completed the study to Week 4 (n=126); and intention to treat analysis using the last observation carried forward (LOCF) method was used for the complete cohort (n=147). SD – standard deviation; df – degrees of freedom; ISI – Insomnia Severity Index; PSQI – Pittsburgh Sleep Quality Index.

Table 4. Number (%) of adverse events according to intervention group (all participants, n=147).

	Adverse Events		Total n (%)	Treatment n (%)	Sham n (%)
HK	**Nervous System Disorders**	Headache/migraine	1 (0.68)	1 (0.68)	0 (0.0)
	Gastrointestinal Disorders	Severe nausea	1 (0.68)	1 (0.68)	0 (0.0)
UK	**Nervous System Disorders**	Headache/migraine	6 (4.1)	5 (3.4)	1 (0.68)
	Eye Disorders	Flashes in peripheral vision	2 (1.4)	2 (1.4)	0 (0.0)
		Shadow in peripheral vision	1 (0.68)	1 (0.68)	0 (0.0)
		Tingling in eye	1 (0.68)	1 (0.68)	0 (0.0)
	Ear disorders	Ear pain	2 (1.4)	0 (0.0)	2 (1.4)
		Tinnitus	2 (1.4)	1 (0.68)	1 (0.68)
		Itching in ear	1 (0.68)	0 (0.0)	1 (0.68)
	Mood disorders	Low Mood	2 (1.4)	2 (1.4)	0 (0.0)
	Mouth/dental disorders	Metal fillings pulsing	1 (0.68)	0 (0.0)	1 (0.68)
		Grinding teeth	1 (0.68)	1 (0.68)	0 (0.0)
	Other	Tingling in arm	1 (0.68)	1 (0.68)	0 (0.0)
	Serious Adverse Events				
UK	**Other**	Minor cerebral vascular accident	1 (0.68)	1 (0.68)	0 (0.0)

The minor cerebral vascular accident was determined to be not device related.

Table 5. Number of 'good sleepers' and 'poor sleepers' based on Pittsburgh Sleep Quality Index (PSQI) score before (Week 0) and after (Week 4) intervention for participants using an electrical vestibular stimulation device compared to those using a sham control device.

		Week 0		Week 4	
		Good sleeper (n)	**Poor sleeper (n)**	**Good sleeper (n)**	**Poor sleeper (n)**
ITT	**Sham**	1	73	11	63
	Treatment	1	72	10	63
PP	**Sham**	1	64	11	54
	Treatment	1	60	10	51

PP – per protocol cohort; ITT – intention to treat analysis using last observation carried forward cohort.

Table 6. Change in mean Pittsburgh Sleep Quality Index (PSQI) component scores for participants using an electrical vestibular stimulation device compared to those using a sham control device.

