Transcutaneous electrical hypoglossal nerve stimulation in OSA patients – a double-blind randomised crossover trial against placebo device.

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ABSTRACT

Transcutaneous Electrical Hypoglossal Nerve Stimulation in OSA Patients – a double-blind randomised crossover trial against placebo device

Background;
Advances in hypoglossal nerve stimulation (HNS) therapy have demonstrated significant promise in treating Obstructive Sleep Apnoea (OSA); however, current approaches require invasive surgical implantation. The ZeusOSA device provides a non-invasive alternative, adhering under the jaw and delivering transcutaneous electrical stimulation to the hypoglossal nerve. This double-blind, randomised, crossover trial was conducted from May 2023 to August 2024 to evaluate whether ZeusOSA could serve as an effective treatment for OSA, by assessing its impact on Apnoea-Hypopnoea Index (AHI) and other metrics in OSA patients, compared with baseline and sham (placebo) ZeusOSA.

Methods:
Adult patients with OSA were prospectively recruited from Dorset County Hospital NHS Foundation Trust, UK whilst awaiting CPAP initiation or undertaking conservative management, including lifestyle changes. Patients with significant sleep-related and cardiovascular comorbidities were excluded. Each participant completed a baseline multi-channel sleep study (MCSS) followed by two, one-week intervention phases: Active ZeusOSA and Sham ZeusOSA. These were in a randomised order with each phase ending with another MCSS. Participants, study staff and MCSS analysts were blind to sequence order. Subjective data was also collected via questionnaires. All analyses followed an intention-to-treat principle. The main analysis was to assess the effect of ZeusOSA active compared to sham device on AHI and ODI using mixed effects Poisson regression, adjusting for baseline AHI and accounting for the within-subject correlations arising from the cross-over design.

Results:
In total 62 patients were recruited to this trial which resulting in 48 full datasets, with 12 participants withdrawing or being excluded from the primary analysis. Analysis of the primary outcome demonstrated no significant difference in AHI between baseline and Active ZeusOSA use ($p = 0.09$). Further post-hoc analysis identified a sub-group of participants (“responders”; n=29, 60%) who had an average reduction in AHI of 5.6/hr and a mean reduction in ODI of 5.3/hr whilst using the Active ZeusOSA device as well as reporting subjective improvements in perceived sleep quality, perceived daytime alertness and perceived daytime functionality. The only characteristics identified as being different between the responder and non-responder groups was that responders had a significantly higher autonomic arousal index at baseline (mean AAI = 31.2/hr vs 19.7/hr respectively, $p=0.0007$). Those using the Active ZeusOSA device also had increases in heart rate compared to baseline (mean increase = 3.9bpm, t-test $p=0.00007$). Overall device compliance rates were >85% with overall positive satisfaction scores with using the device.

Conclusion:
This study supports the therapeutic potential of non-invasive hypoglossal nerve stimulation in OSA. Whilst the overall dataset did not show significant improvements in AHI, a subset of “Responders” (60% of the participant group) demonstrated clinically meaningful improvements in AHI and other subjective outcomes. A higher baseline AAI may indicate responsiveness, but this would require further exploration. Participants found the ZeusOSA device to be highly tolerable and feasible as a treatment, with good compliance and acceptability. These findings suggest that the ZeusOSA device represents a viable alternative to CPAP therapy, especially in those unable to tolerate CPAP, and as part of assessment before consideration for invasive HNS treatments.

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1 INTRODUCTION

Obstructive Sleep Apnoea (OSA) is a common form of Sleep-Disordered Breathing (SDB), characterised by the upper airway muscles relaxing during sleep, resulting in snoring and partial or full obstruction to airflow, despite respiratory effort (Senaratna et al., 2017). These episodes lead to oxygen desaturation and a compensatory rise in heart rate which triggers an arousal of the brain, bringing the patient out of deep restorative sleep and into a lighter stage of sleep sufficient to engage the muscles of the throat and upper airway and enable normal airflow. This cycle can repeat dozens of times an hour during sleep, preventing sustained periods of deep sleep and putting greater strain on the cardiovascular system and other body systems. OSA is strongly associated with increased risk of heart disease, stroke, Type-2 diabetes, hypertension, and depression, amongst other comorbidities (Mokhlesi et al., 2016). The burden of long term disrupted sleep usually causes OSA patients to be excessively sleepy in the daytime, which can have significant psychosocial repercussions (Jennum et al., 2014). These effects can impair occupational performance, most notably legal rules on sleepiness and driving, wherein all drivers with excessive sleepiness must not drive until adequate control of symptoms has been achieved (DVLA, 2021).

The gold standard treatment for OSA is Continuous Positive Airway Pressure (CPAP), comprising an airtight facemask worn over the nose or nose and mouth connected via a hose to an air pump which pneumatically 'splints' the airway open with increased air pressure (Alford et al., 2024; Mashaqi et al., 2021). When an appropriately fitted mask and optimal air pressure are used consistently, CPAP therapy can lead to full symptomatic resolution of OSA. However, it is only effective when worn during sleep, therefore, is dependent on adherence; cessation of use typically results in the recurrence of apnoeic episodes. In general, 'good' CPAP usage is considered to be as a minimum of four hours per night, for at least 70% of nights (Bakker et al., 2019), sustaining this level of compliance represents a major challenge for both patients and clinicians given the long-term nature of the treatment.

Despite substantial technological advancements in mask design and device functionality, many patients find CPAP therapy difficult to tolerate. Additionally, CPAP use can cause pressure sores, skin irritation, nasal congestion, dental problems, eye dryness, chest infections, disturbed sleep, nightmares and panic (Ghadiri & Grunstein, 2020). Many patients require intensive follow-up regimes to obtain acceptable compliance, and some are never able to tolerate CPAP at all (Virk & Kotecha, 2016). Consequently, approximately 30-40% of patients initiated on CPAP will be non-compliant and will require alternative treatment options (Campos-Rodriguez et al., 2016; Rotenberg et al., 2016). Additionally, in the UK, only patients diagnosed with moderate or severe OSA are routinely referred directly for CPAP – those with mild OSA are advised to first try lifestyle modifications such as weight loss, smoking cessation and alcohol intake reduction (NICE, 2021).

A notable proportion of patients diagnosed with OSA, therefore, remain unable to tolerate or access CPAP therapy and must seek alternative treatment options (Virk & Kotecha, 2016). Unfortunately, as yet, second-line treatments have not been proven to be as effective as CPAP, and often come with similar compliance issues (Johnston et al., 2002; Uniken Venema et al., 2020).