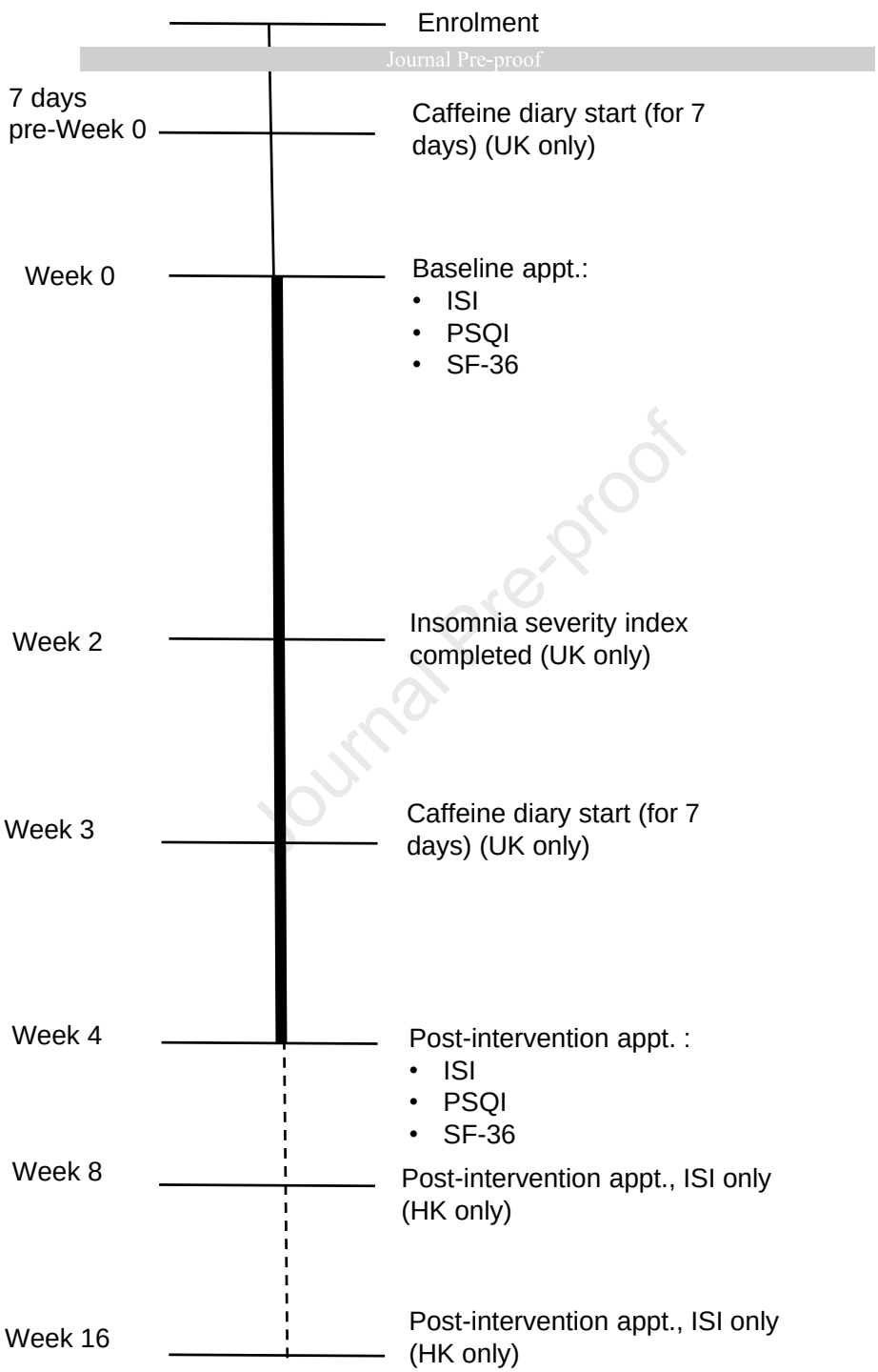
	Week 0		Week 4		Within-group change in score		Between-group difference p-value	Effect size
	Mean (SD)		*Mean (SD)*		*Mean (SD); p-value*			
PSQI Component	**Sham**	**Treatment**	**Sham**	**Treatment**	**Sham**	**Treatment**		
Component 1: Subjective sleep quality	2.36 (0.563)	2.41 (0.642)	1.84 (0.844)	1.75 (0.703)	-0.527 (0.815); <0.001	-0.658 (0.671); <0.001	0.189	0.11
Component 2: Sleep latency	2.34 (0.864)	2.33 (0.958)	1.92 (1.08)	1.89 (0.994)	-0.419 (0.844); <0.001	-0.438 (0.799); <0.001	0.823	0.02
Component 3: Sleep duration	1.88 (0.950)	1.90 (0.988)	1.55 (1.04)	1.41 (1.07)	-0.324 (0.862); 0.002	-0.493 (0.784); <0.001	0.354	0.08
Component 4: Sleep efficiency	1.62 (1.70)	1.66 (1.27)	1.61 (1.25)	1.14 (1.21)	-0.0135 (1.12); 0.805	-0.528 (1.06); <0.001	0.040	0.17
Component 5: Sleep disturbance	1.61 (0.593)	1.66 (0.671)	1.41 (0.571)	1.47 (0.647)	-0.203 (0.496); 0.001	-0.192 (0.518); 0.003	0.786	0.02
Component 6: Medication	0.905 (1.25)	0.932 (1.31)	0.757 (1.21)	0.795 (1.26)	-0.149 (0.771); 0.093	-0.137 (0.673); 0.093	0.711	0.03
Component 7: Daytime dysfunction	1.76 (0.773)	2.05 (0.724)	1.57 (0.812)	1.68 (0.762)	-0.189 (0.771); 0.037	-0.370 (0.697); <0.001	0.073	0.15
Global Score	12.5 (3.16)	13.0 (3.58)	10.7 (4.18)	10.1 (4.02)	-1.82 (3.43)	-2.81 (3.25)	0.118	0.16

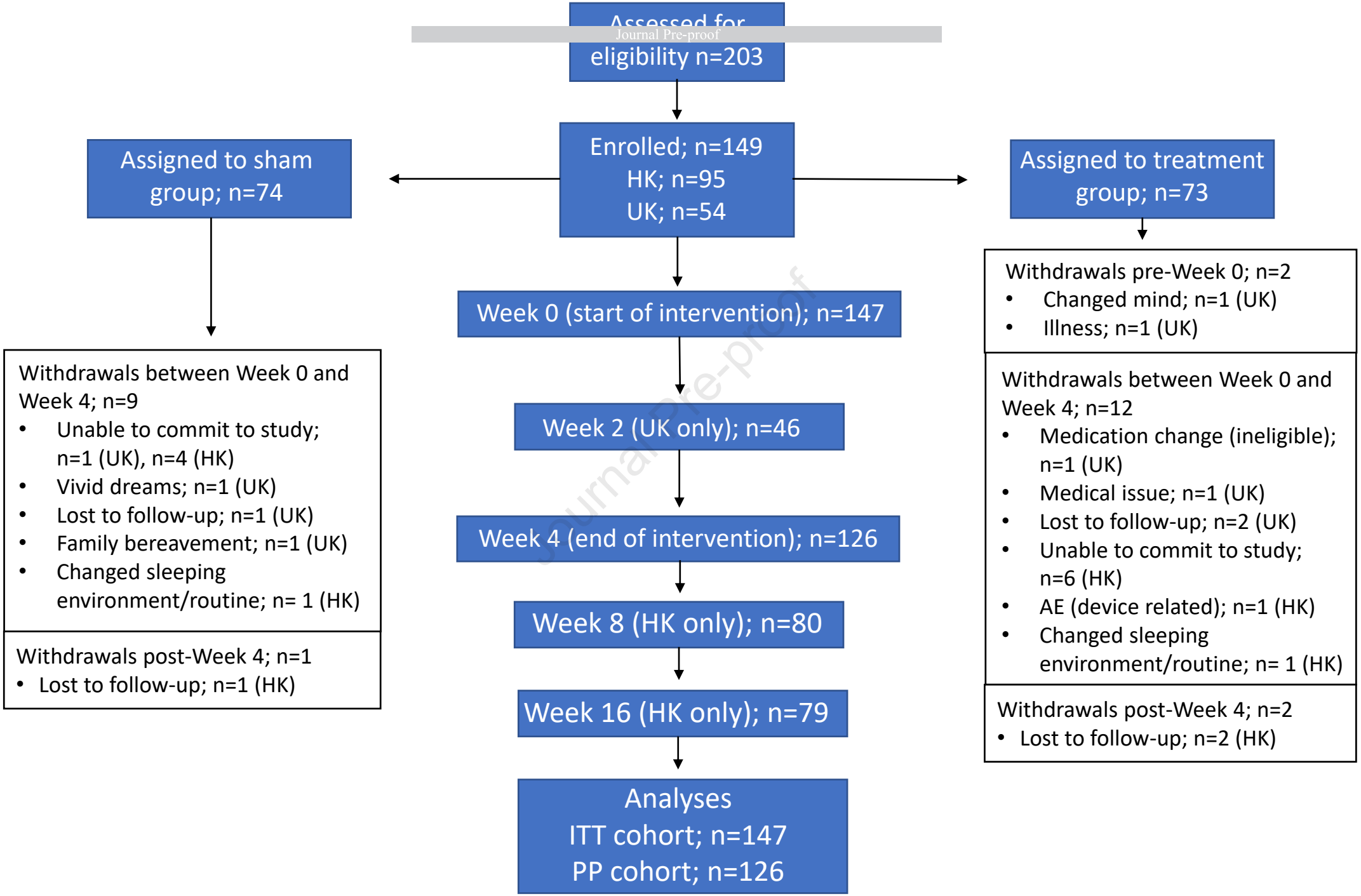
Values displayed for the intention to treat analysis using last observation carried forward (ITT) cohort. P-values considered significant at p≤0.007 after Bonferroni corrections are applied for multiple comparisons. P-values for between-group differences in change in score determined using Mann-Whitney U tests for all scores. Wilcoxon signed rank tests used for within-group difference. Effect size was calculated using $r=Z/\sqrt{n}$. PSQI – Pittsburgh Sleep Quality Index; SD – standard deviation.