A popular second-line treatment option is to use an oral appliance, such as a Mandibular Advancement Device (MAD) or Mandibular Advancement Splint, which is a mouthguard-type device which holds the lower jaw in a semi-open and forward position, thus creating a wider airway space and reducing the likelihood of apnoeas and hypopnoeas. Evidence suggests that MADs are more effective than sham oral devices, however, less effective than CPAP in the treatment of OSA (Johnston et al., 2002; Lim et al., 2006; Uniken Venema et al., 2020).

A relatively recent development in OSA treatment has been the Inspire device – an implantable nerve stimulator which activates the hypoglossal nerve to improve pharyngeal muscle tone and flatten the tongue at the back of the mouth (Cori et al., 2018; Kompelli et al., 2018). This approach has been shown to be very effective in treating OSA, with good patient compliance, however, the procedure necessitates costly and invasive neurosurgery and is unlikely to be considered a cost-effective treatment option for the NHS (Blissett et al., 2021).

Thus, alternative treatments and therapies to CPAP exist but tend to be less effective and/or prohibitively expensive; often with results that diminish with time (Randerath et al., 2022).

Further to the implantable device, the feasibility of hypoglossal nerve stimulation (HNS) via transcutaneous electrodes placed on the skin under the jaw was explored and found to be effective (He et al., 2019; Pengo & Steier, 2015). This technology was developed into the ZeusZS1 device which has been shown to reduce snoring and daytime sleepiness (Bisogni et al., 2017; Pengo et al., 2016; Ratneswaran et al., 2021).

OSA is an increasing problem in the UK, particularly as the population is ageing and the prevalence of obesity rises (Erridge et al., 2021). In addition, causing increased incidences of health problems (Faria et al., 2021; Knauert et al., 2015), OSA is also associated with significant psychosocial and socioeconomic impact for patients, their families, and workplaces. Insufficient restorative sleep leads to daytime sleepiness, irritability, loss of motivation, impaired concentration, reduced occupational performance (Jennum et al., 2014; Moyer et al., 2001). Unfortunately, the most effective treatment, CPAP, also has a high burden for patients (Weaver & Grunstein, 2008), involving resetting of sleeping habits that have been ingrained for decades and adapting to use specialist equipment that is often less than unobtrusive in the patient's home bedroom.

Therefore a need exists to increase the current clinical options for an effective alternative to CPAP to treat OSA which patients find more tolerable, particularly amongst individuals with mild to moderate OSA who have limited access to, or benefit from CPAP therapy (Bakker et al., 2019; Campos-Rodriguez et al., 2016; Mehrtash et al., 2019; Rotenberg et al., 2016; Weaver & Grunstein, 2008). Being able to treat these patient groups will decrease the risk of these patients developing obesity, heart disease, vascular disease, diabetes, depression, etc, while improving quality of life for the patients and their families and mitigating productivity loss and increased sick days.

The study aimed to investigate the effectiveness and safety of an HNS device called ZeusOSA in improving sleep disordered breathing and its related symptoms in OSA patients via a randomised double-blind crossover trial using active and sham (placebo) devices. The primary objective was to assess whether use of ZeusOSA significantly changes Apnoea-Hypopnea Index (AHI) in OSA patients compared with baseline and control ('sham' device), measured by domiciliary multi-channel sleep studies (MCSS). Secondary objectives included assessment of acceptability, risk, and adverse events associated with use of ZeusOSA, assessment of objective changes in oxygen desaturation index (ODI) and snoring, measured by domiciliary MCSS, and assessment of changes in subjective perception of sleep quality and daytime sleepiness, alertness and functionality, measured by questionnaire. Engagement with the study had no impact on participants' care pathways.

2 METHODS

Trial Design

This was a randomised double-blind crossover study comparing active ZeusOSA device against baseline and placebo ('sham') device. This study was performed alongside standard patient care pathways. Participants attended three outpatient appointments at Dorset County Hospital and were loaned devices to facilitate data collection in their own homes. The study was designed to be structurally similar to other RCTs assessing interventions to treat OSA, enabling comparability of outcomes across studies. As the effect of the ZeusOSA device on the hypoglossal nerve – and therefore tongue position and airway openness – works only when the ZeusOSA device is active, it was deemed unnecessary to include a washout period between interventions as no carry-over effect was expected (Heiser et al., 2021; Johnston et al., 2002).

All participants initially performed MCSS with no ZeusOSA device. They were then issued with a pair of ZeusOSA devices (one active, one sham) to be used sequentially. Participants wore the first ZeusOSA device during sleep for one week to familiarise and acclimatise to it, ending with a second MCSS. Participants then completed an equivalent one week period using the second ZeusOSA device, concluding with a third MCSS. Participants also wore an overnight oximeter on every night of the 15-night study so that each participant provided matched baseline, active, and placebo objective datasets. In addition, participants completed short daily and detailed weekly questionnaires, providing robust subjective data regarding daytime sleepiness, alertness, functionality, sleep quality, and acceptability of the ZeusOSA device.

- Unable to provide informed consent
- Any sleep disorder other than OSA alone
- Already commenced CPAP therapy, or scheduled to start CPAP therapy during participation window
- Significant co-morbidities such as heart failure, respiratory failure, uncontrolled diabetes, polyuria, neuromuscular disorders, or other such medical conditions
- Unstable cardiovascular status, including uncontrolled hypertension and arrhythmias
- Recently diagnosed (last two months) deep vein thrombosis (DVT)
- Recurrent seizures, epilepsy, or migraines
- Fitted with a pacemaker, defibrillator, or any other active implantable medical devices
- Fitted with metal implants (excluding fillings and jewellery) in the head and neck region
- Diagnosed with cancer in the head and neck region
- Head or neck surgery in the last six months
- Thick facial hair under the jaw and do not wish to shave, or patients who use moisturising creams on the skin under the jaw and do not wish to pause this routine
- Using any other any other medical devices during sleep
- Swollen, infected, inflamed areas or broken skin under the jaw.
- Unable or unwilling to download, register with, and use the required smartphone app

Table 1.0: Participant exclusion criteria

Participants & Anonymisation

Participants were recruited from a cohort of patients diagnosed with OSA using MCSS at Dorset County Hospital between 2021 and 2023. Eligible participants were either awaiting commencement of CPAP therapy to treat moderate or severe OSA, and/or were undertaking lifestyle changes in accordance with NICE guidelines to control symptoms of mild OSA.