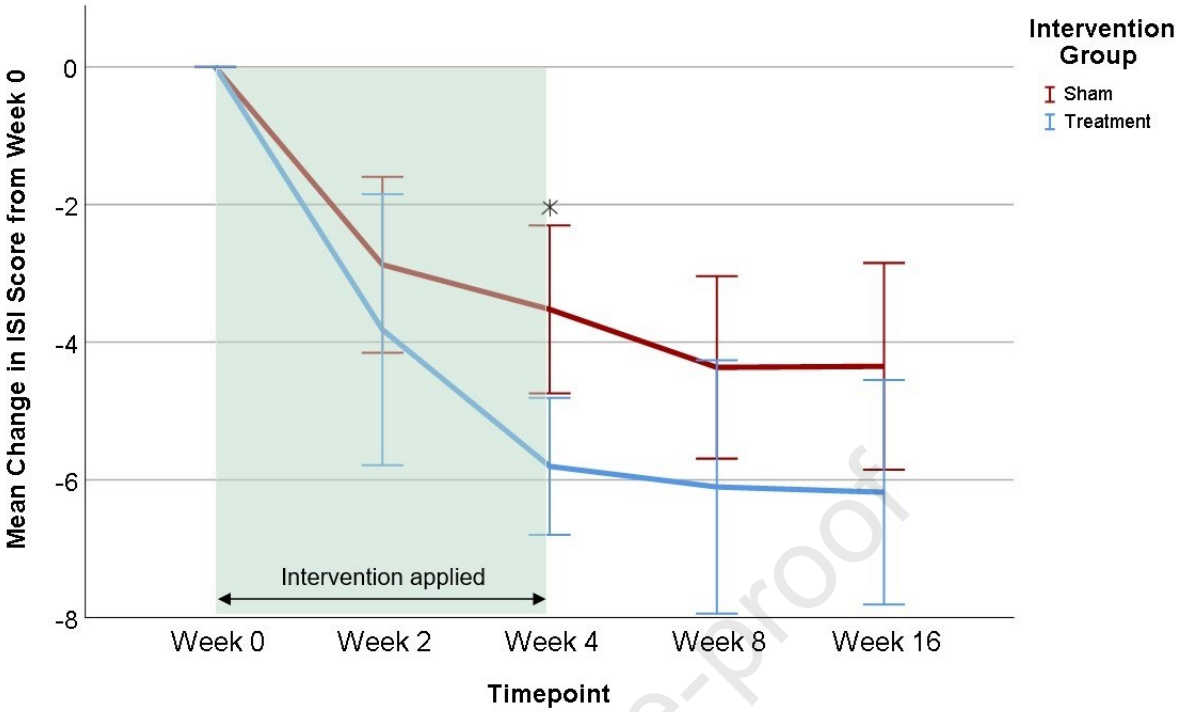
Table 7. Change in Quality of Life (SF-36) component scores for participants using an electrical vestibular stimulation device compared to those using a sham control device.

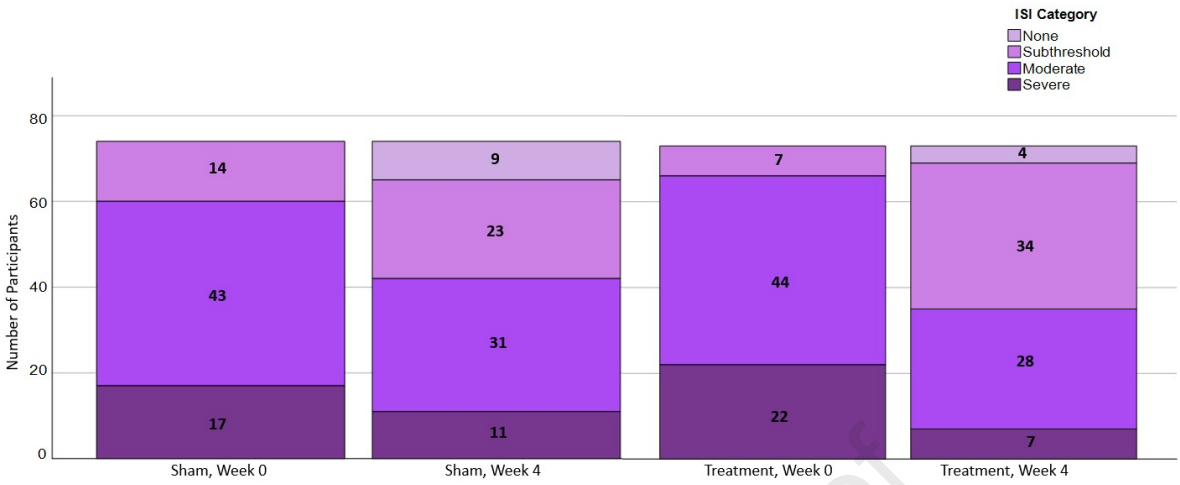
	Week 0		Week 4		Within-group change in score		Between group difference p-value	Effect size
	Mean (SD)		*Mean (SD)*		*Mean (SD); p-value*			
SF-36 Component	**Sham**	**Treatment**	**Sham**	**Treatment**	**Sham**	**Treatment**		
Component 1: Physical functioning	81.6 (20.1)	74.2 (26.2)	86.5 (14.2)	75.1 (26.6)	4.93 (13.8); 0.003	0.890 (15.6); 0.431	0.109	0.13
Component 2: Role limitations due to physical health	49.7 (41.5)	36.6 (39.5)	53.0 (39.5)	52.1 (40.3)	3.38 (37.8); 0.458	15.4 (34.4); <0.001	0.062	0.15
Component 3: Role limitations due to emotional problems	36.5 (42.1)	29.7 (40.3)	45.5 (44.3)	44.7 (39.8)	9.01 (46.3); 0.096	15.1 (42.0); 0.007	0.445	0.06
Component 4: Energy/fatigue	37.6 (21.7)	30.1 (19.2)	43.4 (20.6)	41.3 (18.6)	5.81 (15.9); 0.003	11.2 (12.7); <0.001	0.006	0.22
Component 5: Emotional well-being	53.2 (21.1)	47.1 (21.6)	57.4 (20.1)	56.5 (19.5)	4.16 (14.8); 0.019	9.48 (13.8); <0.001	0.018	0.20
Component 6: Social functioning	56.1 (26.0)	51.2 (24.1)	65.9 (23.5)	62.6 (25.4)	9.80 (27.5); <0.001	11.3 (17.6); <0.001	0.723	0.03
Component 7: Pain	64.8 (24.0)	62.4 (27.5)	73.6 (24.0)	64.9 (27.1)	8.82 (17.3); <0.001	2.43 (16.3); 0.120	0.042	0.17
Component 8: General health	44.5 (20.9)	42.4 (24.5)	49.5 (22.4)	47.3 (22.0)	5.07 (13.7); 0.005	4.86 (14.2); 0.008	0.978	0.00