The study participants had to satisfy the following inclusion criteria: ≥ 18 years old, BMI at diagnosis between 18 – 45 (kg/m^2), AHI at diagnosis between 5 – 35 (/hr), and Epworth Sleepiness Score at diagnosis ≥ 7 (/24). Exclusion criteria are listed in Table 1.0.

To ensure confidentiality, all participants were assigned a pseudonymous identification code. Dates of birth were recorded as month and year only and no other patient-identifying data was recorded.

Participants were informed verbally and in writing, that withdrawal from the study at any stage was permitted, without obligation to provide justification, and that withdrawal would not affect their ongoing care for OSA. Participants also retained the right to withdraw consent for the use of any data collected prior to withdrawal. Investigators could withdraw a participant from the study if necessary for any reason including, but not limited to: ineligibility (either arising during the study or retrospectively having been overlooked at screening), significant protocol deviation, substantial non-compliance with study requirements, and an adverse event which required discontinuation of use of the ZeusOSA or sleep study devices or resulted in inability to continue to comply with trial procedures. Data collection would continue until sufficient datasets had been gathered.

Devices & Randomisation

The manufacturer of ZeusOSA (Morgan Innovation and Technology Ltd, 17 Petersfield Business Park, Bedford Road, Petersfield, GU32 3QA) prepared active and sham devices for the purposes of the study. The active device applied stimulation when switched on to allow adjustment of stimulation strength. Once no buttons had been pressed for one minute, the device stopped stimulation for a period of 20 minutes to allow the user to fall asleep. After 20 minutes of dormancy, the device resumed stimulation throughout the night until it was switched off by the user in the morning. The sham device was visually and functionally identical to the active device, however, following the initial stimulation to adjust strength settings to maintain the impression of device activation, the sham device stopped stimulation entirely and remained inactive for the rest of the night.

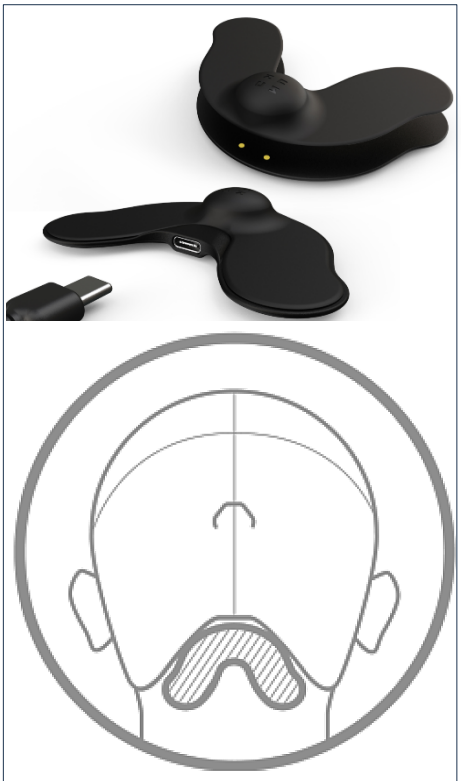

Fig 2.0: Top – photograph of two Zeus devices with charging bases. Bottom – diagram of ZeusOSA correctly fitted under the jaw.

Both ZeusOSA devices had the addition of software designed to record objective device usage parameters, including time and strength of stimulation, and Bluetooth connectivity to transfer this data to a smartphone app. However, due to delays in international app-store approval processes and practical challenges when training patients to connect two different devices to their smartphones via Bluetooth, this function was not used. A planned outcome of the study had been to objectively assess participant compliance with ZeusOSA, however self-reported subjective device usage data was instead gathered via questionnaire.

MCSSs were performed weekly using SOMNOtouch™ RESP ECO devices from SOMNOmedics, and nightly oximetry was conducted using CIRCUL ring oximeters from BodiMetrics (both supplied by S-Med Ltd, 63 Heming Road, Redditch, Worcestershire, B98 0EA). Data from MSCCs was independently, anonymously, and blindly analysed by S-Med to eliminate any potential bias. Data from oximetry was taken by hand from the CIRCUL ring smartphone app which participants installed on their personal devices.

The manufacturer prepared paired active and sham devices and randomly assigned sequence order Active-Sham or Sham-Active to each pair using a random number generator. Allocation concealment was strictly maintained - neither

the study staff nor participants were aware of which device was active, and which was sham from each pair. The unblinding key was held by the manufacturer until all data collection had been completed.

Questionnaires

The questionnaires used in the study are available in full in Appendix 1.

Perceived Sleep Quality was measured using seven questions each scored on a scale 0-6 to give a final score out of 42 where a higher score indicated better sleep quality.

Perceived Daytime Sleepiness was measured using an adapted Epworth Sleepiness Scale questionnaire, where patients were asked to consider their sleepiness over the last week (for the weekly questionnaire) or over the last day (for the daily questionnaire). There are eight questions scored on a scale 0-3 to give a final score out of 24 where a lower score indicated less daytime sleepiness.

Perceived Daytime Alertness was measured using an adapted FOSQ-10 questionnaire, with the addition of two questions exploring socialising inside and outside of the home, and where patients were asked to consider their sleepiness over the last week (for the weekly questionnaire) and over the last day (for the daily questionnaire). There were 12 questions scored 0-3 with an option for N/A and the final score was presented as a percentage of the maximum score of the answered questions where a lower percentage indicated better daytime alertness.

Perceived Daytime Functionality was measured using seven questions scored on a scale 0-6 to give a final score out of 42 where a higher score indicated better daytime functionality.

Tolerance of ZeusOSA Device was measured using seven questions scored on a scale 0-6 to give a final score out of 42 where a higher score indicated better ZeusOSA tolerance.

Trial Protocol

The study was conducted by qualified respiratory and sleep physiologists at Dorset County Hospital NHS Foundation Trust.

Day	Activity
0	Consent
0	Baseline MCSS
1	Randomisation
1 – 6	Active ZeusOSA / Sham ZeusOSA
6	MCSS
7	Crossover
7 – 13	Active ZeusOSA / Sham ZeusOSA
13	MCSS
14	Study End

Figure 3.0 : Study Flow
MCSS = Multi-channel Sleep Study

Recruitment Period

An internal database of sleep studies conducted by Dorset County Hospital NHS Foundation Trust was systematically reviewed to identify patients meeting the predefined inclusion criteria, and with no noted exclusion criteria. This process generated a substantial pool of potential participants, all of whom were sent a letter containing a Participant Information Sheet along with an invitation to contact the study organisers to express interest in taking part. Patients who expressed interest in the study underwent telephone screening to assess their suitability for inclusion. Those who were confirmed as eligible following the screening process were subsequently offered a set of three outpatient appointments to attend to undertake the study.

Baseline Period – One Night

At the initial appointment, understanding of the study was confirmed and formal consent was obtained from the participant prior to commencement. Anthropometric data, including height, weight, and collar size were measured and recorded, and participants completed the first weekly questionnaire, designed to evaluate several aspects such as their sleep quality and daytime sleepiness, alertness, and functionality over the previous week. Each participant was subsequently issued with their first ZeusOSA device, which was demonstrated to ensure correct use. Additionally, they were provided with written and pictorial instruction packs, alongside a calendar - outlining the events for each day of the study. During the entire study, participants could contact the study organisers by phone or email for assistance if required. Participants were instructed to wear the CIRCUL ring oximeter every night for the entire study. On the first night, all participants performed a baseline MCSS with no ZeusOSA device.

First Intervention Period – One Week

Over the course of the first week, participants wore their first ZeusOSA device to familiarise themselves with its use and to acclimatise to sleeping whilst wearing it. On the final night of the week, all participants performed a second MCSS whilst wearing the first ZeusOSA device. Throughout the week, participants also completed a brief daily questionnaire and continued nightly monitoring using the CIRCUL ring oximeter.

Second Intervention Period – One Week

At the second appointment, participants returned all devices for data download, cleaning, and recharging and were issued with their second ZeusOSA device. Nightly oximetry data was recorded from the CIRCUL ring smartphone app. They completed a second weekly questionnaire, and any questions, concerns or comments were addressed. The second intervention period replicated the structure of the first - participants followed the same procedure of acclimatisation to the ZeusOSA device, MCSS, short daily questionnaires, and nightly oximetry, whilst using the second ZeusOSA Device.

Study End

At the third appointment, participants returned their allocated devices for data download and cleaning, as well as returning their daily questionnaire packs and completing a final weekly questionnaire. Nightly oximetry data was recorded from the CIRCUL ring smartphone app. Upon completion, they were thanked for their participation, and

their involvement in the study formally concluded. In recognition of their contribution, each participant received a brand-new Zeus ZS2 device, provided by Morgan IAT, which is currently marketed across the UK and Europe as an anti-snoring device.

Sample Size

Sample size was determined by the study statistician. The cross-over sample size calculation determined that a total of 50 patients' complete data would be required to detect an effect size of 10 events/hour (AHI measurement) between active and sham device with 90% power and a type-1 error (alpha) of 5%, assuming a standard deviation of 15 events/hour in AHI (ref. Johnston et. Al, 2002). Complete data from 38 patients would provide 80% power to detect the same effect in AHI.

Statistical Analysis

All analyses were conducted on an intention-to-treat basis using STATA SE 16.1.

The primary analysis was to assess the effect of ZeusOSA active compared to sham device on AHI (measured as number of events per hour). Comparisons on AHI were made using mixed effects Poisson regression, adjusting for baseline AHI and accounting for the within-subject correlations arising from the cross-over design. Treatment order effect was also explored in the model.

A secondary analysis explored the effect of the ZeusOSA active device compared to sham device on ODI in OSA patients, using the same statistical modelling approach as for the primary outcome.

For other secondary objectives, mixed effects linear regression models explored the effect of the ZeusOSA active device compared to sham device on measures of snoring, perceived sleep quality, daytime sleepiness, daytime alertness and daytime functionality in OSA patients. In addition, adverse events and tolerability of the ZeusOSA device were assessed.

Exploratory, post-hoc descriptive analysis was undertaken to examine whether it was possible to identify responders to the ZeusOSA device according to any baseline characteristics.

3 RESULTS

Participant Flow & Clinical Characteristics

Participant recruitment and flow are summarised in Figure 4.0. Recruitment began in January 2023. Data collection began on 1st May 2023 and ended on 31st August 2024 when sufficient datasets had been collected. The demographics and clinical characteristics of the participants who provided complete datasets are summarised in Table 3.1 (demographics and clinical characteristics for all recruited participants is summarised in Appendix 2).

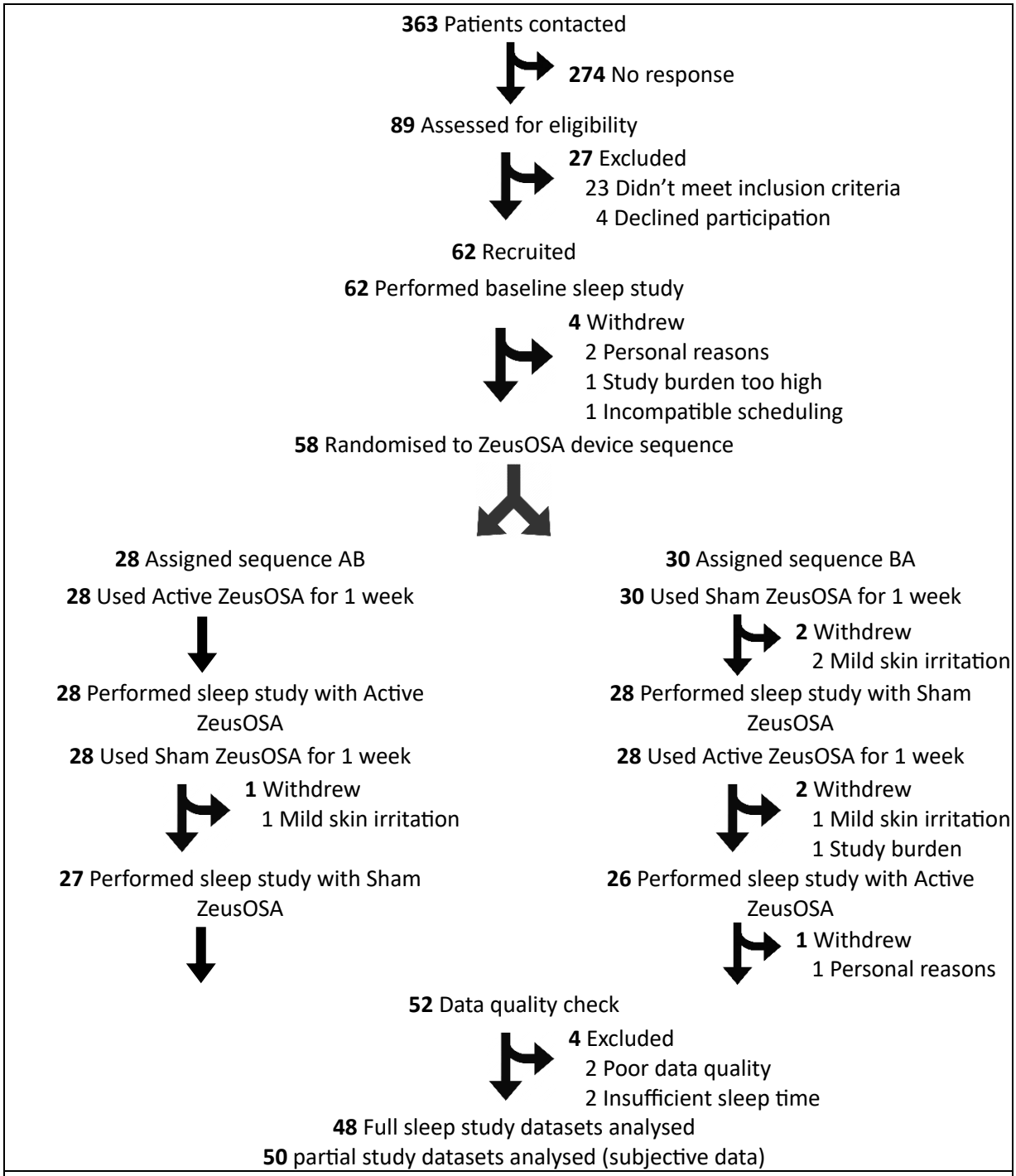

Figure 4.0: CONSORT Participant Flow Diagram
A = active ZeusOSA device, B = sham ZeusOSA device

	Randomly Assigned Intervention Sequence		
Characteristic	**AB (n= 27)**	**BA (n= 21)**	**Total (n= 48)**
Male (%)	20 (74.1%)	13 (61.9%)	33 (68.8%)
Female (%)	7 (25.9%)	8 (38.1)	15 (31.3%)
Age - years	56.0 (12.74)	54.8 (13.58)	55.5 (12.98)
Height - cm	175.6 (8.92)	171.4 (10.22)	173.8 (9.64)
Weight - kg	99.8 (16.02)	93.3 (23.65)	96.9 (19.76)
BMI - kg/m^2	32.4 (5.33)	31.7 (7.49)	32.1 (6.30)
Collar size - inches	16.5 (0.95)	16.1 (1.44)	16.3 (1.19)
AHI at original diagnosis - /hr	15.4 (8.55)	16.3 (9.00)	15.8 (8.67)
ESS - /24	10.0 (5.02)	11.6 (4.84)	10.7 (4.95)

Table 4.1: Baseline demographic and clinical characteristics by assigned device sequence and total: participants with full primary outcome (AHI) data
A = Active ZeusOSA, B = Sham ZeusOSA
Data are mean (standard deviation) except Male and Female which are N (%)

Objective Outcomes

Despite slight improvements from baseline seen in the AHI and ODI across the whole cohort, there were no statistically significant differences between Active ZeusOSA and Baseline or Sham ZeusOSA in any of these MCSS outcomes (Table 4.2). The statistical model confirmed that treatment order had no effect on these outcomes.

Subjective Outcomes

There were statistically significant improvements in all subjective measurements when using Active ZeusOSA compared with baseline. Additionally, perceived sleep quality and perceived daytime functionality were statistically significantly more improved with Active vs. Sham device (Table 4.3). Again, the statistical models confirmed that treatment order had no effect on these outcomes.

Age and sex were minor contributing factors to perceived daytime alertness, with females on average having 7.7 points lower (worse) score than males and older participants having on average a 0.3 lower (worse) score for every additional year. However, these effects did not substantially alter the estimate of the treatment effect and were not statistically significant.

Patients generally tolerated the device well, with 4 out of 62 being withdrawn from the trial due to mild skin irritation at the site of device adhesion. Device compliance rate was >85% and patients reported a strongly positive experience of the ZeusOSA device, giving average satisfaction scores of 30.2 and 27.1 out of 42 in Active and Sham devices respectively. There were no other adverse events.

Variable	Baseline	Active ZeusOSA	Sham ZeusOSA	Difference (Active – Baseline)	Difference (Active – Sham)
AHI (/hr)					
mean (SD)	19.4 (12.51)	17.7 (12.02)	18.8 (11.19)	-1.7 (6.67)	-1.2
95% CI					*-3.2 – 0.9*
p-value				*0.09*[+]	0.27
ODI (/hr)					
mean (SD)	19.0 (12.83)	17.5 (11.28)	18.2 (11.22)	-1.5 (7.19)	-0.8
95% CI					*-2.8 – 1.2*
p-value				0.14[+]	0.42

Snore (%)					
mean (SD)	15.4 (20.19)	16.4 (17.73)	17.2 (19.54)	1.0 (14.15)	-0.6
95% CI					*-4.9 – 3.7*
p-value				0.64[+]	0.78

Table 4.2: MCSS data for baseline, Active ZeusOSA, and Sham ZeusOSA across all complete data (n = 48),

SD = standard deviation, 95% CI = 95% Confidence Interval
AHI = Apnoea-Hypopnoea Index, ODI = 4% Oxygen Desaturation Index, HR = Heart Rate
Difference (Active – Sham) derived from mixed effect Poisson model adjusted for baseline, randomisation sequence and sleep study (first or second)
[+] p-value derived from paired t-test

Variable	Baseline	Active ZeusOSA	Sham ZeusOSA	Difference (Active – Baseline)	Difference (Active – Sham)
ZeusOSA Experience (/42)	N/A	30.2 (5.4)	27.1 (7.74)	N/A	-1.4
mean (SD)					*-3.3 – 0.5*
95% CI					0.149
p-value					
Perceived Sleep Quality (/42)					
mean (SD)	14.9	22.0 (5.35)	19.4 (6.34)	7.1 (6.4)	2.7
95% CI	(6.00)				*0.9 – 4.4*
p-value				<0.001[+]	0.003
Perceived Daytime Alertness (/42)					
mean (SD)	31.55	23.1 (17.57)	24.0 (16.29)	-8.4 (17.7)	-0.8
95% CI	(19.81)				*-4.0 – 2.3*
p-value				0.0015[+]	0.61
Perceived Daytime Sleepiness (/24)					
mean (SD)	10.9	8.5 (4.95)	9.0 (4.88)	-2.4 *(4.1)*	-0.6
95% CI	(5.27)				*-1.4 – 0.3*
p-value				<0.001[+]	0.21
Perceived Daytime Function (%)					
mean (SD)	15.0	22.2 (8.19)	19.4 (8.42)	7.3 (8.4)	2.9
95% CI	(8.98)				*0.99 – 4.78*
p-value				<0.001[+]	0.003

Table 4.3: Questionnaire data for baseline, Active ZeusOSA, and Sham ZeusOSA for all complete data (n = 50)

SD = standard deviation, 95% CI = 95% Confidence Interval
Difference (Active – Sham) derived from mixed effect linear model adjusted for baseline, randomisation sequence and sleep study (first or second)
[+] p-value derived from paired t-test

Responder Group Analysis

Whilst the planned analyses did not show statistically significant differences between active and sham devices, further exploratory, post-hoc analysis was undertaken to examine those participants who were observed to have a positive (non-zero) response to active ZeusOSA device compared to baseline for their AHI measurements (N=29, 60% of all participants). Figure 5.1 displays the range of AHI changes between baseline and Active ZeusOSA use.

These responders experienced a mean reduction in AHI of 5.6 (95% CI 3.7 – 7.5) and a mean reduction in ODI of 5.3 (95% CI 2.8 – 7.8). They also reported improved perceived sleep quality (mean change from baseline 7.7, 95% CI 4.6 – 10.1), improved perceived daytime alertness (mean change from baseline 10.2, 95% CI 3.1 – 17.4), and improved daytime function (mean change from baseline 7.8, 95% CI 4.1 – 11.5). There were no discernible differences in any demographic metrics, baseline objective metrics, or subjective metrics between Responders and the whole cohort or Non-Responders (Table 5.0, subjective responses not presented).

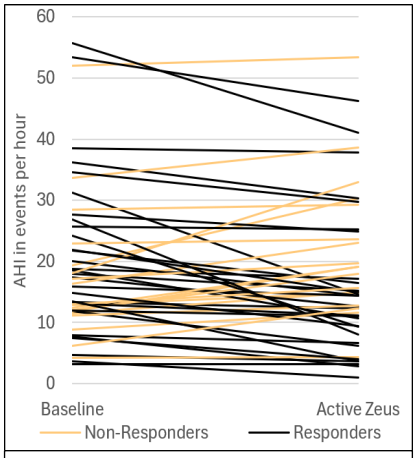

Figure 5.1: Change in AHI between Baseline and using Active Zeus

Characteristic	Non-Responders (n=19)	Responders (n=29)
Male (%)	13 (68%)	20 (69%)
Age - years	53.5 (11.61)	56.8 (13.85)
Height - cm	172.8 (10.60)	174.4 (9.09)
Weight - kg	95.1 (23.92)	98.1 (16.85)
BMI - kg/m^2	31.7 (6.94)	32.4 (5.96)
Collar size - in	16.1 (1.26)	16.5 (1.13)
AHI at original diagnosis - /hr	17.5 (8.28)	14.7 (8.87)
ESS - /24	9.8 (4.91)	11.3 (4.98)

Table 5.0: Characteristics of Responders and Non-Responders

Additional Analyses

An increase in heart rate was observed when using Active ZeusOSA compared with baseline with a mean increase of 3.9bpm (SD 7.8bpm), and this was statistically significant, (t-test p = 0.0114).

This led us to perform additional analyses on participants' Pulse Rise Index (PRI) and Autonomic Arousal Index (AAI), which were both auto-scored by the sleep study analysis software and included in the independently analysed MCSS reports. Responders were found to have a statistically significantly higher rate of autonomic arousals at baseline than Non-Responders (mean AAI = 31.2/hr vs 19.7/hr respectively, t-test p=0.0007), with no difference in PRI.

4 DISCUSSION

This trial successfully recruited a total of 62 participants to undertake a randomised, double-blind, crossover trial. Twelve participants withdrew or were excluded due to a range of factors, with four of these attributing to mild skin irritation resulting from device use. As a result, 48 full datasets were complete to undergo analysis, representing a near achievement of the intended target of 50. Overall, adherence to wearing the device was well maintained throughout the study and participant satisfaction consistently rated high. No adverse events were encountered.

Although no statistically significant improvements in objective data were observed from baseline across all participants, there were notable improvements in subjective outcomes among those using the active ZeusOSA device. A subset group of 'Responders' (n=29, 60%) demonstrated measurable gains in both objective and subjective metrics. These findings are consistent with other research on HNS in OSA. Baseline autonomic arousal index (AAI) may represent a potential indicator for responsiveness to this type of HNS therapy in OSA and may warrant further exploration as a potential predictive factor for this modality.

Zeus OSA Responder Outcomes/ Pragmatic effectiveness

Participants classified as Responders exhibited clear therapeutic benefit, showing a positive response following use of the active ZeusOSA device. These data/findings align with other previously published studies examining hypoglossal nerve stimulation as a treatment for snoring and/or OSA, wherein there are 'Responders' and 'Non-Responders' to treatment. (Heiser et al., 2019; Op de Beeck et al., 2021).

The present results further indicate that a transcutaneous hypoglossal nerve stimulator is well tolerated amongst patients with OSA and can be effectively used, in a domiciliary setting with minimal training, achieving a high degree of success. Because patient compliance is frequently the principal obstacle to OSA management, the observation from this study supports ZeusOSA device as a practical treatment option. While this study has not demonstrated efficacy equivalent to CPAP therapy, it does perform comparatively with CPAP-alternative treatments for OSA such as MAD and positional therapy (Deane et al., 2009; Durán-Cantolla et al., 2015; Farid-Moayer et al., 2013; Johnston et al., 2002; Kram et al., 2017; Mok et al., 2020; Perger et al., 2022) and may be a valuable treatment option for OSA patients who cannot use or tolerate CPAP.

Cardiovascular effects

The elevation in heart rate observed during Active ZeusOSA use was an unanticipated finding. Apnoeas and hypopnoeas often cause a characteristic rise in heart rate, as the body compensates for a dip in oxygen saturation, which resolves when the respiratory event resolves. Accordingly, an intervention that effectively decreases the frequency or severity of apnoeic and hypopnoeic events would ordinarily be expected to decrease overall average heart rate paradoxically, the opposite was observed in this trial. This counterintuitive result underscores the need for further work to examine the physiological cause of this. It was found that the only potential predictor of responsiveness to HNS therapy was having a higher AAI at baseline, which would likely cause a more variable heart rate and may be linked to the increases in heart rate when using HNS observed in this study (Dedhia et al., 2019; Qin et al., 2021).

Considerations

Device Tolerance

The ZeusOSA device was found to be a highly tolerable and feasible option as a treatment, with good compliance rate and acceptability amongst participants. Its practicality suggests potential as an alternative therapy for individuals who are unable to tolerate CPAP and considering invasive HNS treatments.

Four participants experienced some mild skin irritation at the device adhesion site under the jaw (7.5%), all of which resolved rapidly after they were withdrawn from the study and self-treated at home with over-the-counter skin creams. In all cases, the irritation appeared to be due to the mechanical stress of peeling away the adhesive each morning, as opposed to an allergic response. This is consistent with general findings regarding adhesive treatments wherein 6-15% of patients experience similar irritation in response to adhesive use on skin, with irritation increasing with patient age (Grove et al., 2022; Karwoski & Plaut, 2004; Konya et al., 2010; Tokumura et al., 2005).

Technical Challenges

Participant recruitment was facilitated by sending out a Patient Information Sheet with a letter inviting interested parties to contact the study organisers to take part. This study had a high rate of completion; two participants found the study burden too great, two experienced difficulties with the devices and apps involved in data collection, and a further two reported that they were unable to fall asleep whilst wearing the required devices. Three separate devices were used for the study and a bespoke app to be installed on personal smartphones, therefore, a moderate degree of technological literacy was required. Future studies could reduce this dependency by integrating simplified monitoring methods such as PAT based sensors, which are available on physically smaller and more discreet devices less likely to interfere with natural sleep.

All data collection was undertaken in the participants' own homes, without direct supervision from the study staff, although all participants had continuous access to support and were able to contact study staff for help and advice while they were enrolled. There were a limited number of failed sleep studies which were repeated at the earliest

opportunity. Use of the ZeusOSA device was intended to be objectively monitored via an app, collecting usage times and stimulation strength setting through a Bluetooth connection to a smartphone. However, the app was not available on online app stores in time for the commencement of data collection, thereby, necessitating reliance on participant self-reporting to document device use with no objective measure to confirm accuracy. Patients were instructed on how to set the strength of the stimulation from the ZeusOSA device during their first appointment, along with a practical demonstration to familiarise them with the expected sensation. While there was no way to be sure that the ZeusOSA device had been correctly placed and an appropriate strength setting selected during the study, this does reflect real-world domiciliary usage amongst OSA patients, providing a more realistic representation of how patients would use the device outside formal healthcare supervision.

The Sham ZeusOSA device was manufactured to provide electrical stimulation upon switching on and setting the stimulation strength but does not provide any further stimulation after this. In contrast, the Active ZeusOSA device begins to provide treatment stimulation twenty minutes after set-up process is complete. This was intended to minimise any perceptible difference in participant experience between the two devices as part of the double-blind nature of the study. However, if a participant woke during the night, they would have been able to feel the stimulation from the Active ZeusOSA and the absence of any stimulation from the Sham ZeusOSA, potentially unblinding the order of devices for this patient. For future studies, a sham device could be made to provide sub-therapeutic stimulation, or to provide intermittent stimulation throughout the night to try to negate this unblinding effect. Despite this, the sequence in which participants received their devices did not appear to influence the outcomes of the study.

Study Population

This was a single-centre study and participants were ethnically homogenous (white British) which is largely consistent with the population of our recruitment pool in Dorset which is 97.1% white (ONS, 2023). Therefore, our data derived from this exploratory study do not represent an accurate ethnic cross section of the population of the UK or beyond. Further research across broader populations would be necessary to assess any population differences and to ensure that this treatment model is free from health inequality.

Future Considerations for this Technology

Given the range of responses between Responders and the group as a whole, more work needs to be done to ascertain whether there is a demographic, clinical, or anatomical factor causing this difference. A potential predictor for responsiveness was found to be baseline autonomic arousal index (AAI), which was significantly higher in Responders than Non-Responders, however there is little in the available literature to evidence this, therefore this finding requires further exploration.

It is well-documented that the anatomy of the upper airway has an impact on likelihood of a patient having OSA, and how severe the OSA may be (Edwards et al., 2017; Shrikrishna, BH et al., 2023). Documenting the anatomical features of the upper airway – for example, by Mallampati score – was not a part of data collection for this study, though this may play a role in whether patients respond to transcutaneous hypoglossal nerve stimulation to treat OSA and may be a very useful metric to collect in future studies.

Drug-Induced Sleep Endoscopy (DISE) has been used to investigate the differences between Responders and Non-Responders to the implanted Inspire device (Baptista et al., 2020; Chao & Thaler, 2020), with a suggestion that upper airway patency may be the critical factor which may influence candidate selection for devices of this type in the future. However, DISE is an expensive and invasive procedure. The ZeusOSA device could be used as an alternative indicator of potential success with an implanted device. A trial of using a ZeusOSA device offers a much cheaper, non-invasive, and simple route to determining response than DISE and could play an important role as a stand alone Sleep Apnoea treatment or as part of routine candidate assessment for implanted HNS devices to treat OSA. This would both improve treatment compliance, reduce assessment costs and risks, as well as improving success rates for the implanted devices, particularly in cases where drug-induced sleep may not be recommended due to comorbidities.

6 OTHER INFORMATION

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APPENDICES

Appendix 1 – Questionnaires used in the study

Perceived Sleep Quality

Participants were asked to choose a response using the below scale, for seven descriptor pairs.

Please tick the box on the scale that best fits your quality of sleep whilst using the Zeus Device for a week								
< Restless	☐	☐	☐	☐	☐	☐	☐	Restful >
< Broken	☐	☐	☐	☐	☐	☐	☐	Undisturbed >
< Uncomfortable	☐	☐	☐	☐	☐	☐	☐	Comfortable >
< Dreamless	☐	☐	☐	☐	☐	☐	☐	Dream-filled >
< Loud snoring	☐	☐	☐	☐	☐	☐	☐	No snoring >
< Couldn't sleep	☐	☐	☐	☐	☐	☐	☐	Slept easily >
< Partner annoyed	☐	☐	☐	☐	☐	☐	☐	Partner happy >

For each question, the boxes from left to right are given values from 0 – 6.
Scores from each question are summed to give a **total score from 0 – 42**.

Perceived Daytime Sleepiness

A modified Epworth Sleepiness Scale questionnaire was used; the modification was in the wording of the question to specify that participants should consider only the last week when they choose their responses. Daytime sleepiness was assessed using modified version of the Epworth Sleepiness Scale (ESS). The only alteration was a clarification instructing participants to consider only the previous seven days when selecting their responses.

Imagine doing each of these things over the last week. **What do you think your chances of dozing off would be in these situations?**	No chance of dozing	Small chance of dozing	Medium chance of dozing	High chance of dozing
Sitting and reading for an hour	☐	☐	☐	☐
Watching TV for an hour	☐	☐	☐	☐
Sitting and waiting in a public place for an hour	☐	☐	☐	☐
As a passenger in a car for an hour	☐	☐	☐	☐
Lying down to rest in the afternoon for an hour	☐	☐	☐	☐
Sitting and talking to someone for an hour	☐	☐	☐	☐
Sitting quietly after lunch (without alcohol) for an hour	☐	☐	☐	☐
Driving a car, while stopped for a few minutes in traffic	☐	☐	☐	☐

For each question, the boxes from left to right are given a score from 0 – 3.
Scores from each question are summed to give a total score from **0 – 24**.

Scores for each question were assigned on a 0-3 scale and summed to produce a total ESS score (range: 0-24).

Perceived Daytime Functionality

A modified FOSQ-10 questionnaire was used; the modification – comprised the inclusion of two supplementary questions addressing social interaction in domestic and community settings.

How much did tiredness or sleepiness reduce your ability to do the following things over the last week?	Tiredness did not affect this	Tiredness made this slightly harder	Tiredness made this much harder	Tiredness made this impossible	N/A - I didn't do this at all
Concentrating or staying focused on a task	☐	☐	☐	☐	☐
Remembering things	☐	☐	☐	☐	☐
Preparing and eating a meal	☐	☐	☐	☐	☐
Working on hobbies (e.g. sewing, gardening)	☐	☐	☐	☐	☐
Doing housework	☐	☐	☐	☐	☐
Taking a short drive (less than 30mins)	☐	☐	☐	☐	☐
Taking a long drive (more than 30mins)	☐	☐	☐	☐	☐
Errands involving driving or taking public transport	☐	☐	☐	☐	☐
Doing paperwork or dealing with financial affairs	☐	☐	☐	☐	☐
Doing employed or volunteer work	☐	☐	☐	☐	☐
Socialising with your family or people in your home	☐	☐	☐	☐	☐
Socialising with friends or colleagues outside of home	☐	☐	☐	☐	☐

For each question, the first four boxes from left to right are given a score from 0 – 3. If the 'N/A' box is indicated, the entire question was excluded from the final summation. Each response (excluding 'N/A') was assigned a score from 0 to 3. Responses (items?) marked 'N/A' were omitted from the final summation.

Scores for each question were tallied and presented as a **percentage** of a maximum score for the number of questions asked. Aggregate scores were presented as a percentage of the maximum score based on the number of questions asked.

Perceived Daytime Alertness

Participants were asked to choose a response, using the scale below, for seven descriptor pairs.

Participants were asked to rate

Please tick the box on the scale that best fits how you felt in the day after using the Zeus Device for a week								
< Sleepy	☐	☐	☐	☐	☐	☐	☐	Refreshed >
< Unhappy	☐	☐	☐	☐	☐	☐	☐	Cheerful >
< Forgetful	☐	☐	☐	☐	☐	☐	☐	Attentive >
< Unproductive	☐	☐	☐	☐	☐	☐	☐	Productive >
< Unsociable	☐	☐	☐	☐	☐	☐	☐	Sociable >
< Tired	☐	☐	☐	☐	☐	☐	☐	Alert >
< Lethargic	☐	☐	☐	☐	☐	☐	☐	Energetic >

For each question, the boxes from left to right are given values from 0 – 6.
Scores from each question are summed to give a **total score from 0 – 42**.

ZeusOSA Experience

Participants were asked to choose a response on a scale between to opposing descriptors for seven descriptor pairs.

Please tick the box on the scale that best fits your experience of using the Zeus Device for a week								
< Uncomfortable	☐	☐	☐	☐	☐	☐	☐	Comfortable >
< Complicated	☐	☐	☐	☐	☐	☐	☐	Simple >
< Ineffective	☐	☐	☐	☐	☐	☐	☐	Effective >
< Difficult	☐	☐	☐	☐	☐	☐	☐	Easy >
< Long-winded	☐	☐	☐	☐	☐	☐	☐	Quick >
< Useless	☐	☐	☐	☐	☐	☐	☐	Useful >
< Impractical	☐	☐	☐	☐	☐	☐	☐	Practical >

For each question, the boxes from left to right are given values from 0 – 6.
Scores from each question are summed to give a total score from **0 – 42**.

Appendix 2: Demographic and clinical characteristics for all recruited participants

	Intervention Sequence		
Characteristic	**AB (n= 29)**	**BA (n= 33)**	**Total (n= 62)**
Male (%)	21 (72.4%)	17 (51.5%)	38 (61.3%)
Female (%)	8 (27.6%)	16 (48.5%)	24 (38.7%)
Age - years	56.6 (13.73)	55.2 (12.78)	55.8 (13.14)
Height - cm	175.4 (8.88)	169.7 (11.28)	172.4 (10.55)
Weight - kg	98.8 (15.90)	92.9 (23.21)	95.7 (20.18)
BMI - kg/m^2	32.2 (5.24)	32.5 (8.10)	32.3 (6.86)
Collar size - in	16.4 (0.93)	16.0 (1.41)	16.2 (1.22)
AHI at original diagnosis - /hr	15.7 (8.32)	15.6 (8.35)	15.7 (8.27)
ESS - /24	9.8 (4.96)	11.5 (4.57)	10.7 (4.80)

Appendix 2: Baseline demographic and clinical characteristics by sequence and total: all participants
SD = standard deviation, A = Active ZeusOSA, B = Sham ZeusOSA
Data are mean (SD) except Male and Female which are number (%)