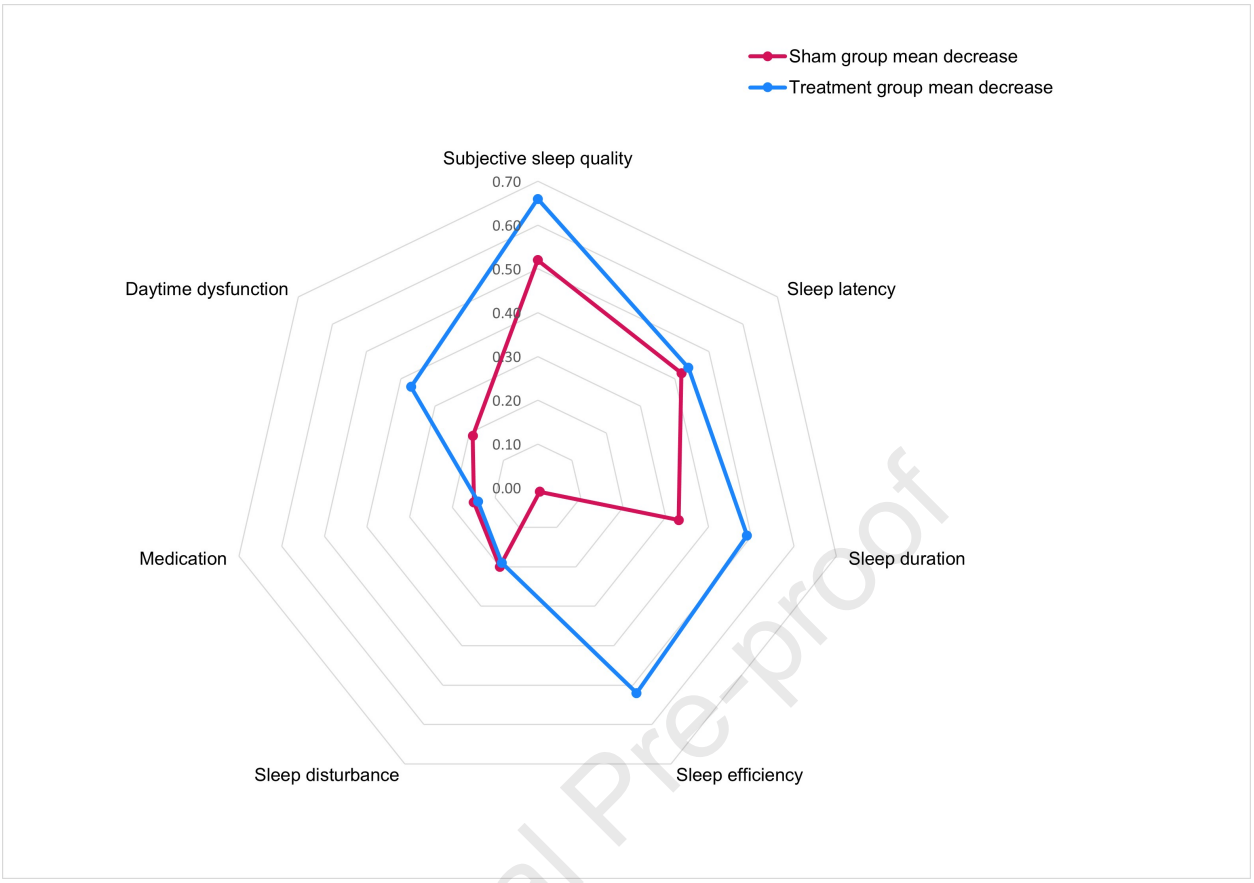
Values displayed for the intention to treat analysis using last observation carried forward (ITT) cohort. P-values considered significant at $p \leq 0.006$ after Bonferroni corrections are applied for multiple comparisons. P-values were determined using Mann-Whitney U tests for between group differences, and Wilcoxon signed rank tests for within-group differences. Effect size was calculated using $r=Z/\sqrt{n}$ for component scores. SD – standard deviation. SF-36; RAND 36-Item Short Form Survey, Quality of Life.

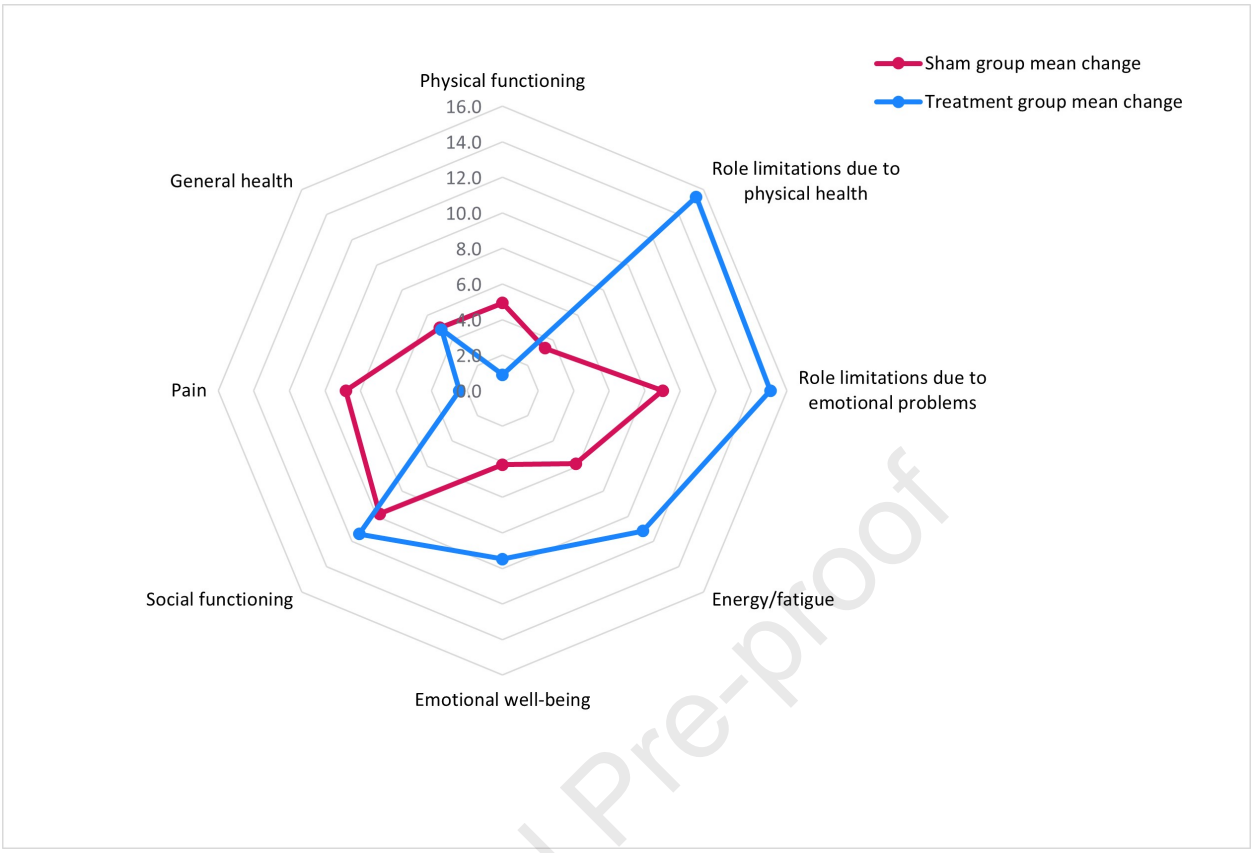












HIGHLIGHTS

- Repeated VeNS with below parameters improved insomnia severity and fatigue
- Stimulation was effective when provided for 30 minutes daily for five days per week
- Treatment group mean ISI score decrease approached clinically meaningful improvement

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: