The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders

Abdullah Saad S ALQarni

CID: 01658832

This thesis is submitted in partial fulfilment of the requirement for a Doctor of Philosophy degree at Imperial College London

Clinical and Academic Department of Sleep and Breathing,

National Heart and Lung Institute

06 January 2022

Supervisors

Professor Mary J Morrell, Imperial College London

Dr Julia Kelly, Royal Brompton Hospital, Imperial College London

Declaration of Originality

I, Abdullah Saad ALQarni, declare that this PhD thesis comprises my own work except where otherwise acknowledged. The studies in this thesis were designed with the support of my supervisors, Professor Mary Morrell and Dr Julia Kelly. For Study 1 (Chapter 3), I designed the review; Searching the literature, assessment of eligibility, and extraction of the data were performed by the author and Dr Julia Kelly; I also performed all associated analyses. A Research for Patient Benefit grant (grant no. PB-PG-0817-20049) from the National Institute for Health Research (NIHR) was awarded to my supervisor Dr Julia Kelly to conduct Study 2 as a principal investigator (Chapter 4, The POSA Trial) in collaboration with Oxford Respiratory Trial Unit. During the first year, I worked in collaboration to develop the protocol, set up and support all the participating nationwide sites (n=7 sites) and collect data. For Study 3 (Chapter 5), I designed the study and developed the novel analysis method for scoring arousability and recovery. I collected data from the healthy participants from Saudi Arabia (n=22), whereas Alexis Perkins collected data from London (n=5). In addition, I performed all associated analyses including statistical analyses. Data collected as a patient case study were collected by my supervisor Dr Julia Kelly.

Copyright Declaration

Acknowledgements

First and foremost, I would like to express my sincere gratitude to my supervisors, Professor Mary Morrell and Dr Julia Kelly, for their guidance throughout my PhD; your unwavering support to me in completing this thesis will not be forgotten.

I am deeply grateful for my parents for their heart-warming support throughout my PhD and for my two sons for tolerating my absence during my studies.

I am also very grateful for my teacher Dr Ghazi ALOtaibi, who supported me to overcome all administrative challenges throughout the years of my postgraduate studies.

I would like to extend my sincere thanks to the POSA Trial team for their support in enabling me to do the trial and special thanks for the NIHR for funding it.

I also would like to thank the research laboratory of my supervisor Professor Mary Morrell for providing me with sleep equipment while I was not in the UK because of the COVID-19 pandemic.

I would like to offer my special thanks to the director and staff of The Sleep Medicine and Research Center at King Abdulaziz University Hospital for their exceptional support during the COVID-19 pandemic and for their generosity in providing me with free workspace, sleep studies equipment and all associated accessories. Specifically, I want to extend my thanks to the director of the centre, Professor Siraj Omar Wali, as well as Dr Faris Alhejaili, Dr Hajed ALOtaibi, Ms Haneen ALMotary, and Dalyah ALQaidi.

Finally, this PhD was not possible without the generous fund and support of my employer, Imam Abdulrahman Bin Faisal University, and the Saudi Arabian Cultural Bureau in the UK.

Abstract

Vibrotactile positional therapy (PT) is a relatively new treatment for positional obstructive sleep apnoea (POSA). It uses vibrotactile stimulus to encourage the sleeper to change position when supine. The overall aim of this thesis was to investigate the efficacy of vibrotactile PT as a clinical treatment for patients with POSA. To achieve this, different experimental approaches were used, including a systematic review and meta-analysis, a clinical trial, and a physiological study.

The systematic review was carried out to evaluate the effect of vibrotactile PT on apnoea hypopnoea index (AHI), percentage of time spent in supine (%Tsupine), and patient-centred outcomes in patients with POSA compared to baseline. The results showed that vibrotactile PT was effective in reducing both AHI and %Tsupine. Although the Epworth Sleepiness Scale and the Functional Outcomes of Sleep Questionnaire minimally improved, these changes did not reach clinically important differences; however, limited data were found on quality of life (SF-36) vitality score.

A prospective, three-month, multicentre, randomised, parallel, double-blind trial (The POSA Trial, ISRCTN51740863) was developed to investigate the effect of vibrotactile PT on AHI, quality of life and daytime functioning at follow-up, adjusted for the baseline, in patients with POSA compared to sham-vibrotactile PT. Baseline data (AHI, quality of life and daytime functioning) obtained from the participants recruited at the Royal Brompton Hospital are presented in the thesis. The mean baseline AHI for RBH participants was in the mild OSA category compared to the patients in the systematic review; however, a higher baseline %Tsupine was found. The baseline patient-centred outcomes were also comparable to those found in the systematic review.

A physiological study in healthy participants (n=27) was carried out to investigate the effect of vibrotactile stimulus on arousability from sleep. A novel analysis method was developed to measure arousability. This included the duration from the vibrotactile stimulus to the position change using polysomnography. The results of this study showed heterogenous arousability responses to the vibrotactile stimulus with different phenotypes. Compared to males, healthy females took longer to respond to the vibrotactile stimulus and, therefore, were more resilient to arousability.

In summary, the findings of this thesis have shown that vibrotactile PT devices are effective in treating patients with POSA. However, limited data on sensitive patient-centred outcomes exist. The POSA trial will provide data to address this evidence gap. Furthermore, the physiological findings in people without OSA showed that males are more arousable than females. This information may be of value when considering personalisation of clinical treatment. Future research of POSA will need to consider the arousability phenotype when planning treatment options.

Table of Contents

List of Tables

List of Figures

Appendices

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnoea hypopnoea index
APAP	Auto-titrated positive airway pressure
BMI	Body Mass Index
CGI-C	Clinical Global Impression of Change
CI	Confidence interval
CO_2	Carbon dioxide
CRFs	Case Report Forms
ECG	Electrocardiography
EDS	Excessive daytime sleepiness
EEG	Electroencephalography
EMG	Electromyography
EOG	Electrooculography
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire
FRC	Functional Residual Capacity
IQR	Interquartile range
MAD	Mandibular advancement device
MCID	Minimum clinically important difference
MRI	Magnetic resonance imaging
NHS	National institute of health
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
ODI	Oxygen desaturation index
ORTU	Oxford Respiratory Trials Unit
OSA	Obstructive sleep apnoea
Pcrit	Critical closing pressure
PGI-C	Patient Global Impression of Change
POSA	Positional obstructive sleep apnoea
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses

PROSPERO	International Prospective Register for Systematic Reviews
PSG	Polysomnography
PSQI	Pittsburgh Sleep Quality Index
PT	Positional therapy
Q1	First quartile
Q3	Third quartile
RBH	Royal Brompton Hospital
RCT	Randomised controlled trial
REM	Rapid eye movement sleep
RLS	Restless leg syndrome
SD	Standard deviation
SF-36	36-Item Short Form Survey
SIVs	Site initiation visits
SOPs	Standardised operating procedures
SpO2	Oxygen saturation as measured by pulse oximeter
TBT	Tennis ball technique
TMF	Trial Master File
TST	Total sleep time
VAS	Visual Analogue Scale

CHAPTER 1: General Introduction

1.1 Overview of the Thesis

This introduction will provide the background to this thesis, starting with an overview of the prevalence, physiological, clinical phenotypes, and treatments of obstructive sleep apnoea (OSA). Positional obstructive sleep apnoea (POSA) is included in a separate section because it is the core topic of this thesis. This section includes a detailed discussion of the definitions, prevalence, and clinical features of POSA. In addition, the underlying anatomical and physiological abnormalities are discussed. The various treatments available for POSA are also included, with a focus on the new generation vibrotactile positional therapy (PT). Because the measurement of arousability is an integral part of this thesis, arousability and the previous methods of measuring it are also reviewed in detail. Moreover, gender differences and how they influence subjective and objective sleep quality and the clinical presentations of OSA are reviewed. In the final section of this chapter, the aims of the thesis are presented.

1.2 Background

OSA is a prevalent respiratory disorder estimated to occur in nearly 1 billion people worldwide (Benjafield *et al.*, 2019; Yingjuan *et al.*, 2019). It is characterised by repetitive partial or complete obstruction of the upper airway during sleep, which results in hypoxemia and frequent arousals that can lead to sleep fragmentations. OSA has been linked to several health consequences, such as cardiovascular diseases (CVDs) (Floras, 2018), neurocognitive disfunction (Olaithe *et al.*, 2018), and poor quality of life (Moyer *et al.*, 2001).

OSA is a multifactorial disorder. Accumulating evidence shows that various anatomical and physiological factors contribute to the pathogenesis of OSA. In the majority of cases, the anatomical abnormality is the most important factor determining who develops OSA (White, 2016). OSA patients tend to have an upper airway with small cross-sectional area (Ciscar *et al.*, 2001). However, the airways are also more prone to collapse, and this factor has been linked to enlarged upper airway soft tissues (Sforza *et al.*, 2000) due to obesity (Carter &

Watenpaugh, 2008). Abnormalities in the craniofacial bony structures have also been identified as a risk factor for developing OSA (Lowe *et al.*, 1996; Schwab *et al.*, 2003).

More recent evidence suggests various physiological traits play an important role in the development of OSA (Jordan *et al.*, 2014; Shin *et al.*, 2016). These traits vary widely in OSA patients, and they include a low respiratory arousal threshold, a high loop gain, and poor function of the upper airway muscles (Eckert & Wellman, 2015). In the following section, the physiological and clinical OSA phenotypes that have been identified are summarised.

1.3 Physiological Phenotypes of OSA

Although it is known that OSA is a disorder of anatomical compromise, researchers in the field are currently identifying other physiological mechanisms that could also contribute to the development of OSA. Physiological traits that have been identified to contribute to the development of OSA include a low respiratory arousal threshold, high loop gain, and compromised function of the upper airway muscles.

1.3.1 Respiratory arousal threshold

The respiratory arousal threshold has been defined as the level of intrathoracic pressure, at which point a person will wake up from sleep, immediately before cortical arousal (Eckert & Younes, 2013). A low arousal threshold indicates that the sleeper can be easily awoken from sleep. Conversely, a person with a high arousal threshold may require more stimuli to awake from sleep.

It is now recognised that patients who suffer from OSA have a higher respiratory arousal threshold (≤25 cmH_2O), compared to those who do not have OSA (Osman *et al.*, 2018; Shin *et al.*, 2016). This occurs in those who have had the disease for some time, where they developed a high respiratory arousal threshold as a compensatory mechanism. However, a number of studies have shown that at least 30% of patients with OSA have a low respiratory arousal threshold (Eckert, 2018). Interestingly, this subgroup of OSA patients are not obese (Gray *et al.*, 2017), which may demonstrate that non-anatomical aspects can contribute to the development of OSA.

A low arousal threshold means that a negative intrathoracic pressure (as low as –15 cm H_2O) can lead to waking up from sleep (Eckert, 2018). It has been long thought that waking up

early following a respiratory disturbance is a protective mechanism for OSA patients. However, it has now been shown that arousals do not occur, or they occur after a respiratory event in a majority of respiratory events (75%) in OSA patients (Eckert & Younes, 2014). This means that arousal from sleep is a consequence of OSA for a majority of respiratory events. Waking up prematurely can prevent the accumulation of ventilatory stimulus, which effectively recruits upper airway muscles to reopen obstructed upper airways (Eckert & Younes, 2013). This premature and frequent arousal from sleep stops OSA patients from entering stable and deep sleep (stage N3). The consequence of this is that the sleeper enters a vicious cycle of premature arousal, which will lead to light sleep, which in turn predisposes the sleeper to another respiratory event that leads to premature arousal, and so the cycle goes on (Eckert & Younes, 2013). However, when sleepers enter a state of deep sleep and then develop a respiratory event, it is harder for them to arouse from sleep and therefore get enough time to recruit upper airway muscles. This phenomenon has been demonstrated in people with a respiratory arousal threshold that was higher during deep sleep (Carberry *et al.*, 2016; Ratnavadivel *et al.*, 2009).

Because of the improved understanding of the underlying pathophysiological mechanism, the low arousal threshold is now targeted with drug therapy, at least in research settings. This treatment option is discussed in section 1.6.

1.3.2 Ventilatory control instability (high loop gain)

The high loop gain (so called ventilatory control instability) has been identified as another important pathophysiological trait that contributes to the pathogenesis of OSA. Originally, loop gain was an engineering concept used to describe the stability of negative feedback control systems (Shin *et al.*, 2016). In OSA, loop gain is defined as the ratio of the amount of ventilatory response to a given ventilatory disturbance (Osman *et al.*, 2018). This loop gain has three main components: (1) plant gain, (2) controller gain, and (3) circulation delay (Osman *et al.*, 2018). The plant gain represents the reservoir of carbon dioxide (CO_2) in the blood, lungs, and tissues (Osman *et al.*, 2018). The controller gain represents chemosensitivity (Osman *et al.*, 2018). The circulation delay is the time it takes for CO_2 to mix with blood and to reach chemoreceptors (Osman *et al.*). Patients with high loop gain produce an exaggerated ventilation response to minimal changes in CO_2 (Osman *et al.*,

2018). High loop gain has been shown to be present in approximately a third of OSA patients (Eckert, 2018). As a result of this suggestion, therapeutic options have been identified to modify the loop gain (Wellman *et al.*, 2008). These therapeutic options are discussed in section 1.6.

1.3.3 Poor function of the upper airway muscles

The third pathophysiological trait that has been identified to contribute to the pathogenesis of OSA is poor function of the upper airway muscles. Two main mechanisms have been identified to contribute to the compromised upper airway muscles. They include poor muscles responsiveness and effectiveness (Lai *et al.*, 2019). Muscle responsiveness is defined as the ability of the upper airway muscles to increase activity in response to the increased neural drive that results from respiratory stimuli during sleep. These stimuli include changes in the negative pharyngeal pressure or changes in arterial blood gas (most frequently CO_2) (Lai *et al.*, 2019). Patients with poor muscle responsiveness have a reduced ability to increase muscle activity, according to the level of neural drive. Poor effectiveness of the upper airway muscles is also the inability of these muscles to dilate the upper airway in the presence of airway narrowing, despite the presence of satisfactory neural drive (Lai *et al.*, 2019). In approximately one third of OSA patients, these dysfunctionalities (poor responsiveness and effectiveness) are considered the most important mechanism leading to the development of OSA (Eckert *et al.*, 2013). Personalised treatment for such underlying pathophysiological mechanisms is discussed in section 1.6.

To summarise, the field has taken major steps to identify the three physiological traits (i.e. low respiratory arousal threshold, high loop gain, and poor upper airway muscle function) that are linked to the development of OSA. Efforts are now being made to develop relatively simplified methods to identify these traits. There is also a search for new therapeutic options, which are discussed in section 1.6.

1.4 Clinical Phenotypes of OSA

In addition to the identification of different physiological phenotypes, there is also great interest in the clinical phenotyping of OSA patients. The current approach to the diagnosis of OSA does not fully take into consideration the multifactorial nature of the disease. OSA is a heterogenous disease associated with a number of risk factors, a number of clinical

presentations, and multiple disease consequences. Taking this heterogeneity into consideration is important for the success of any treatment.

A recent review paper identified 16 major studies that have attempted to clinically phenotypes OSA (Zinchuk & Yaggi, 2020). These studies used different analytical approaches to cluster OSA based on demographic data, anthropometric data, symptoms, polysomnographic features, and associated comorbidities. In these studies, three to seven clusters were found. Based on these clusters, the authors of the review paper derived four common clinical phenotypes (Zinchuk & Yaggi, 2020). These four phenotypes are based on demographic data, anthropometric data, symptoms, polysomnographic features, and associated comorbidities (Figure 1.1). In addition, two clusters based on polysomnographic features were identified (Figure 1.2).

The four clinical phenotypes included the following:

1- '*Classic OSA*': in which patients tend to be predominantly younger, obese, male, and complain of drowsy driving and excessive sleepiness. They present with low comorbidities, high AHI, and moderate hypoxemic burden. This phenotype is at a higher risk of coronary heart disease (CHD) and heart failure. These patients seem to benefit the most from CPAP treatment.
2- '*Oldest comorbid OSA*': in which patients tend to be predominantly older, obese males with low to moderate symptom burden (e.g. excessive sleepiness, snoring, disturbed sleep). In addition, these patients suffer from significant hypoxemic burden, high AHI, and are considered at the highest risk of comorbidities such as diabetes, hypertension, and CVDs. This phenotype seems to be the lowest in terms of CPAP adherence and benefit.
3- '*Insomnia, female OSA*': in which patients tend to be predominantly female, middle age, slightly obese, and have significant insomniac symptoms. These symptoms include difficulty to enter and or maintain sleep and early morning awakenings. These patients present with moderate AHI and hypoxemic burden. CPAP treatment can offer this phenotype a medium benefit, in which apnoeic symptoms are relieved. However, it is associated with medium adherence. CPAP adherence and benefit may be boosted by the use of cognitive behavioural therapies for insomnia.

4- '*Upper airway symptoms, youngest OSA*': Patients in this cluster tend to be the youngest — and predominantly male. They present mainly with upper airway symptoms such as chocking, snoring, breathing cessation, and sudden awakening from sleep. These patients tend to be non-sleepy and non-insomniac. AHI in this phenotype is moderately high, but the hypoxemic burden is lowest across the phenotypes. In this phenotype, adherence to CPAP is low.

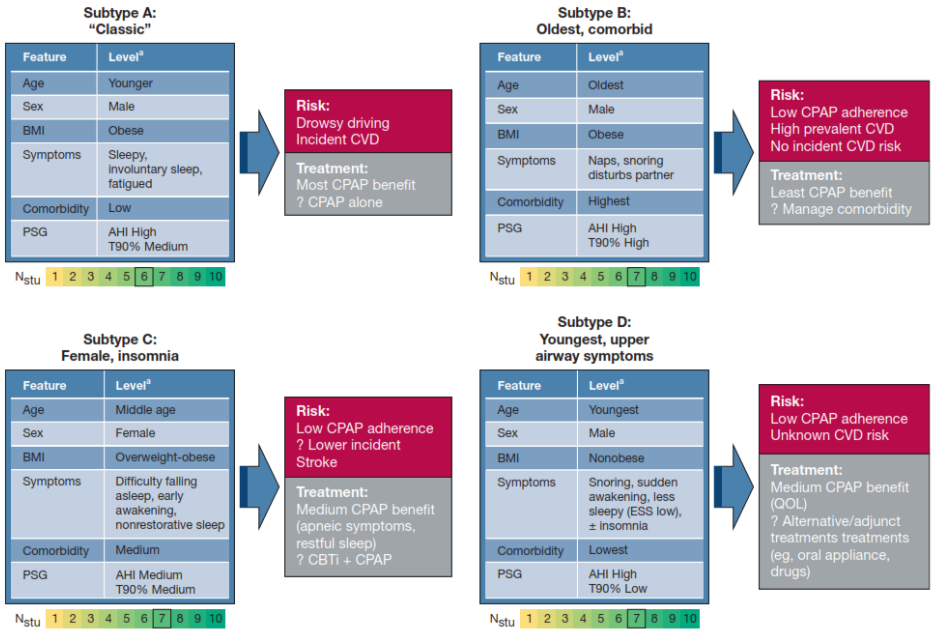


Figure 1.1: Clinical phenotypes of OSA

This figure shows the clinical phenotypes identified based on 16 OSA phenotyping studies. AHI: apnoea-hypopnoea index; T90%: percent of total recording or sleeping time spent with oxygen saturation under 90%; ESS: Epworth Sleepiness Scale; CBTi: cognitive behavioural therapy for insomnia; CVD: cardiovascular disease; QOL: quality of life (assessed by using the Short Form-36 Health Survey); PSG: polysomnography; The subtypes included in the figure were drawn from 16 different studies that tried to phenotype OSA. Therefore, N_{stu}: is the number of phenotyping studies that identified similar subtypes. The figure is adopted from (Zinchuk & Yaggi, 2020) with permission (appendix 1).

In addition to the clinical phenotypes, two other phenotypes were identified (Zinchuk & Yaggi, 2020). These were based on studies that used polysomnographic features. The authors described these two phenotypes as follows:

1- '*Severe, hypoxemic OSA*': in which patients tended to be predominantly male, and the highest in terms of body mass index (BMI), hypoxemia, and respiratory events, especially apnoeas.

2- '*Severe, non-hypoxemic OSA*': in which patients tended to be predominantly male, but with a lower BMI, sleepiness, and the lowest hypoxemic burden.

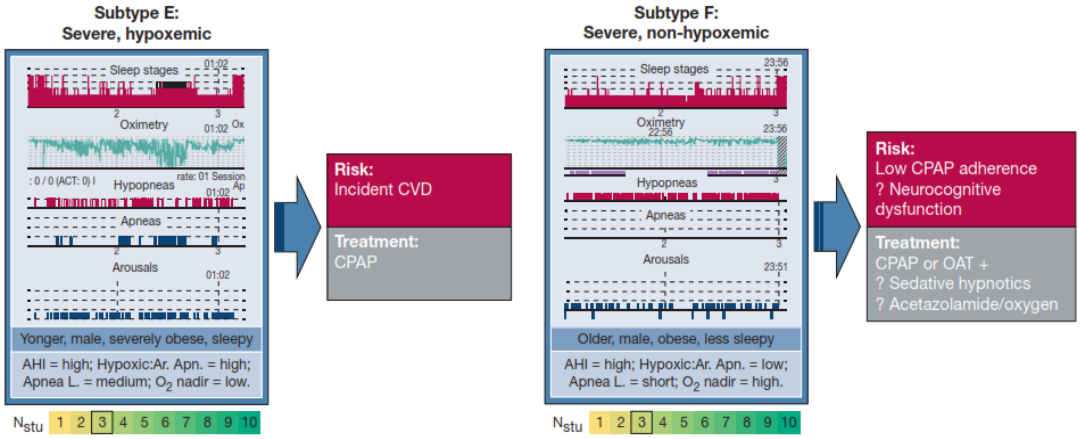


Figure 1.2: Polysomnographic phenotypes

This figure shows the polysomnographic phenotypes identified by (Zinchuk & Yaggi, 2020). AHI: apnoea-hypopnoea index; CPAP: continuous positive airway pressure; Hypoxic:Ar Apn.: ratio of apnoeas with 4% desaturation only to apnoeas with arousal only; Apn. L.: apnoea length; CVD: cardiovascular disease; OAT: oral appliance therapy. The subtypes included in the figure were drawn from 16 different studies that tried to phenotype OSA. Therefore, N_{stu}: is the number of phenotyping studies that identified similar subtypes. This figure is adopted from (Zinchuk & Yaggi, 2020) with permission (appendix 1).

The identification of these clinical phenotypes has facilitated multiple research pathways to improve both diagnosis and treatment. However, it is important to note these phenotypes are not fully reproducible; and therefore, searching for better identification methods to might enhance reproducibility of phenotyping (Zinchuk & Yaggi, 2020).

Other phenotypes that have been reported in the literature are based on polysomnographic features. These include REM-predominant and supine-predominant OSA (Zinchuk *et al.*, 2017).

The REM-predominant OSA includes patients who are predominantly female and of younger age. Their PSG features include reduced total sleep time, REM duration, and sleep efficiency. During REM, these patients show lower respiratory drive and long and severe hypoxia. ***The supine predominant OSA is the main topic of this thesis and, therefore, is discussed in detail in section 1.5***.

1.5 Positional Obstructive Sleep Apnoea (POSA)

OSA is affected by the sleeping position (Cartwright, 1984), and the supine position is known to be the position in which the upper airway is most likely to collapse (Frank *et al.*, 2015). When OSA occurs in the supine position, it is referred to as positional obstructive sleep apnoea (POSA) (Frank *et al.*, 2015). As shown in Figure 1.3, respiratory events (desaturations and apnoeas) are predominantly seen during the supine position (van Kesteren & Hilgevoord, 2015).

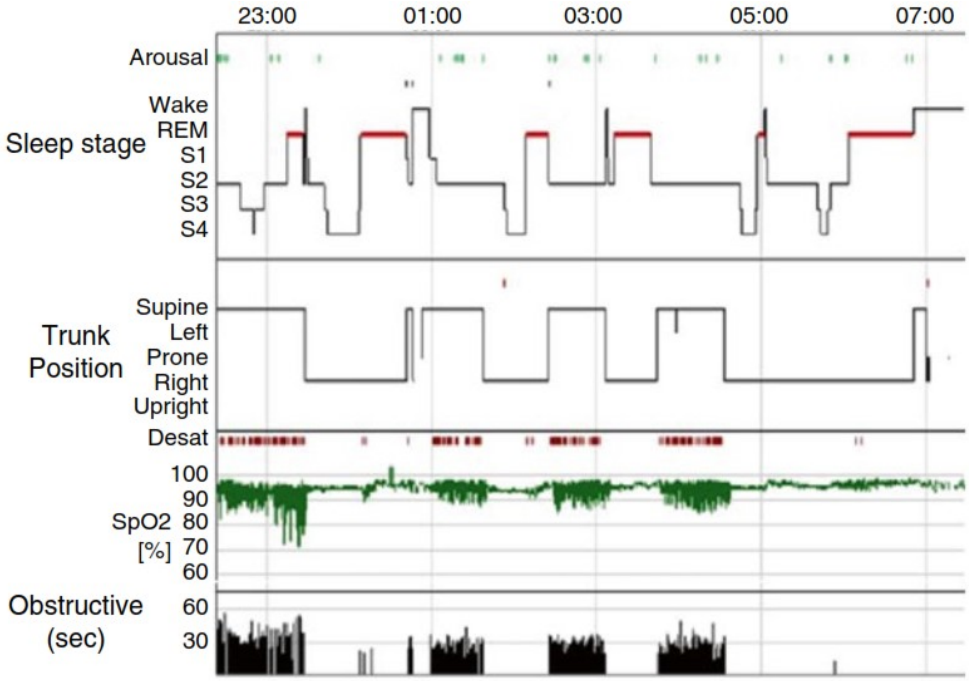


Figure 1.3: A polysomnographic hypnogram showing positional obstructive sleep apnoea

This figure shows an overnight sleep study. Please note that, when in the supine position, patients start having obstructive events (in black) and desaturation events (in green). Moreover, note the arousal marker at the top of the picture shows that the arousal events also predominantly occurred in the supine position. S1: stage N1; S2: stage N2; S3: stage 3; S4: stage 4; Sec: seconds; SpO_2: Oxygen saturation as determined by pulse oximetry. Modified from (van Kesteren & Hilgevoord, 2015) with permission (appendix 2).

1.5.1 Definitions of POSA

The POSA definition varies in the literature; Cartwright defined the POSA as having an AHI in the supine position that is twice that of AHI in the non-supine position, along with an AHI of more than five events/hr (Cartwright, 1984). Mador et al. amended this definition by adding a non-supine AHI of less than five events/hr and a minimum of 15 minutes of sleep time in the supine and non-supine position (Mador *et al.*, 2005). Marklund et al*.,* however, defined it as having an AHI of ≥ 10 events/hr in the supine position, along with an AHI < 10 events/hr in the non-supine position. Bignold et al. was the first to combine the Cartwright criteria and a minimum of 20 minutes in the supine, as well as the non-supine position, along with a non-supine AHI that is less than 15 events/hr (Levendowski *et al.*, 2018). In the Amsterdam Classification of POSA, it was proposed that, once a patient is diagnosed as an OSA patient, and has at least 10% of the total sleep time spent in the non-supine and supine sleeping position, they can be classified into three categories based on their response to PT (Frank *et al.*, 2015). One classification was patients who were treatable (i.e. a true positional patient). A further classification was patients who could not benefit from PT and were therefore non-positional. A final classification was being treatable but not curable (i.e. the OSA was a multifactorial patient) (Frank *et al.*, 2015). Levendowski et al. introduced a new definition in which the overall AHI needed to be at least as 1.4 times the non-supine AHI (Levendowski *et al.*, 2014). The same group revised their criteria so the overall AHI needed to be 1.5 times that of the non-supine AHI (Levendowski *et al.*, 2018). The reason for this revision was to increase the likelihood that the AHI would improve by a minimum of 50% by avoidance of supine sleep (Levendowski *et al.*, 2018). In one study, the researchers compared all the above criteria and found the overall/non-supine AHI criteria was the most consistent criteria for the detection of POSA patients, who were most likely to show significant and important decreases in terms of the overall AHI if the supine position was avoided (Lee *et al.*, 2017; Levendowski *et al.*, 2018).

1.5.2 Prevalence of POSA

The prevalence of POSA differs based on the criteria used in each study. However, a number of studies have shown that more than 50% of patients with OSA have POSA (Lee *et al.*, 2017; Mo *et al.*, 2011; Oulhaj *et al.*, 2017; Ravesloot *et al.*, 2016). A recent population-based study, which screened more than 1,700 individuals using PSG, found that POSA was present in 75%

of OSA patients (Heinzer *et al.*, 2015). In addition, they found that POSA was present in 53% of the entire population they screened and that exclusive POSA (non-supine AHI < 5 events/hr) was as prevalent as 36% (Heinzer *et al.*, 2018). POSA patients tended to be more prevalent in the mild and moderate categories of AHI, with a prevalence of more than 80% in either category (Mo *et al.*, 2011). This compares to a prevalence of about 40% in the severe AHI category (Mo *et al.*, 2011).

1.5.3 Clinical features of POSA

The clinical features of POSA patients are usually different, compared to non-positional OSA patients. Typically, POSA patients are younger than non-positional OSA (Yingjuan *et al.*, 2019). It is also more common in men than women (Yingjuan *et al.*, 2019). Positional patients tend to occur in the mild and moderate categories of AHI severity (Mo *et al.*, 2011). Furthermore, their snoring is noticeable by their partners to be louder when in the supine position (Joosten *et al.*, 2014). In addition, their objectively measured daytime sleepiness using maintenance of wakefulness test is less than non-positional OSA patients (Oksenberg *et al.*, 2009). BMI in POSA patients is typically lower than non-positional OSA patients (Mo *et al.*, 2011). In addition, POSA patients have a smaller neck and waist circumference (Yingjuan *et al.*, 2019). Moreover, they have a lower Mallampati score (Yingjuan *et al.*, 2019). In terms of ethnicity, POSA has been reported to be more prevalent in Asian patients (Mo *et al.*, 2011).

1.5.4 Anatomical abnormalities associated with POSA

A full understanding of the anatomical abnormalities in patients with POSA is still not well developed, compared to OSA patients. However, over the past two decades, progress has been made in uncovering the anatomical compromise in patients with POSA. It has been shown that, when OSA patients change body position, the size and shape of their upper airway is affected (Walsh *et al.*, 2008). Specifically, the upper airway changes to a more circular shape in the lateral position, compared to a more traverse elliptical airway in the supine position (Walsh *et al.*, 2008). This is represented in Figure 1.4.

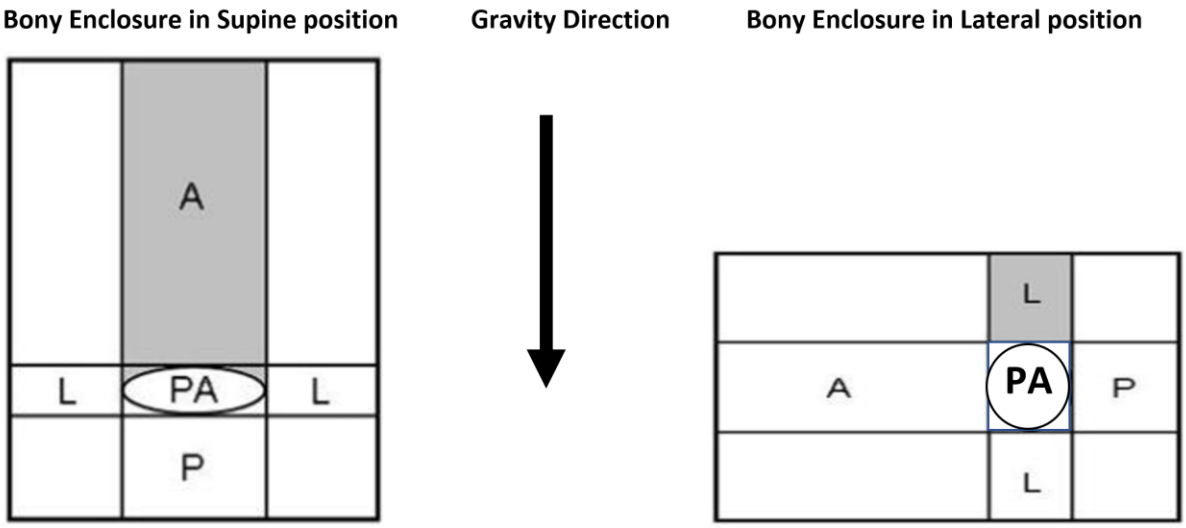


Figure 1.4: A schematic diagram of the upper airway size and shape in supine and lateral position in OSA patients

This figure represents a schematic diagram of the bony enclosure of the upper airway in supine and lateral positions for OSA patients. Note that the compartments represent how the upper airway tissues are arranged around the pharyngeal airway. Please also note that, on the left diagram (supine position), the pharyngeal airway shape is elliptical, compared to the more circular airway on the right diagram (lateral position). The shaded area in the left diagram (supine) represents the anterior soft tissues mass acting on the pharyngeal airway. This is compared to the right diagram (lateral), which has a smaller shaded area, representing the mass of lateral soft tissues. A: anterior soft tissues mass; L: lateral soft tissues mass; P: posterior soft tissues mass; PA: pharyngeal airway; OSA: obstructive sleep apnoea. Modified from (Walsh et al., 2008) with permission (appendix 3).

One study used magnetic resonance imaging (MRI) with three-dimensional reconstruction of the images to compare the upper airway morphology in POSA patients to non-positional OSA patients and healthy control participants (Saigusa *et al.*, 2009). They found that POSA patients had a smaller pharyngeal lateral wall and soft tissues compared to non-positional OSA patients. This may indicate that smaller gravitational forces could be exerted on the lumen of the pharynx compared to non-positional OSA patients (Saigusa *et al.*, 2009). In addition, they found that POSA patients had lower facial height and smaller craniofacial volume. Additionally, they found POSA patients had a backward mandible position, compared to the maxilla.

The site of the upper airway collapse seems also to differ in POSA patients compared to non-positional OSA patients. A drug-induced sleep endoscopy study compared sites of collapse between POSA and non-positional OSA patients (Victores *et al.*, 2014). They found that the most common site of collapse for both POSA and non-positional OSA patients (in the supine position) was the palatal collapse, accounting for 91% and 82%, respectively. They also found most POSA patients showed a combined tongue and palatal collapse. In the supine position, both tongue-related collapse, and epiglottic collapse, were twice as frequent in POSA patients (73% and 64%, respectively) compared to non-positional OSA patients (36% and 36%, respectively) (Victores *et al.*, 2014). As seen in Figure 1.5, 91% of POSA patients improved their upper airway obstruction upon change in body position from supine to lateral (Victores *et al.*, 2014). However, in non-positional OSA patients, the pattern of obstruction was not significantly altered by the changing body position.

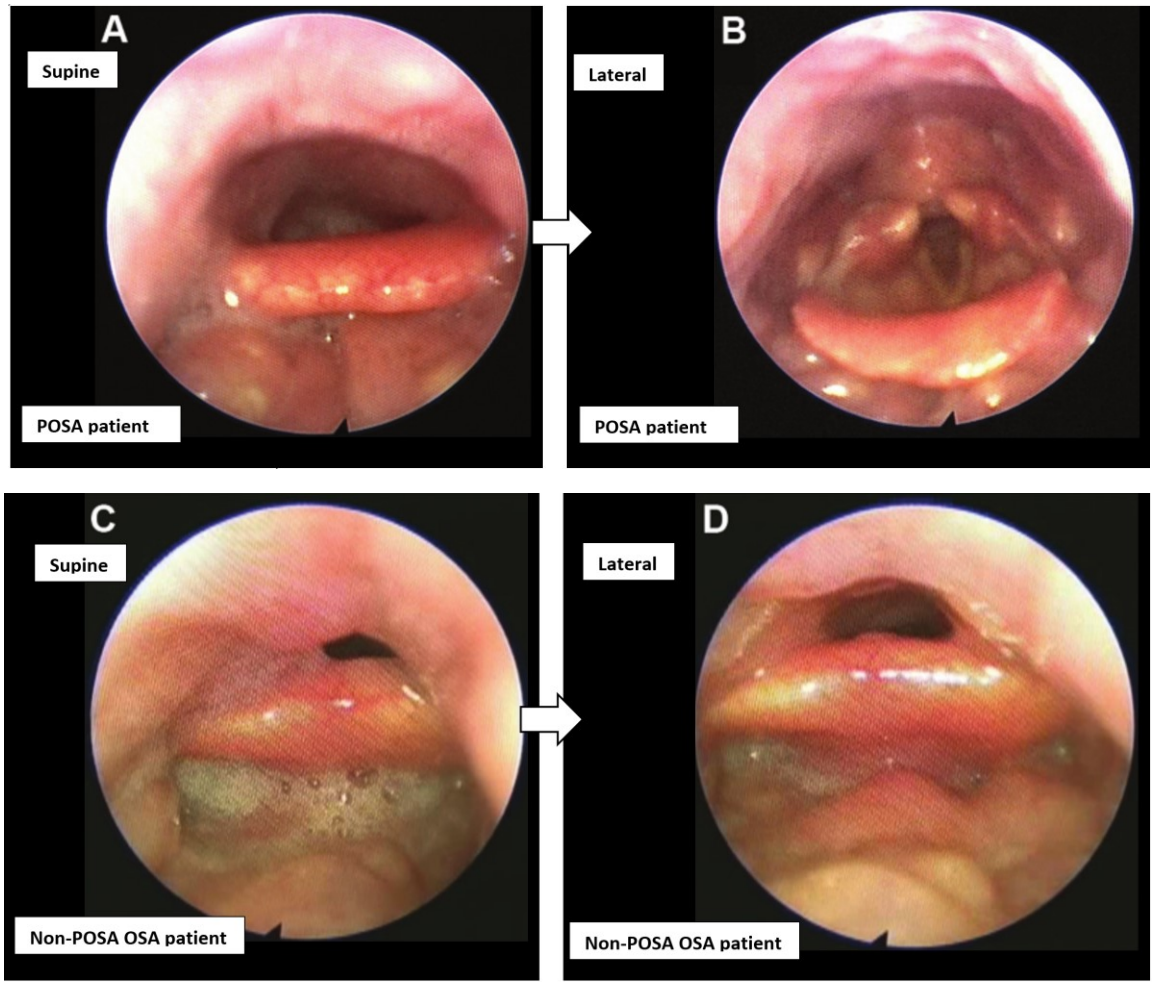


Figure 1.5: Site of collapse in supine compared to lateral position in POSA patients

The nasopharyngoscopic view of a POSA (A and B) and non-positional OSA patient (C and D). Note that, when the POSA patient was in the supine position (A), the airway collapsed, but when the same patient moved into the lateral position (B), the airway remained open. However, when the non-positional OSA patient was in the supine position (C), the airway collapsed, and there was almost no improvement when they switched to the lateral position (D). Modified from (Victores et al., 2014) with permission (appendix 4).

A recent study investigated whether moving from the supine to the lateral position improved the upper airway patency in OSA patients and simultaneously measured the epiglottic pressure and airflow (Marques *et al.*, 2017). By grouping participants according to the structure that caused the collapse, the authors were able to define three groups, using natural supine endoscopy. The groupings were (1) epiglottis collapse, (2) tongue-related collapse, and (3) non-tongue related collapse (lateral walls and palatal collapse). Contrary to common belief, they found that tongue-based collapse did not improve when the position was changed from the supine to the lateral position. Similarly, the associated airflow did not improve (Figure 1.6). This refutes the belief that the tongue falls back during supine sleep, associated with gravitational forces. Only epiglottic collapse had a significant improvement when moving from the supine to the lateral position, with a significant improvement in the associated airflow. Non-tongue-related collapse slightly improved following a change position.

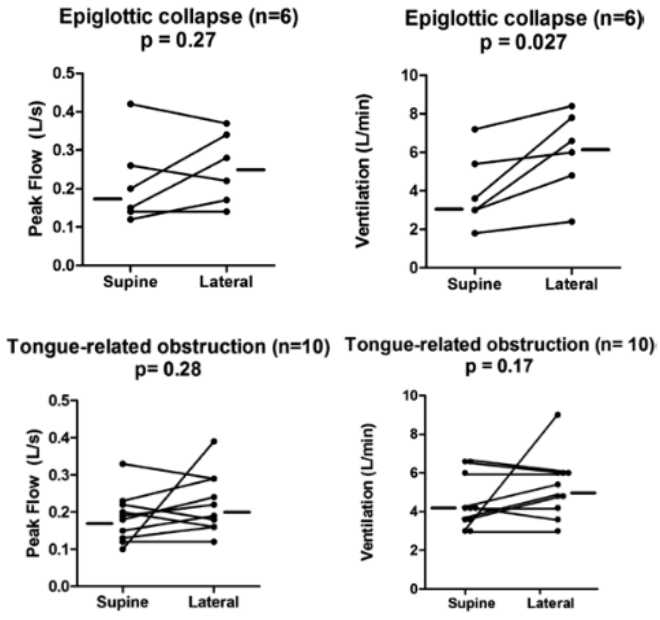


Figure 1.6: Airflow between the supine and lateral positions in both tongue-based collapse and epiglottic collapse

Note that ventilation and airflow did not improve with tongue-based collapse when the patients changed from the supine to the lateral position. However, in patients with epiglottic collapse, both ventilation and airflow were improved when the position was changed from the supine to the lateral position. Modified from (Marques et al., 2017) with permission (appendix 5).

1.5.5 Physiological traits in POSA

Physiological traits in POSA are less studied compared to OSA. A recent review on this topic showed that sleeping in the supine position, compared to the lateral position, in OSA patients during NREM stages resulted in higher (positive) critical closing pressure (Pcrit) values (2–3 cm H_2O) (Joosten *et al.*, 2014). Such findings indicate a more collapsible upper airway in the supine position (Joosten *et al.*, 2014). The studies included in the review found the supine position was determined by the trunk. Recent studies, however, have demonstrated that, even if the neck/head position is in the supine position, regardless of the trunk position, higher Pcrit values were noted (Joosten *et al.*, 2015).

Other physiological traits include the upper airway gain, arousal threshold, and loop gain. In a physiological study, Joosten et al. investigated the effect of the lateral position on these physiological traits in severe OSA patients (Joosten *et al.*, 2015). They also conducted a sub-analysis on POSA patients and found that switching from the supine to the lateral position significantly increased both passive and active muscle responsiveness, and there was also a significant reduction of the upper airway critical closing pressure. However, no improvements were noted in the loop gain or arousal threshold. In the sub-study on the POSA patients, moving to the lateral position significantly improved the upper airway gain and Pcrit, resulting in almost complete resolution of the OSA (Joosten *et al.*, 2015)**.**

Similar to other physiological traits, most lung volume studies have not focused on POSA patients. However, moving from the lateral to the supine position is known to result in a reduction of functional residual capacity (FRC). It has previously been proposed that a reduction in FRC during sleep can trigger several potential mechanisms that can contribute to the development of OSA. These include a reduction in lung compliance, a reduction of outward chest wall recoil, and a shift of blood centrally (Avraam *et al.*, 2019). A recent study that investigated FRC during sleep in healthy males and females (both normal and overweight participants) demonstrated that FRC was significantly reduced when moving from the lateral to supine position during sleep (Avraam *et al.*, 2019). This reduction was independent of weight and gender. A similar drop in the FRC (340 ml = 13%) was noted in another study that compared awake FRC when moving from the lateral to the supine position in POSA patients (Joosten *et al.*, 2015).

1.6 Treatment of OSA

The field is currently moving toward a personalised approach for the management of OSA. In this section, the therapeutic options currently available for OSA are discussed. This includes continuous positive airway pressure (CPAP), mandibular advancement devices (MADs), hypoglossal nerve stimulation, surgical treatments, and pharmacological treatments.

1.6.1 Continuous positive airway pressure (CPAP)

There are numerous treatment options for OSA. However, the first line and the most clinically effective treatment is CPAP. This works by applying a positive pressure to the upper airway, splinting and preventing its collapse (Sullivan *et al.*, 1981). CPAP reduces the AHI to less than five events/hr in greater than 90% of patients (Gottlieb & Punjabi, 2020). In addition, a recent systematic review and meta-analysis of 184 studies demonstrated that CPAP, compared to no treatment, resulted in a clinically significant reduction of excessive daytime sleepiness, motor vehicle accidents, and blood pressure (Patil *et al.*, 2019). In addition, it resulted in an important improvement in sleep-related quality-of-life measures (Patil *et al.*, 2019). Although it is considered the gold standard and most efficacious treatment, its effectiveness is hindered by poor patient adherence rates, which can be as low as 29% (Wozniak *et al.*, 2014).

1.6.2 Mandibular advancement devices (MADs)

While CPAP is the first line of therapy for OSA, mandibular advancement devices (MADs) can be offered to patients with mild or moderate OSA severity who are intolerant to CPAP (Gottlieb & Punjabi, 2020). It can also be prescribed for patients with mild and moderate OSA who prefer an alternative therapy to CPAP (Gottlieb & Punjabi, 2020). MADs consist of bespoke, denture-like plates designed to fit the lower and upper teeth (Gottlieb & Punjabi, 2020). They can be adjusted to advance the mandible in a forward motion, which increases the upper airway space (Gottlieb & Punjabi, 2020). These devices are less effective in reducing the AHI, and compared to CPAP, MADs result in AHI reduction of approximately 50% (Sutherland *et al.*, 2015). However, because of greater adherence to MADs, the efficacy of MADs may be comparable to CPAP (Phillips *et al.*, 2013). Many health outcomes have been shown to be improved by MADs. These include, blood pressure, daytime sleepiness,

and quality of life (Phillips *et al.*, 2013). An important point is that MADs are less effective in REM and supine-dependent OSA (Sutherland *et al.*, 2015). Some adverse events that have been reported with MADs include movement of teeth and temporomandibular joint discomfort. The recent European Respiratory Society guidelines reviewed data from 13 studies (n=597 patients) that compared CPAP and MAD. Despite effectiveness of MAD, the task force suggested that CPAP should be used as first line treatment (Randerath *et al.*, 2021).

1.6.3 Hypoglossal nerve stimulation

Another treatment option for OSA is a surgically implanted hypoglossal nerve stimulation device. This treatment works by stimulating the hypoglossal nerve, which enhances tongue protrusion (Gottlieb & Punjabi, 2020). This device consists of a pulse generator with effort sensor and stimulation lead (Strollo Jr *et al.*, 2014). The effort sensor is used to detect the ventilatory effort and is implanted between the internal and external intercoastal muscles. This stimulation lead is implanted in the submental area and is used to stimulate the branches of the hypoglossal nerve responsible for tongue protrusion. This device has been tested for selected OSA patients with (1) moderate to severe OSA with AHI less than 50 events/hr, (2) inability to use CPAP, (3) BMI less than 32 kg/m², and (4) patients without concentric upper airway collapse, as confirmed by endoscopy (Strollo Jr *et al.*, 2014). In the STAR trial, this device was effective in reducing the AHI by approximately 70% (Strollo Jr *et al.*, 2014). However, the applicability of such treatment is limited because of its invasive nature, and it is associated with a high cost.

An alternative to this invasive option is the transcutaneous electrical stimulation of the upper airway dilator muscle. In a feasibility study, Steier *et al.* found a reduced AHI with treatment, from 28 to 10 events/hrs. When the stimulation was withheld, the AHI increased back to 27 events/hr (Steier *et al.*, 2011). In a sham-controlled RCT (the TESLA trial; *n* = 36), the device was effective in reducing the ODI by a mean of 4 (95% CI -0.6 to 8.9) events/hr (Pengo *et al.*, 2016). However, when sub-group analysis was performed in responders (with predominantly mild to moderate OSA), there was a reduction in the group mean AHI by 9 (95% CI 2.0 to 16.2) events/hrs and in the ODI by 10 (95% CI 3.9 to 16.0) events/hr (Pengo *et al.*, 2016). The modest reduction of the respiratory events in the whole sample showed that

the higher effectiveness in the 'responders' is another indication that OSA is a heterogenous disease, and, therefore, a personalised treatment approach is needed. The selection of participants may also explain the significant results from the STAR trial, compared to the TESLA trial. In the STAR trial, patients were assessed for absence of concentric collapse of the upper airway. This was used as a major inclusion criterion, which was assessed via endoscopy. However, this was not performed in the TESLA trial because the trial procedures were non-invasive.

1.6.4 Surgical treatments

Another treatment option for OSA is surgical treatments. Most of the surgical procedures focus on modifying anatomical structures, rather than bypassing structures (such as tracheostomy). The most common surgery is the uvulopalatopharyngoplasty (Gottlieb & Punjabi, 2020). This surgery is a partial or complete excision of the soft palate and the uvula, as well as the tonsillectomy (Gottlieb & Punjabi, 2020). The success rate of this surgery was about 50% (Caples *et al.*, 2010). A number of other surgical procedures exist, such as radiofrequency ablation, and laser-assisted uvulopalatoplasty. A systematic review and meta-analysis has concluded that most of these procedures are associated with inconsistent results, small sample sizes, and misleading definitions, which may also influence the reported success rates (Caples *et al.*, 2010; Elshaug *et al.*, 2007).

Another surgical procedure is the maxillomandibular advancement. This procedure is achieved by the *LeFort I* maxillary plus bilateral mandibular osteotomies and with forward fixation of the facial skeleton (Gottlieb & Punjabi, 2020). Recent meta-analysis that included 45 studies showed that MMA produced a mean percentage reduction of the AHI by 80% (Zaghi *et al.*, 2016). In addition, the recent ESR guidelines reviewed the data from one study that compared the auto-titrated positive airway pressure (APAP) and the maxillomandibular advancement. The task force suggested that either the CPAP or MMA can be used as treatment in adult OSA patient (Randerath *et al.*, 2021).

1.6.5 Pharmacological treatments

The pharmacological treatments discussed in this section are relatively new options for OSA, and they are still under investigation. However, recent efforts to identify and understand

the underlying physiological traits, discussed in section 1.3, have increased the viability of pharmacological therapy as an option for OSA patients.

- **Drugs targeting upper airway dilator muscles**

Recent trials using drug therapy to improve upper airway patency by modifying muscle responsiveness are promising. These studies targeted the serotonergic and noradrenergic neurons because the firing frequencies of these neurons are substantially reduced during sleep (White, 2016). When serotonin and noradrenaline were applied to the neurons responsible for genioglossus (GG) muscle activity, the GG muscle activity increased significantly (White, 2016). However, during REM sleep, these neurons are under muscarinic cholinergic inhibition and therefore are mostly unresponsive to excitation by neurotransmitters such as serotonin and noradrenaline (White, 2016). This may explain the modest improvements in OSA, when selective serotonin reuptake inhibitors were used, such as fluoxetine (Hanzel *et al.*, 1991), paroxetine (Kraiczi *et al.*, 1999), and ondansetron (Stradling *et al.*, 2003). Similar results were found when using noradrenergic reuptake inhibitors such as protriptyline (Brownell *et al.*, 1983). This finding may be explained by the high alerting properties of adrenergic agonist drugs, which negatively affect sleep (White, 2016).

- **Drugs targeting high loop gain**

High loop gain has been targeted by two main treatments: oxygen therapy and acetazolamide. Oxygen therapy may reduce the high loop gain by reducing responsiveness to PCO_2 at the central chemoreceptor and carotid bodies (assuming healthy respiratory control and sea-level atmospheric pressure) (White, 2016). In OSA patients with high loop gain, oxygen therapy reduces AHI by approximately 50% (Edwards *et al.*, 2014; Wellman *et al.*, 2008). However, such treatment effects on other non-selected OSA populations (without high loop gain) were not so promising (White, 2016). This finding may highlight the need for a personalised approach to the diagnosis and treatment of OSA. Acetazolamide, which is a respiratory stimulant, was also tested for the treatment of patients with high loop gain; it resulted in approximately a 50% reduction in AHI (Edwards *et al.*, 2012).

- **Drug targeting low arousal threshold**

Another physiological trait that has been targeted with drug therapy is the low arousal threshold, discussed in section 1.3.1. For the upper airway muscle to activate and open the upper airway, enough time is needed before arousal occurs. Thus, by elevating the arousal threshold in OSA patients with a low arousal threshold, enough time is given for the upper airway muscle to dilate the airway. Therefore, using a hypnotic to increase the arousal threshold, such as eszopiclone, has shown promising results and resulted in significant improvements in sleep quality and daytime functioning (Roth *et al.*, 2005).

A common theme in all of the treatment options discussed above is that the success rate was variable across patients with different OSA severity. This variability may also be accounted for by the different physiological traits in the patients selected. This could be a catalyst for the field to adopt a more personalised approach to the diagnosis and treatment of OSA. However, because many health-care systems do not have the capacity to test for these different traits, simple and clinically applicable tests are much needed.

- **Drugs targeting daytime symptoms**

Excessive daytime sleepiness (EDS) is one of the most frequent symptoms in patients with OSA (Mehra *et al.*, 2021). Despite effective treatment of OSA, residual sleepiness can persist (Mehra *et al.*, 2021). The prevalence of the residual sleepiness ranges from 16% to 58% despite adequate adherence to CPAP (Mehra *et al.*, 2021). Number of therapeutic agents were developed to treat this residual sleepiness.

Modafinil which is a wakefulness promoting agent can be used to treat residual sleepiness in OSA patients (Rosenberg *et al.*, 2021). This medication is approved in the United States and was approved in Europe but it had been recently withdrawn because of possible risks of CVDs and neuropsychiatric disorders (Mehra *et al.*, 2021). Number of trials have shown that Modafinil was effective in reducing EDS. A recent meta-analysis on data from 1466 patients found that Modafinil was effective in reducing ESS by 2.2 points (Chapman *et al.*, 2016). In addition, the review showed that it improved the maintenance of wakefulness test compared to placebo by 3 minutes (Chapman *et al.*, 2016). However, this medication has been shown to be linked to a higher risk of stroke in patients with OSA (Mehra *et al.*, 2021). In addition, it has been shown to increase systolic blood pressure by 3 mmHg compared to placebo (Mehra *et al.*, 2021).

Another agent that promotes wakefulness is Solriamfetol. This medication is a norepinephrine and dopamine reuptake inhibitor (Rosenberg *et al.*, 2021). Solriamfetol is currently approved in the United States and in Europe. A recent study that randomised 459 OSA patients showed that a minimum of 75mg of Solriamfetol significantly reduced the ESS to less than 10 points in more than 50% of the studied patients compared to 38% in the placebo group (Schweitzer *et al.*, 2019). In addition, the maintenance of wakefulness test was reduced by more than 20 minutes in 54% of participants who used Solriamfetol compared to 23% in the group that used placebo drug (Schweitzer *et al.*, 2019). Side effects of this medication were mild or moderate and were more common in the group using Solriamfetol compared to placebo (Schweitzer *et al.*, 2019). Most frequent side effects were headache, insomnia, nausea, anxiety, and upper respiratory tract infections (Mehra *et al.*, 2021).

Another therapeutic agent that can be used for treatment of EDS is Pitolisant (Rosenberg *et al.*, 2021). It is a selective histamine H3-receptor antagonist which can be used to promote wakefulness in OSA patients who suffer from EDS (Mehra *et al.*, 2021). Recently, the effect of Pitolisant was investigated compared to placebo on 244 OSA patients who were adherent to CPAP but had residual EDS (Pépin *et al.*, 2021). The ESS was significantly reduced by 2.6 points compared to placebo (Pépin *et al.*, 2021). Most common sides effects were headache and insomnia (Pépin *et al.*, 2021).

One of the therapeutic options that can be used for OSA patients is positional therapy. Because positional therapy is a core topic of this thesis, it was given a separate section in which it will be discussed in more details.

1.7 Positional therapy (PT) as a treatment for POSA

PT has been shown to be a promising treatment in patients with POSA (Ravesloot *et al.*, 2017). PT is any technique that can be used to prevent sleeping in the supine position (Ravesloot *et al.*, 2013). A number of techniques have been used, and they include traditional PT and the new generation vibrotactile PT devices.

1.7.1 Traditional PT techniques

Traditional PT techniques are usually bulky objects, like a tennis ball, or an object of similar size that are inserted in a pocket and sewn into the back of nightwear. These traditional

techniques work by causing discomfort when patients move into the supine position, thus urging them to move to a non-supine position. These techniques cause significant discomfort and frequent awakenings. A number of studies have evaluated the efficacy of these techniques and found they are efficacious in reducing supine sleep time and therefore AHI (Bignold *et al.*, 2009; Loord & Hultcrantz, 2007; Oksenberg *et al.*, 2006). However, they are very poorly received by patients, mainly due to excessive discomfort (Bignold *et al.*, 2009; Loord & Hultcrantz, 2007; Oksenberg *et al.*, 2006). This has resulted in a low long-term compliance rate (10%) (Bignold *et al.*, 2009). Therefore, traditional PT techniques are not considered a satisfactory treatment that can be used routinely for POSA patients for a long period of time.

1.7.2 Vibrotactile PT devices

As a result of the poor tolerability and compliance with traditional PT techniques, a number of devices have recently been developed; these are referred to as vibrotactile PT devices. All of these devices work by producing gentle vibrotactile stimuli to urge patients to avoid sleeping in the supine position (Ravesloot *et al.*, 2016).

There are currently four vibrotactile PT devices that have been tested clinically and are available in the market. These different vibration devices are worn on different sites on the body, including the back of the neck (Levendowski *et al.*, 2014), the chest (Bignold *et al.*; van Maanen *et al.*, 2013), and the forehead (Hidalgo Armas *et al.*, 2019). The Night Shift™ Sleep Positioner (Advanced Brain Monitoring Inc., California, USA) is worn on the back of the neck (Levendowski *et al.*, 2014). The NightBalance™ Sleep Positioner Trainer (Den Haag, the Netherlands) and the BuzzPOD Body Position Orientation Device (Gorman ProMed Pty Ltd., Victoria, Australia) are worn around the chest (Bignold *et al.*, 2011; van Maanen *et al.*, 2013). The Somnibel™ Positional Therapy System (Sibel, Barcelona, Spain) is secured over the forehead (Hidalgo Armas *et al.*, 2019). Figure 1.7 displays pictures of these devices.

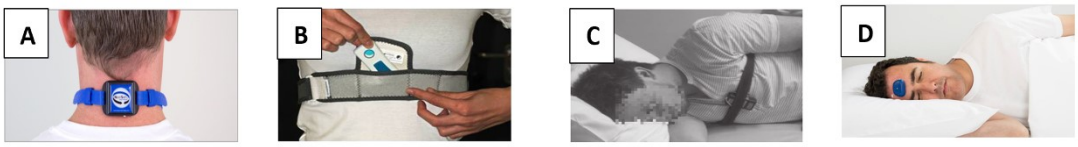


Figure 1.7: Positional therapy devices on different bodily sites

This figure shows the different positional therapy devices in their different bodily sites. In picture (A), the Night Shift device is shown; it is worn around the neck. In picture (B), the Night Balance Sleep Positioner device is shown; it is worn around the chest. In picture (C), the BuzzPOD device is shown; it is also worn around the chest. In picture (D), the Somnibel is shown; it is secured on the forehead. Pictures are modified from (Bignold et al., 2011; Dieltjens et al., 2015; Hidalgo Armas et al., 2019; Levendowski et al., 2014) with permission (appendix 6).

In the following section, a brief description will be given of the common features to all of these devices. A detailed description of the devices used in this thesis is given in chapter 2, section 2.6.

All the above devices are small, simple, and lightweight vibrotactile devices. As described above, the different devices are worn on different bodily sites, which include the neck, chest, or forehead. These devices contain position sensors to determine the sleeping position. In addition, they contain small vibrating motors that are similar to the ones in contemporary smartphone devices. These motors are responsible for producing the vibrotactile stimulus. These devices can be worn on different bodily sites via Velcro type belts (chest worn devices), silicon rubber bands (neck worn device), or they can be secured using clips to a sticker (forehead secured device). All of them work by detecting the supine position during sleep, and in response they start producing gentle vibrations, which increases gradually until a change in sleep position is detected. All of the devices are able to monitor usage and compliance data.

- **Efficacy of the PT devices**

The efficacy of the vibrotactile PT devices has been investigated by many studies. A systematic review and meta-analysis has been performed as part of this thesis and is presented in chapter 3.

1.8 Arousability and PT

One of the potential consequences of using the vibrotactile stimulus is that it may cause arousal from sleep and sleep fragmentation. This fragmentation might be due to either

frequent awakenings or frequent cortical arousals. An awakening is classified to have occurred when a cortical arousal lasts for more than 15 seconds (Berry *et al.*, 2012).

1.8.1 The AASM criteria for scoring an arousal from sleep

A cortical arousal is defined by the AASM as 'an abrupt shift in EEG to a higher frequency, including alpha, theta, or beta, for at least 3 seconds, with at least 10 seconds of stable sleep preceding the change' (Berry *et al.*, 2012). Arousals are part of the normal sleep process. Indeed, a recent comprehensive meta-analysis has shown that cortical arousals frequently occur during normal sleep (Boulos *et al.*, 2019). Table 1.1 represents data from this study — these data are included in this thesis as an example of normative data for arousals and sleep quality indices in 5,000 healthy subjects.

Table 1.1: Normative data for arousability and sleep quality

Variable	Total Sample	Mean Age (years)					First Night PSG	Second Night PSG
		18–34	35–49	50–64	65–79	≥80		
Arousal index (events/hr)	12·6 (11·8–13·3)	9·6 (8·8–10·5)	12·5 (10·7–14·2)	16·5 (14·9–18·2)	18·8 (15·3–22·3)	31·6 (15·4–47·8)	13·5 (12·5–14·6)	9·6 (8·0–11·2)
Sleep onset latency (min)	15·4 (14·2–16·7)	14·3 (12·5–16·1)	14·4 (12·3–16·6)	15·7 (13·7–17·8)	19·5 (15·2–23·8)	41·4 (14·2–68·6)	14·7 (13·3–16·1)	14·4 (12·3–16·4)
Total sleep time (min)	394·6 (388·4–400·8)	410·6 (404·5–416·6)	386·6 (371·4–401·9)	372·0 (358·1–85·89)	346·0 (326·7–365·4)	198·6 (142·5–254·7)	371·6 (361·8–381·3)	419·7 (412·0–427·4)
Sleep efficiency (%)	85·7% (84·8–86·6)	89·0% (88·0–90·0)	85·4% (83·7–87·1)	83·2% (81·0–85·4)	77·5% (73·0–81·9)	45·7% (33·7–57·7)	84·2% (83·0–85·4)	89·3% (88·0–90·5)
Wake after sleep onset (min)	48·2 (43·8–52·6)	32·1 (28·2–36·1)	51·1 (41·1–61·1)	64·0 (55·1–72·9)	77·1 (57·3–96·9)	_	52·7 (46·7–58·7)	37·9 (30·6–45·2)

hr: hour; PSG: polysomnography. These data are adopted from reference (Boulos et al., 2019) with permission (appendix 7) .

In addition, this study showed that arousals from sleep increase proportionally with age; for each decade of age, the arousal index (AI) increases by 2.1 (1.5–2.6) events/hr. This relationship is represented in Figure 1.8.

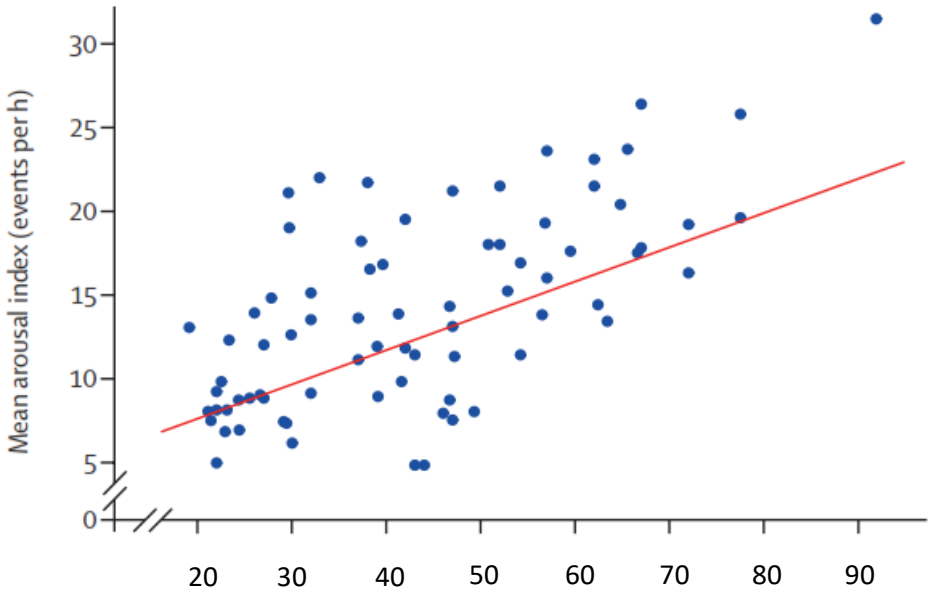


Figure 1.8: The arousal index and its association with age

This figure shows the relationship between the mean arousal index (events/hr) and the mean age (years). Each dot in this figure represents data from a single study. The red line indicates the mixed-effects meta-regression line. It shows that, as age increases, the arousal index is increased proportionally. Modified from (Boulos et al., 2019) with permission (appendix 7).

In patients with OSA, frequent arousals from sleep have been shown to be associated with clinically significant outcomes (White & Younes, 2012), including EDS (Bonnet & Arand, 2003; Thomas, 2003), substantial activation of the cardiovascular responses (Trinder *et al.*, 2003), and cognitive dysfunction (Bucks *et al.*, 2013).

Several studies have evaluated the effect of vibrotactile PT on the arousal index, and these will be reviewed in chapter 3, section 3.3.2. The arousal index is the frequency of arousals, but this measure disregards other important characteristics such as the duration and intensity of the arousal. Therefore, it may be more useful for investigating the effect of the vibration stimulation on the EEG rhythm, rather than count the number of arousals to calculate an index. None of the studies reviewed to date have reported the impact of the vibration stimuli on cortical arousals. There is a need for studies focusing on the impact of PT on sleep quality (Ravesloot *et al.*, 2017). Additionally, it is important to evaluate whether a change in objective sleep is associated with changes in subjective sleep quality and daytime function.

1.8.2 Using arousal intensity to measure arousals from sleep

Previous research has attempted to categorise cortical arousals into four visually different groups (Younes, 2004). In OSA patients, researchers have found these groups were correlated with the amount of ventilatory overshoot (Younes, 2004). Subsequently, Azarbarzin et al. categorised arousals into different intensity levels (Azarbarzin *et al.*, 2014). Using wavelet transformation, EEG signals at the beginning and end of each cortical arousal (during NREM sleep) were decomposed into five signal coefficients. Based on these five coefficients, the wavelet transformation generated 14 different characteristics. These characteristics were based on different time and frequency characteristics. Based on these characteristics, each cortical arousal was given a scale from zero (No changes in EEG) to nine (highest arousal intensity). The developers found that arousal intensity was stable within individuals when measurements were repeated over two nights (Azarbarzin *et al.*, 2015). One disadvantage of this method was that it is based on subjective judgement.

1.8.3 Defining the arousal threshold in response to a respiratory stimulus

The respiratory arousal threshold, defined as the nadir negative intrathoracic pressure at the last breath immediately before a cortical arousal, can be measured in patients with OSA (Eckert & Younes, 2013). This method has been described in detail elsewhere (Wellman *et al.*, 2011; Wellman *et al.*, 2013). Briefly, however, the patient sleeps in the supine position and is fitted with PSG and a customised nasal mask, which is similar to a nasal CPAP mask and a nasopharyngeal catheter — secured to stay in the epiglottic area. Airflow is measured using a pneumotachometer, and both negative and positive pressure are applied via a breathing circuit.

Prior to the measurement of the respiratory arousal threshold, optimal CPAP is maintained until the patients' sleep is stabilised in NREM. Once stabilised, the CPAP is reduced until the airflow is limited. The breathing effort is monitored until the patients reach the most negative intrathoracic pressure, as indicated by the epiglottic pressure (the nadir pressure just before arousal). This process is repeated multiple times throughout the night, and the average is taken to represent the respiratory arousal threshold.

This is a complex, invasive, and labour-intensive method that can only be done in physiological sleep research laboratories, and few laboratories around the world have the skill needed to carry out these measurements. Therefore, this method is not clinically applicable. Modifications to the invasive method have been tried (Wellman *et al.*, 2013). Another simplified method showed that the respiratory arousal threshold can be extracted from the PSG (Sands *et al.*, 2018). However, it was only moderately correlated to the invasive method (Sands *et al.*, 2018).

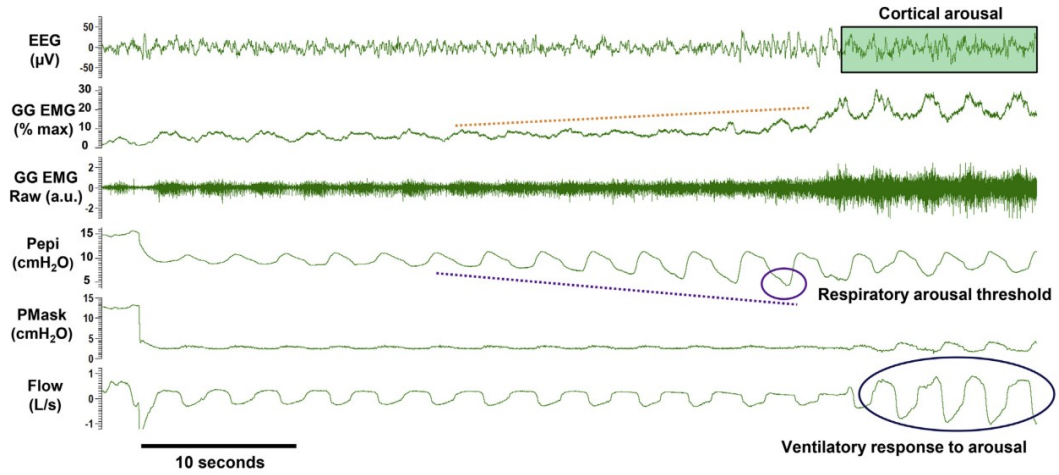


Figure 1.9: Respiratory arousal threshold measurement

This figure shows how the respiratory arousal threshold is measured. Once flow limitation has been reached, as indicated in the flow channel by the flatting of the waveform, the most nadir (lowest) epiglottic pressure represents the respiratory arousal threshold. This is represented by a small circle on the Pepi channel. Picture adopted from (Eckert, 2018) with permission (appendix 8).

Taken together, these methods show it is important to evaluate arousability in OSA patients. However, there is a need for a simpler method that can be used in patients using vibrotactile PT. This thesis describes the development of a novel method that can quantify arousability and sleep recovery in participants using PT.

1.9 Gender Differences and Sleep

Over the past few decades, a number of differences have been recognised in the causes and consequences of OSA occurring in males and females. These differences have been observed in the clinical presentation and specifically in the subjective sleep quality, objective sleep quality, and prevalence of sleep disorders.

1.9.1 Gender differences in subjective and objective sleep quality

Females are more likely to report poorer subjective sleep quality than males (Dorsey *et al.*, 2021), as shown by the higher Pittsburgh Sleep Quality Index, which is indicative of poorer sleep quality. In addition, sleep onset latency has been shown to be longer in females than males (Dorsey *et al.*, 2021). Furthermore, females are more likely to report frequent awakenings during the night (Dorsey *et al.*, 2021). Complaints of non-restorative sleep has also been shown to be higher in females compared to males (Kaplan *et al.*, 2017).

Similarly, objective sleep quality has been shown to be different between males and females. Deep sleep has also been shown to be higher in females than males (Basoglu & Tasbakan, 2017; Redline *et al.*, 2004; Zhou *et al.*, 2021). In a large study, the researchers found that females have 106% more deep sleep than males (Redline *et al.*, 2004). This finding seems to be generalised to all age groups in which females showed a higher percentage of deep sleep (Basoglu & Tasbakan, 2017; Redline *et al.*, 2004; Zhou *et al.*, 2021). In addition, females seem to have less of stage N1 and N2 than males.

1.9.2 Gender differences in the prevalence of sleep disorders

The prevalence of sleep disorders has been shown to be different between males and females. Males have been shown to have a higher prevalence of OSA (24%) than females (9%) (Jordan & McEvoy, 2003). Interestingly, the prevalence of OSA almost doubles in postmenopausal females. This observation is independent of BMI and age (Young *et al.*, 2003). However, females also seem to have a higher prevalence of insomnia (40%) than males (Mallampalli & Carter, 2014). In addition, the prevalence of restless leg syndrome seems to be higher in females than males (Mallampalli & Carter, 2014).

1.9.3 Gender differences in OSA

In the context of OSA, females tend to present more with insomnia complaints, daytime fatigue, and morning headache (Basoglu & Tasbakan, 2017; Wheaton *et al.*, 2012). Conversely, males are more likely to report witnessed apnoeas, snoring, and daytime sleepiness (Wheaton *et al.*, 2012). Females with OSA also present higher depression and mood disturbance than males (Basoglu & Tasbakan, 2017; Shepertycky *et al.*, 2009).During pregnancy, females tend to exhibit more snoring than before pregnancy (Dunietz *et al.*, 2018).

Objective sleep quality in males with OSA is reduced, compared to females, across all ages (Basoglu & Tasbakan, 2017; Gabbay & Lavie, 2012; Zhou *et al.*, 2021). Females seem to have more of a partial airway (hypopnoeas), compared to the complete obstruction that occurs in males (Anttalainen *et al.*, 2007). In addition, females have longer duration of respiratory events (e.g. apnoeas and hypopnoea) than males (Vagiakis *et al.*, 2006). Interestingly, mild and moderate OSA has been shown to be more prevalent in females, than males (Basoglu & Tasbakan, 2017; Vagiakis *et al.*, 2006). Unlike males who commonly have respiratory events that are not sleep stage dependent, females seem to have more REM-dependent respiratory events, which may reflect the higher prevalence of mild to moderate OSA in females (Basoglu & Tasbakan; O'Connor *et al.*, 2000). POSA has been shown to be more prevalent in males than females (Basoglu & Tasbakan, 2017; O'Connor *et al.*, 2000).

1.9.4 Gender differences in OSA mechanisms

The differences in the prevalence and severity of OSA have been attributed to gender differences in the anatomical and pathophysiological mechanisms that contribute to the development of OSA. Females have smaller and narrower upper airways, in both the supine and sitting position, than males (Lin *et al.*, 2008). This would support that females are, potentially, greatly predisposed to OSA compared to males (Lin *et al.*, 2008). However, as discussed above, OSA is more prevalent in males than females. This suggests there are other mechanisms that protect females from developing OSA (Lin *et al.*, 2008). A possible explanation is that the critical closing pressure has been shown to be lower (less collapsible) in females than males (Sforza *et al.*, 1999). This was observed despite that females had a higher BMI; and that the age, OSA severity, and ODI were similar between both males and females (Sforza *et al.*, 1999).

Another potential explanation for the lower prevalence of OSA in females is hormonal changes. Studies have investigated the prevalence in OSA pre and post-menopausal females. Postmenopausal females who were using hormone replacement therapy were not at increased risk of OSA, compared to premenopausal females (Bixler *et al.*, 2001). However, when postmenopausal females without hormone replacement therapy were compared to premenopausal females they were at higher risk (approximately four-fold) of OSA (Bixler *et al.*, 2001). Another study of 589 females who were enrolled in the Wisconsin Sleep Cohort showed postmenopausal females were at a higher risk of OSA than premenopausal females;

this finding was independent of other known factors (Young *et al.*, 2003). Interestingly, when the odds ratio was calculated for having OSA (AHI> 15 events/hr), it was 3.5 times higher for postmenopausal female than premenopausal female (Young *et al.*, 2003). More recently, researchers investigated the longitudinal data of sleep in the Midlife Women Study and found, in females who were perimenopausal, each additional year was associated with a 4% higher AHI (Mirer *et al.*, 2017).

Despite these potential anatomical and hormonal differences in females with OSA, the exact mechanisms for OSA in females are not known. The potential role of hormones is further supported by the integral role they play in fat distribution. For example, in postmenopausal females, fat is more likely to occur in the trunk and upper body, compared to premenopausal females who have more fat in the lower body (Lin *et al.*, 2008; Manber *et al.*, 2003). This observation was independent of aging and body habitus changes.

Another explanation is that progesterone has a stimulant effect on neural respiratory control (Lin *et al.*, 2008). This suggestion is supported by the evidence that, when postmenopausal females are given estrogen (Manber *et al.*, 2003) or a combined therapy of progesterone and estrogen (Pickett *et al.*, 1985), the AHI is reduced significantly. However, these studies had small sample sizes, and a recent review concluded that the evidence on hormone replacement therapy is weak, and the current literature cannot support this conclusion (Lindberg *et al.*, 2020).

Taken together, it is clear that sleep and sleep disorders are different in females than males. However, the exact mechanisms that explain these differences are not known. Therefore, more research (both physiological and clinical) is needed in females to uncover the possible underlying mechanisms. Similarly, it is not known how females will differ from males in terms of their responses to the PT. Additionally, it is not known whether objective and subjective sleep quality are different in females compared to males following the use of vibrotactile PT.

1.10 Aims of the Thesis

1.10.1 Evidence gaps

POSA is prevalent among patients with OSA, and it usually occurs within the mild and moderate spectrum of OSA. It is currently known that patients with this severity of OSA are less adherent to the most effective treatment, CPAP. In addition, traditional PT is associated with significant discomfort and low adherence, despite being effective. Relatively new vibrotactile PT devices have been developed to deliver a gentle vibrotactile stimuli when patients are in the supine position, urging them to change position. Although such stimuli are considered gentle, there are concerns they might lead to arousal from sleep.

This thesis has evaluated the effectiveness of vibrotactile PT and the possible approaches that can assist with the personalisation of therapy — and thus the success of this treatment. The overall aim of this thesis was to investigate the effect of vibrotactile PT devices on arousal from sleep in patients with POSA. To achieve this aim, three experimental studies were carried out: a systematic review, a clinical trial, and a physiological study.

1.10.2 The systematic review (chapter 3)

The primary aim of the systematic review and meta-analysis was to investigate the effect of vibrotactile PT devices on AHI and the percentage of time spent in the supine position (%Tsupine) in patients with POSA, compared to the baseline. The secondary aims were to investigate the effect of vibrotactile PT devices on the following:

- Excessive daytime sleepiness using the Epworth Sleepiness Scale
- Daytime functioning using the Functional Outcomes of Sleep Questionnaire
- The 36-Item Short Form Health Survey (SF-36) vitality score
- Sleep efficiency
- The arousal index

1.10.3 The POSA trial (chapter 4)

A prospective, three-month, multicentre, randomised, parallel, double-blind trial (The POSA Trial, ISRCTN51740863) was developed to investigate the effect of vibrotactile PT on AHI, quality of life, and daytime functioning at follow-up, adjusted for the baseline, in patients with POSA, compared to sham-vibrotactile PT.

In this chapter, the baseline data (AHI, quality of life, and daytime functioning) obtained from the participants recruited at the Royal Brompton Hospital were compared to the data obtained from the systematic review (chapter 3).

1.10.4 Arousability and sleep recovery responses in healthy participants (chapter 5)

The physiological study was carried out to investigate the effect of the vibrotactile stimulus on arousability from sleep using a novel analysis method developed to measure arousability. The secondary aim tested the hypothesis that females are more resilient to arousability than males, as well as to specifically evaluate whether:

1- Arousability and sleep recovery responses are influenced by gender.
2- Arousability and sleep recovery responses are sleep state dependent.
3- Subjective sleep quality is influenced by gender.
4- There are different arousability and sleep recovery phenotypes.

CHAPTER 2: General Methods

This chapter describes the methods that are common to the experimental chapters included in this PhD thesis (chapters 3–5), including the methods used for measuring sleep, both objectively and subjectively. Methods of subjective sleep quality measurement are also described, including both validated questionnaires and a bespoke questionnaire that was developed to assess the participants' experience using a vibrotactile positional therapy (PT) device and to evaluate its impact on sleep quality (chapter 5).

The final section of this chapter reports the data obtained from comparing two different vibrotactile PT devices. This comparison was carried out prior to the development of the protocol described in chapter 5.

2.1 Participants and Patient Recruitment Information

The participants included in this thesis were recruited between March 2019 and August 2021. For the systematic review (chapter 3) and the POSA Trial (chapter 4), participants were patients with POSA. In the POSA Trial, data were reported for patients recruited from the Centre for Sleep at the Royal Brompton Hospital (RBH). A detailed description of the recruitment process and eligibility criteria for these participants can be found in chapter 4, section 4.2.1

Chapter 5 required the recruitment of healthy participants. Due to the lockdowns imposed by the COVID-19 pandemic and the repatriation of the author to the Kingdom of Saudi Arabia, healthy participants were recruited from both Imperial College London and the Kingdom of Saudi Arabia, specifically from Imam Abdulrahman bin Faisal University in Dammam or King Abdullaziz University and Hospital in Jeddah. Full details of the recruitment process and eligibility criteria for these participants are shown in chapter 5, section 5.2.1.

2.2 Ethical Approval and Conduct of Research

The studies included in this thesis were carried out with ethical approval, which is summarised in table 2.1. Copies of these ethical approval documents can be found in appendices (13, 14,19, and 20).

Participants were supplied with patient information sheets (PIS) prior to participation in the study (appendices 16, and 21). Written informed consent was obtained from each participant (appendices 17, and 22). The research was conducted in accordance with Good Clinical Practice guidelines (Imperial College London). The author completed both the Good Clinical Practice guidelines and local consent training at RBH.

Table 2.1: Ethical approval information for the experimental studies

Chapter No.	Title of the Study	Approval Body	Approval No.
Chapter 3	*The Efficacy of Vibrotactile Positional Therapy Devices on Patients with Positional Obstructive Sleep Apnoea: a Systematic Review and Meta-Analysis*	International Prospective Register for Systematic Reviews (PROSPERO)	CRD42020188617
Chapter 4	*Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to Assess the Effect on Health and Wellbeing in Older and Younger People. (The POSA Trial)*	Yorkshire and the Humber – South Yorkshire REC	REC Reference: 19/YH/0222 IRAS Reference: 252494
Chapter 5	*Different Arousal and Recovery Responses in Healthy Individuals Using a Vibrotactile Neck-Worn Positional Therapy Device*	Imperial College London	ICREC 20IC5874
		Imam Abdulrahman Bin Faisal University	IRB-2020-04-275

2.3 Study Environment and Participant Safety

The collection of data during sleep using portable polysomnography (PSG) did not occur until such procedures were permitted by the approving body. This restriction was put in place to minimise unnecessary travel and to reduce the risk of COVID-19 transmission.

PSG was performed in the participants' homes (chapter 5) following strict cleaning and disinfection procedures before, during, and after each sleep study. Each participant was contacted three weeks after the study to ensure that they had not contracted the COVID-19 infection. None of the participants reported contracting the COVID-19 infection. PSG is described in section 2.4.1.

2.4 Methods Used for the Objective Measurement of Sleep

2.4.1 Overnight home sleep study

A type II overnight portable PSG was performed in the study described in chapter 5. Data were recorded on a compact flash card using sleep monitoring equipment (SOMNOscreen Plus, OMNOmedics GmBH, Randersacker, Germany). On the morning following the sleep study, the data were transferred directly to an encrypted laptop computer.

Participants were instructed to maintain a consistent overnight sleep pattern for at least one week prior to the study. Prior to the night of the study, participants were asked to prepare for their usual bedtime sleep routines. The author visited the participants at their homes at least two hours prior to their usual sleeping time to set up the PSG for data collection.

The author performed an overnight PSG while participants slept with the neck-worn vibrotactile PT device. The set-up and recording of the PSG were performed in accordance with the American Academy of Sleep Medicine (AASM) Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification (Berry *et al.*, 2012). The complete set-up of the PSG, including application of the electrodes, impedance check, and calibration, took approximately one hour.

PSG electrode application included six electroencephalogram (EEG) channels (two frontal, two central, and two occipital), two electrooculogram (EOG) channels, three chin electromyogram (EMG) electrodes, electrocardiogram (ECG), position sensor, finger pulse oximetry, nasal pressure and oral–nasal thermal flow, a snore-measuring microphone, thoracic and abdominal effort bands, and two lateral anterior tibialis EMG electrodes.

- **Electroencephalogram (EEG)**

The electrical activity of the brain was recorded across the surface of the scalp using ten 10 mm goldcup electrodes (Grass Technologies, Rhode Island, USA), including eight active electrodes and two reference electrodes (C3, C4, Cz, F3, F4, O1, O2). The odd-numbered electrodes (left hemisphere of the brain) were referenced to the right mastoid (M2), and even-numbered electrodes (right hemisphere of the brain) were referenced to the left mastoid (M1). An additional electrode was applied and secured to the midpoint of the

forehead and served as a ground electrode. As recommended by the AASM, the electrodes were positioned on the scalp in accordance with modified international 10–20 EEG system (figure 2.1). This system includes the inion to nasion and left preauricular to right preauricular as reference points from which measurements are taken, and the distance between the electrodes is either 10% or 20% of these measurements along the sagittal or the traverse line (figure 2.1). The position of each EEG electrode was identified and marked using a removable pencil prior to the application of the electrodes. Using an abrasive medical paste (Nuprep, Weaver and Company, Colorado, USA), each electrode site was gently abraded and cleaned of the excess paste using non-woven gauze. This step was necessary to reduce impedance at the site of the electrode and to improve transmission of brain electrical activity from the scalp to the goldcup electrode. Each electrode was then filled with a conductive paste (Ten20 conductive paste, Weaver and Company, Colorado, USA) and secured using a thin layer of non-woven gauze. The same application process was used for the ground electrode, which was placed at the midpoint of the forehead. The reference electrodes were applied using the same process, with M1 and M2 secured over the left and right mastoid processes, respectively.

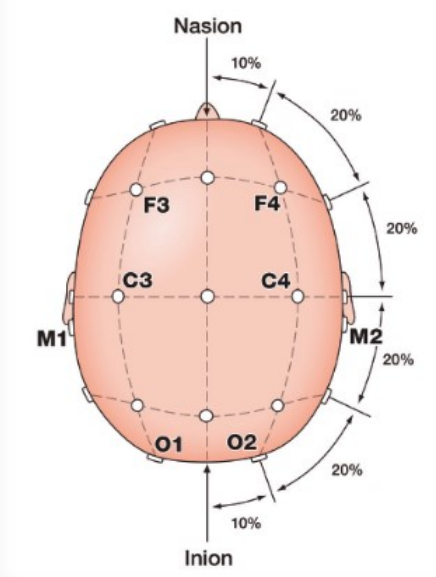


Figure 2.1: The placement of EEG electrodes using the modified international 10–20% system

This figure shows the applied electrodes (C3, C4, Cz, F3, F4, O1, O2). These electrodes are spaced by either 10% or 20% from each other using the modified international 10–20 system. This system uses the inion to nasion and left preauricular to right preauricular as reference points. In addition, two reference electrodes (M1 and M2) are shown. This figure is adapted from the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification, V2.5.

- **Electrooculogram (EOG)**

EOG electrodes were applied using an identical process as described for EEG electrodes with the exception that they were secured in place using adhesive tape. The right electrode was placed 1 cm above and 1 cm lateral to the outer canthus of the left eye, and the left electrode was placed 1 cm below and 1 cm lateral to the outer canthus of the left eye (figure 2.2).

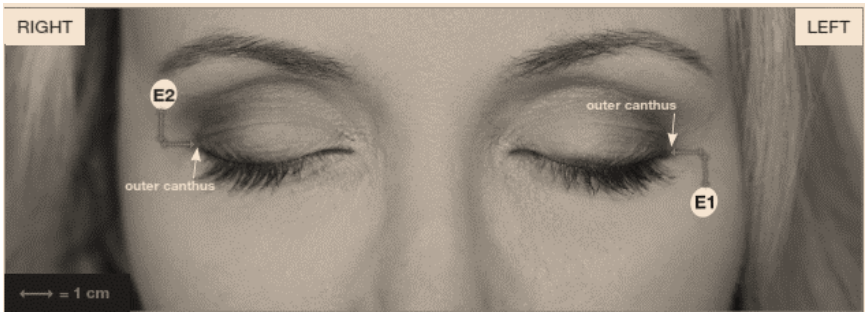


Figure 2.2: The placement of EOG electrodes

The right EOG electrode was placed 1 cm above and 1 cm lateral to the outer canthus of the right eye (E2). The Left EOG was placed 1 cm below and 1 cm lateral to the outer canthus of the left eye (E1). This figure is adapted from the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification, V2.5

- **Chin electromyogram (EMG)**

Three chin EMG electrodes were applied to the mental and submental areas. Following the same prepartion and cleaning process as for EEG and EMG, two goldcups were applied 2 cm apart below the inferior edge of the mandible, and one goldcup was applied at the midline above the inferior edge of the mandible (figure 2.3). The electrodes were secured using an adhesive tape.

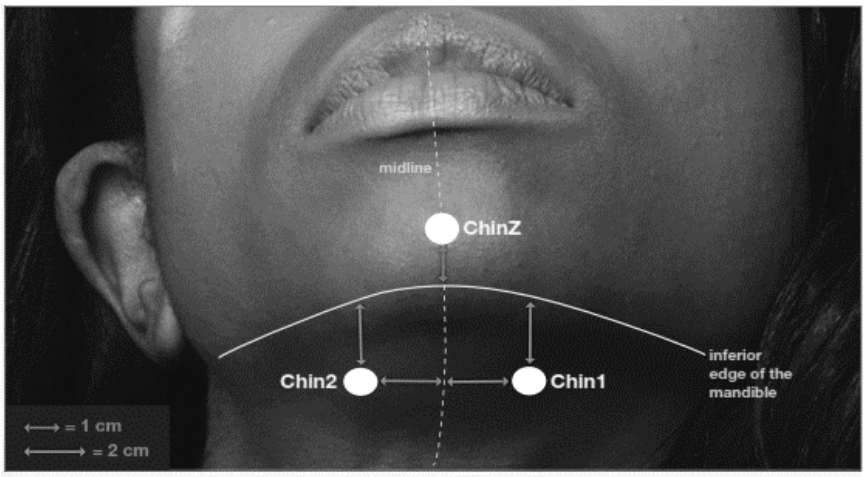


Figure 2.3: The placement of the chin EMG electrodes

Three EMG electrodes were applied to the mental and submental areas. Following the same prepartion and cleaning process, two goldcups were applied 2 cm apart below the inferior edge of the mandible (Chin1, Chin2), and one goldcup was applied at the midline above the inferior edge of the mandible (ChinZ). This figure is adapted from the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specification, V2.5.

An impedance check was perfomed following application of the electrodes. For appropriate signal transmission, impedance of < 5000 Ω was deemed acceptable. If the impedance was above the acceptable limit, troubleshooting of the electrode site was carried out, and conductive gel was applied until an acceptable level was met.

- **Measurement of respiratory signals**

Respiratory measurements were made by monitoring nasal and oral airflow, thoracoabdominal movements, and oxyhaemoglobin saturation.

Oronasal airflow was measured using a thermistor oronasal airflow device, which detected changes in the temperature induced by airflow (Berry *et al.*, 2012); specifically, cooler air during inspiration and warmer air during exhalation. These changes in temperature led to changes in the resistance of the airflow. This technology is only recommended for the detection of apnoeas as it is only accurate in detecting the presence or absence of airflow (Berry *et al.*, 2012), not the reduction in airflow that occurs during hypopnoea.

Nasal airflow was measured by a nasal cannula connected to a pressure transducer, which used differences in pressure across the nares in relation to atmospheric pressure to quantify

airflow (Berry *et al.*, 2012). This technology is recommeded for detection of hypopnoeas and airflow limitation (Berry *et al.*, 2012).

Throacic and abdominal breathing movements were measured using respiratory inductance plethysmography (RIP) belts worn around the chest and abdomen. The belts contained wires that were attached in a zig-zag manner. Chest wall and abdominal movements were measured using changes in voltage (inductance) across the wires (Berry *et al.*, 2012).

Oxygen saturation was measured by pulse oximetry using somnomedics finger probe. Two principles govern how the pulse oximeter works (Jubran, 2015): the first is that arterial blood flow generates a pulsatile signal; and the second is the property of spectral analysis, which dictates that oxidized haemoglobin (oxyhaemoglobin) has a different absorption length than reduced haemoglobin (deoxyhaemoglobin). Pulse oximeters contain two main components: light-emitting diodes (LEDs) and a photosensor. The LEDs emit red light at a wavelength of 660 nm and infrared light at a wavelength of 940 nm. The photosensor measures how much of the light is transmitted, and using this value the oxygen saturation is estimated.

- **Measurement of snoring**

A microphone (piezoelectric vibration sensor) is typically used to measure snoring; however, during the collection of data in chapter 5, the microphone was instead used for the recording of vibrations produced by the vibrotactile PT device, so snoring was measured based on a flow interruption method using a nasal pressure cannula. This method was previously used by (Hernandez *et al.*, 2001); snores are identified as rapid oscillations in the nasal pressure signal. This method is also recommended for the measurement of snoring in the 2012 AASM manual (Berry *et al.*, 2012).

- **Body position, ECG, and leg EMG**

The body position during sleep was determined using a position sensor built in to the SOMNOscreen Plus (SOMNOmedics GmBH, Randersacker, Germany). This sensor differentiates between various body positions (right, left, upright, supine, and prone).

The electrocardiogram (ECG) electrodes were applied using AASM modified lead II placement (Berry *et al.*, 2012). Two electrodes were applied: one below the right clavicle at the midclavicular line, and one the left midaxillary line around the sixth intercostal space.

Leg EMG was recorded by attaching two adjacent electrodes each on the left and right anterior tibialis muscle. The same prepartion and cleaning process was used as for chin EMG.

After the application of all the electrodes, mechanical and physiological calibrations were performed. Instructions for physiological calibration are shown in table 2.2. Figure 2.4 shows the complete set-up for the PSG.

Table 2.2: Commands used for physiological calibration during PSG

Command	Targeted Measurement
Look straight ahead and keep your eyes closed.	EEG
Open your eyes and keep them open.	EEG
Look left, right, down, up, and blink your eyes.	EOG
Grind your teeth.	EMG
Make a snoring sound.	Nasal pressure
Breath in, out, and then hold your breath.	Airflow sensors and belts
Kick your legs.	Leg EMG
Lay in supine position.	To activate vibration of vibrotactile PT device and check function of microphone before sleeping
EEG: electroencephalogram; EOG: electrooculogram; EMG: electromyogram.	

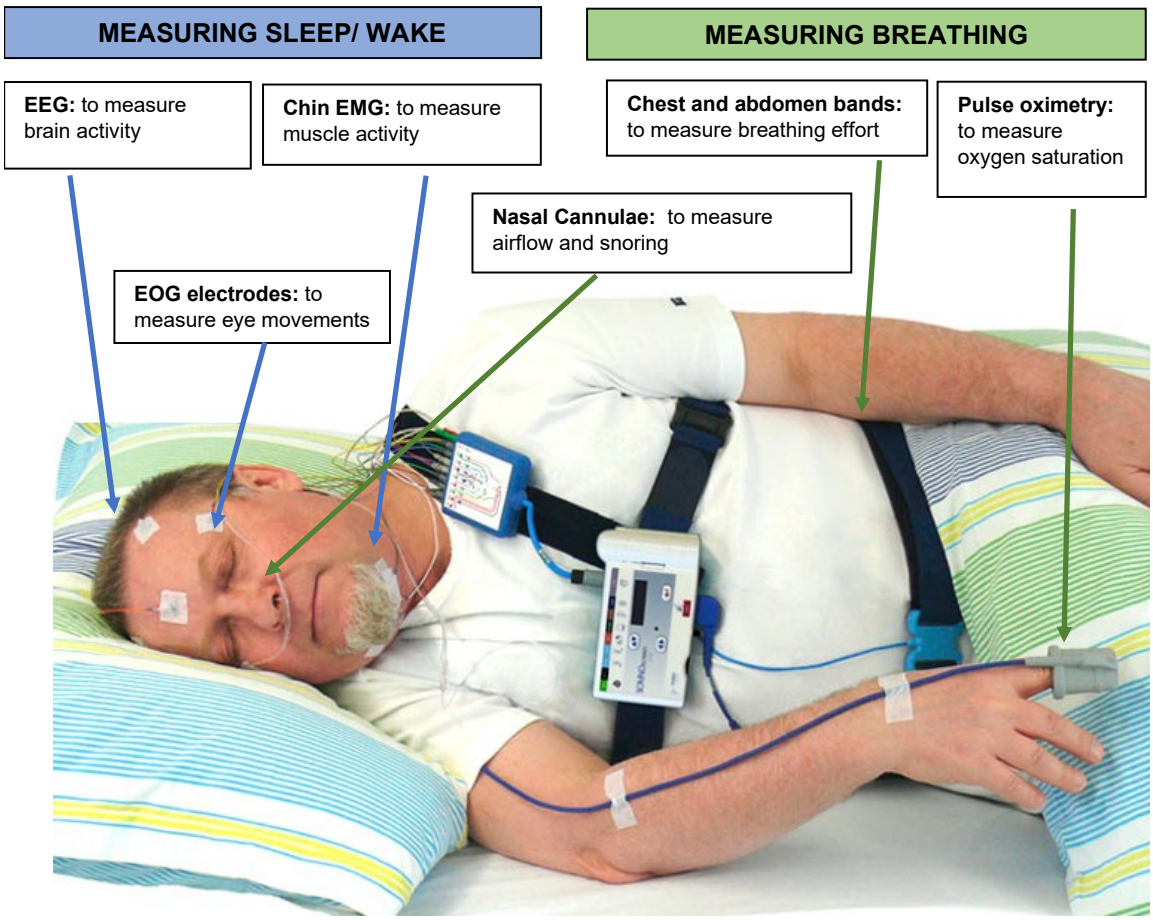


Figure 2.4: A sleeper wearing the kit for polysomnography (SOMNOscreen Plus device)

The figure shows a sleeper wearing the PSG equipment (picture adapted from SOMNOmedics GmbH website).

The sampling frequency and filters used to collect the data during PSG are shown in table 2.3. These settings are in accordance with the AASM 2012 recommendations (60).

Following the application of the electrodes, the SOMNOscreen Plus device was temporarily connected to a laptop computer to ensure all signals were functioning properly. Participants were informed that they could move freely during the night of data collection and were further instructed to note the time that they turned the lights on or off. In addition, the SOMNOscreen Plus device was pre-programmed to stop recording at the participant's usual wake time.

In the morning after the sleep study, the equipment and questionnaire were collected from the participant's home and data were transferred from the SOMNOscreen Plus device to an encrypted laptop computer for analysis.

Table 2.3: Sampling rates and filters used during PSG

	Low-Frequency Filter (Hz)	High-Frequency Filter (Hz)	Sampling Rate (Hz)
Electroencephalography	0.3	35	256
Electrooculography	0.3	35	256
Electromyography	10	100	256
Electrocardiography	0.3	70	256
Thermal Airflow	0.1	15	32
Microphone	10	100	256
Effort	0.1	15	128
Body Position	1	1	4
Hz: Hertz			

2.4.2 Polygraphy

A type III portable sleep monitor (polygraphy) was used to assess eligibility in the POSA Trial (chapter 4). This method was only used in the POSA Trial (chapter 4), and therefore a full description can be found in chapter 4.

2.5 Methods Used for the Measurement of Subjective Sleep Quality

2.5.1 Validated questionnaires

In this section the three validated questionnaires that were used in chapter 3 and chapter 4 will be described: the Epworth Sleepiness Scale (ESS), the Functional Outcomes of Sleep Questionnaire (FOSQ), and the 36-Item Short Form Survey (SF-36). Additionally, studies that were used to determine the minimum clinically important difference (MCID) for each questionnaire will be discussed.

- **Epworth Sleepiness Scale (ESS)**

The ESS was used at the beginning and at the end of the POSA Trial to evaluate the impact of the intervention on daytime sleepiness (chapter 4). The ESS was also used in the systematic review to evaluate the impact of the vibrotactile PT on sleepiness (chapter 3).

The ESS is the most widely used questionnaire to evaluate sleepiness (appendix 15). It consists of eight items about the likelihood of dozing off or falling asleep in eight different situations (Johns, 1991). Each item is scored from 0 to 3, in which 0 = would never doze, 1 = slight chance of dozing, 2 = moderate chance of dozing, and 3 = high chance of dozing. The

total possible score is 24 points. The interpretations of the scores are as follows: 10 or less indicating no daytime sleepiness, 11–12 indicating mild daytime sleepiness, 13–15 indicating moderate daytime sleepiness, and 16–24 indicating excessive daytime sleepiness (Johns, 1991).

The MCID of the ESS has been investigated in two prior studies: Patel *et al*, conducted a prospective study that included 125 OSA patients who completed the ESS before and after three months of CPAP treatment (Patel *et al.*, 2017). The determination of the MCID was made using both distribution-based methods and anchor-based methods. The anchor was based on response to a seven-point Likert global rating scale in which participants were asked to rate the change in their daytime sleepiness from 0 to 7, which 1 indicating "much less sleepy" and 7 indicating "much more sleepy". Both statistical estimation methods indicated that the ESS MCID lies between -2 and -3 points. One of the major disadvantages of this MCID is that it was not based on an objective measure of sleepiness, nor did the authors use a quality of life measure as an anchor. In addition, the study did not result in a single number that could be used clinically or during calculation of sample size in clinical trials.

A second study by Crook et al. (Crook *et al.*, 2019) used data from three published clinical trials to estimate the ESS MCID. All three randomized controlled trials (RCTs) included ESS as an outcome measure. The methods used to determine the MCID were based on anchor-based methods and distribution-based methods. The anchors used were the SF-36 Vitality score and FOSQ global score. A method of triangulation of the resulting estimates from each statistical method was used to produce a single-number MCID, which was 2 points. While this is useful, none of the anchors used were used clinically.

- **Functional Outcomes of Sleep Questionnaire (FOSQ)**

The FOSQ is a self-administered disease-specific quality of life questionnaire that is used to evaluate functional status in adults (Weaver *et al.*, 1997) (appendix 15). This questionnaire is used to assess the impact of excessive daytime sleepiness on normal, everyday activities, and to evaluate the impact of the effectiveness of treatment on these activities (Weaver *et al.*, 1997).

The questionnaire consists of thirty items which are categorised into five subscales: activity levels, general productivity, social outcome, vigilance, and intimacy and sexual relationships. The respondent is asked to rate the difficulty (due to excessive sleepiness) of performing a certain activity on 4-point Likert scale. On average, the respondent can take approximately 15 minutes to complete the questionnaire. Scores range from 5 to 20, with higher scores indicating lower sleepiness (i.e., better functional status).

Recently, the developer of the FOSQ questionnaire investigated the FOSQ MCID. This was part of a trial that evaluated the use of Solriamfetol, a norepinephrine–dopamine reuptake inhibitor, for three months in 690 OSA or narcolepsy patients suffering from excessive daytime sleepiness (Weaver *et al.*, 2021). Determination of the MCID was based on anchor-based methods and distribution-based methods. A single-item Patient Global Impression of Change (PGI-C) score and a single-item Clinical Global Impression of Change (CGI-C) score were used as anchors to determine MCID. The resultant MCID was 2.2 in OSA patients.

- **36-Item Short Form Survey (SF-36)**

The SF-36 is a self-administered, generic, well-validated quality of life questionnaire (appendix 15). It was developed as part of the Medical Outcomes Study (Ware & Sherbourne, 1992). The purpose of the questionnaire was to evaluate limitations related to quality using thirty-six items distributed among eight different domains: physical functioning, role limitations due to physical health as well as due to emotional problems, vitality, emotional well-being, social functioning, pain, and general health. The score of each domain ranged from 0 to 100, with higher scores indicating better quality of life.

A number of studies have shown that OSA affects several domains of the SF-36 score, and that these scores can be improved with the use of CPAP (Bennett *et al.*, 1999; D'Ambrosio *et al.*, 1999). In addition, a large population study showed that a higher AHI was associated with lower scores in a number of SF-36 domains (Finn *et al.*, 1998). However, only the domain of vitality reflected that milder OSA was associated with poorer quality of life (Silva *et al.*, 2016). Recent studies have shown that vitality in SF-36 may be a more sensitive outcome measure than other questionnaires such as ESS and FOSQ (Craig *et al.*, 2012; Wimms *et al.*, 2020).

A summary of the three questionnaires is presented in table 2.4.

Table 2.4: Summary of three common questionnaires used in chapters 3 and 4

	ESS	FOSQ	SF-36
Function(s) assessed	Daytime sleepiness.	The effect of EDS on functional status in five different domains.	Quality of life measures on eight different domains.
Range of possible scores	0–24	5–20	0–100
Interpretation	• ≤ 10: no daytime sleepiness • 11–12: mild daytime sleepiness • 13–15: moderate daytime sleepiness • 16–24: excessive daytime sleepiness	A higher score indicates lower sleepiness (better functional status).	A higher score indicates better quality of life.
Domains	• none	• activity level • general productivity • social outcome • vigilance • intimacy and sexual relationships	• physical functioning • role limitations due to physical health • role limitations due to emotional problems • vitality • emotional well-being • social functioning • pain • general health
Most frequently used score on domain of OSA	Total ESS score	FOSQ global score	Vitality
Regular clinical use	Yes	No	No
MCID for OSA	-2 to -3; or -2	2.2	-

ESS: Epworth Sleepiness Scale; FOSQ: Functional Outcomes of Sleep Questionnaire; SF-36: 36-Item Short Form Survey; MCID: minimum clinically important difference; OSA: obstructive sleep apnoea; No.: number; EDS: excessive daytime sleepiness.

2.5.2 Subjective, bespoke, visual analogue scale questionnaire

Because there is no validated questionnaire for assessing vibrotactile PT devices, an in-house questionnaire was developed using a visual analogue scale to assess sleep quality and patient experience with the device.

Item development for the bespoke questionnaire focused on three aspects: 1) sleep quality, 2) daytime functioning, and 3) ease of falling asleep. Additional questions were asked following the sleep studies to characterise the participants' experience with the vibrotactile

PT device: 1) feeling of the vibrations, 2) disturbance of sleep, and 3) disturbance partner's sleep.

To ensure the face validity of this newly developed questionnaire, questions were developed in consultation with experts in the field. Items were chosen so that each question targeted a single, specific construct. Pilot testing of the questionnaire was completed with the help of an expert in the content area, and also on the targeted respondents. Based on the expert's and respondents' feedback, several revisions were made to improve the clarity of the questions.

The bespoke questionnaire is shown in appendix 23 and consists of two parts, which are shown in table 2.5 and 2.6. Part 1 was completed before the sleep study and included three questions about the participant's sleep quality over the previous week. These questions and corresponding response formats are shown in table 2.5. The total number of items in the questionnaire was small, and the entire questionnaire took only 2–4 minutes to complete.

Table 2.5: Part 1 of the bespoke vibrotactile PT questionnaire

Question number	Question text	Response
1	Overall, how do you rate your sleep quality over the last week?	0 to 100mm scale, which represents worst-ever and best-ever anchors, respectively
2	Overall, during the day how fresh and well rested have you been over the last week?	0 to 100mm scale, which represents worst ever and best ever anchors, respectively
3	On average, how easy did you find falling asleep over the last week?	0 to 100mm scale, which represents worst ever and best ever anchors, respectively
mm: millimetre		

The second part of the bespoke questionnaire was completed on the morning following the sleep study and asks participants about sleep quality over the past night as well as questions about their experience with the vibrotactile PT device. These questions and corresponding response styles are shown in table 2.6.

Table 2.6: Part 2 of the bespoke vibrotactile PT questionnaire

Question number	Question text	Response
1	Overall, how do you rate your sleep quality last night?	0 to 100mm scale, which represents worst ever and best ever as anchors, respectively
2	Overall, how fresh and well rested did you feel when you woke up today?	0 to 100mm scale, which represents worst ever and best ever as anchors, respectively
3	On average, how easy did you find falling asleep while wearing the positional therapy device over the last night?	0 to 100mm scale, which represents worst ever and best ever as anchors, respectively
4	Over the last night, did you feel the vibrations of the positional therapy device after falling asleep?	Yes or no
5	On average, how many times you felt the vibrations of the positional therapy device per night over the last night? Please respond by a number in the box below.	Open numerical response
6	If applicable, how much did the vibrations of the positional therapy device disturb your sleep over the last night?	0 to 100mm scale, which represents not at all and very much as anchors, respectively
7	If applicable, how much did the vibrations of positional therapy device disturb your bed partner's sleep over the last night?	0 to 100mm scale, which represents not at all and very much as anchors, respectively
mm: millimetre		

2.6 Vibrotactile PT Devices Used in This Thesis

Newly developed vibrotactile PT involves the use of small, non-invasive, watch-like devices that use vibration to deter users from sleeping in the supine position. These devices can be worn around the chest, neck, or forehead. An introduction to these devices is included in chapter 1, section 1.7.2, and chapter 3 presents a systematic review and meta-analysis investigating the effect of vibrotactile PT devices on the AHI and the %Tsupine in patients with POSA. In the following section, the two devices used in this study are described in detail; furthermore, the justification for their use is discussed.

2.6.1 Neck-worn vibrotactile positional therapy device (Night Shift device™)

The Night Shift™ (Advanced Brain Monitoring, Carlsbad, CA, USA) was developed and validated by Levendwoski *et al.* (figure 2.5)(Levendowski *et al.*, 2014; Levendowski *et al.*, 2015). It consists of a small vibrating device measuring 55 mm (*L*) x 38 mm (*W*) x 16 mm (*H*) and weighing 44 g. The device is powered by a non-removable, rechargeable battery. It is worn around the back of the neck using an adjustable, non-latex, silicon rubber strap which is secured using a magnetic clasp.

The Night Shift™ contains a position sensor that uses a three-dimensional digital accelerometer to detect sleep position and to determine actigraphy-based classification of wakefulness and sleep. This position sensor has been validated against position determined by in-laboratory video recording and shows strong and significant agreement and correlation (r = .93) (Levendowski *et al.*, 2015).

In addition, the Night Shift™ measures loud snoring (more than 50 decibel) using an acoustic microphone. The ability of this microphone to detect loud snoring has been used to evaluate its ability to predict AHI in comparison with laboratory PSG with good success in which it was highly correlated with supine, non-supine, and total AHI (Levendowski *et al.*, 2015). The Night Shift™ vibrating motors, similar to those found in contemporary smartphones, are two 1G haptic motors.

Figure 2.5: Vibrotactile PT device, The Night Shift™ (Advanced Brain Monitoring, Carlsbad, CA, USA)

This device determines sleep position by detecting when the wearer is in supine position. Once a supine sleep position is detected by the enclosed position sensor, the vibrotactile stimulus turns on and ranges from level 1 (very light vibrations) to level 6 (strong vibrations); then, level 7 vibrations are delivered continuously until a non-supine position is

detected. The stimulus is delivered incrementally over 6 levels of vibration that progressively increase in intensity using a single vibrating motor. Each level of vibration consists of six similar vibrations which are separated by two seconds. Once all 6 levels have been activated, the second motor is activated alongside the first one to deliver the level 7 vibrations and consists of a stronger, random pattern of vibrations. The hardware and software features of the Night Shift™ device are summarised in table 2.7.

2.6.2 Forehead-secured vibrotactile PT device (Somnibel™ PT System)

The Somnibel™ PT System (Sibel S. A. U., Barcelona, Spain) is another vibrotactile PT device. It is a small, battery-powered, lightweight (16.8 g) device with a surface area of 4 cm^2 and dimensions of 51.9 mm (*L*) x 31.7 mm (*W*) x 14.5 mm (*H*) (Armas *et al.*, 2019) (figure 2.7, panel A). The device consists of a vibrating motor and an accelerometer that are used to determine sleeping position. It can be secured on the forehead using clips attached to a fastening adhesive sticker (figure 2.7, panel B). The device automatically turns on when clipped to the adhesive sticker. The device has a sleep delay of 15 min, which allows the patient to fall asleep without vibration even when the supine position is detected. Once this time has elapsed and the supine position is detected, the device will allow 30 s to pass before vibration is activated. Vibrations are delivered incrementally over four levels of intensity with the fourth level representing the maximum intensity.

The hardware and software features of the neck-worn and forehead-secured devices are summarised in table 2.7, and data comparing the two devices are presented in section 2.9.

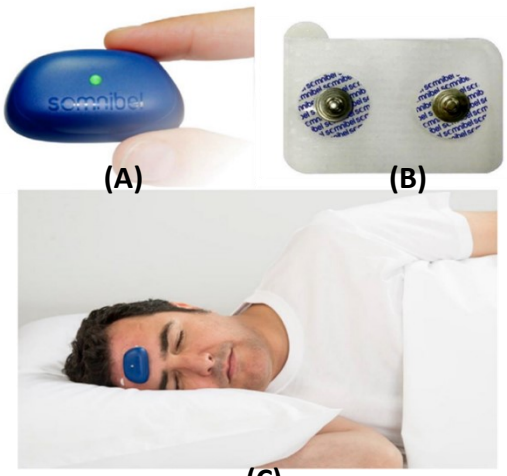


Figure 2.6: Forehead-secured vibrotactile PT device, Somnibel™ PT System (Sibel S. A. U., Barcelona, Spain)

The figure shows the forehead-secured device, which was developed by Sibel S. A. U., Barcelona, Spain in collaboration with researchers (Duran-Cantolla et al., 2013).

Table 2.7: Summary of the features of vibrotactile PT devices

Brand name	Night Shift™ PT	Somnibel™ PT System*
Country of Origin	USA	Spain
Weight	44 g	16.8 g
Powered by	non-removable, rechargeable battery	non-removable, rechargeable battery
Dimension	55 mm (L) x 38 mm (W) x 16 mm (H)	51.9 mm (L) x 31.7 mm (W) x 14.5 mm (H)
Bodily site	back of neck or front of the chest	forehead or chest
Secured by	*Neck:* adjustable non-latex silicone rubber strap secured by a magnetic clasp *Chest:* device secured in a belt	clipping of the device into the adhesive sticker
Position sensor	three-dimensional digital accelerometer	Accelerometer[$]
Vibrating motors	two 1G haptic motors	not specified
Charging/Length of work	up to 3 nights	> 3 nights @ 10 h/night
Sleeping delay	can be set to 15 or 30 min	15 min
Feedback delay	none	30 s
Levels of vibration	7 levels	4 levels
Pattern of vibration	separated by 2 s and consists of six vibrations	separated by 2 s
Data recorded	supine sleeping time, frequency and duration of feedback, snoring, and sleep/wake	none

PT: positional therapy; W: weight; H: height; L: length.
*The specifications are for the Somnibel base version. The device comes in another version (Somnibel Pro) which has more features.[$] The type of accelerometer was not specified by the developers.

It should be noted that there is a third vibrotactile PT device that is available in the UK. The NightBalance™ Sleep Positioner Trainer (Den Haag, The Netherlands) is worn around the chest. The reason I did not include this device in the study was because the NightBalance™ device monitors the position of the truck. The AHI was significantly lower when measured on the trunk compared with the forehead (van Kesteren & Hilgevoord, 2015; Van Kesteren *et al.*, 2011) .

2.7 Data Analysis

2.7.1 Analysis of the PSG

All PSG data collected in this study were analysed by the author. The scoring proficiency of the author was assessed by the American Board of Sleep Medicine (September 2020) with a score of 95.75%.

All sleep scoring was completed in accordance with AASM 2012 criteria (Berry *et al.*, 2012) and is summarised in table 2.8.

Table 2.8: Summary of AASM 2012 criteria for scoring sleep

Sleep stage	EEG	EOG	EMG
W	When alpha waves (over occipital channels) occupy more than 50% of the epoch.	Slow eye movements are optional when eyes closed	Variable but often high
	If no discernible alpha, but is associated with ➔	Eye blinks (0.5–2 Hz) Or Reading eye movements Irregular conjugate eye movements Rapid eye movements	Normal or high
N1	If subject generates alpha waves with eyes closed: rhythm of alpha is reduced and replaced by low-amplitude mixed-frequency activity (4–7 Hz) for more than 50% of the epoch.	Slow eye movements are optional when eyes are closed	Less than in W
	If no alpha waves are generated during eye closure, score if any of the following: 1) Vertex sharp waves or 2) Rhythm shows 4–7 Hz activity with slowing of background frequencies by ≥ 1 Hz when compared with stage W.	Slow eye movements	Variable but less than in W
N2	If either or both of the following criteria occur: 1) ≥ K complex* not associated with arousal 2) ≥ Trains of sleep spindles[$]	Usually none	Variable but less than in W
N3	Slow wave activity (0.5 to 2 Hz and peak to peak amplitude more than 75 microvolt) is ≥ 20%	Usually none	Lower than N2 but can be equal as REM
REM	Definite REM: low-amplitude mixed-frequency activity (4–7 Hz)	Rapid eye movements	Lowest

EEG: electroencephalogram; EOG: electrooculogram; EMG: electromyogram; REM: rapid eye movement; N: non-rapid eye movement; W: wake; Hz: hertz. * A K-complex is a well delineated, sharp upward deflection, followed by a negative deflection which stand out from the background EEG and with a minimum duration of 0.5 seconds. [$] a sleep spindle is a train of unique sinusoidal EEG waves with a frequency of 11 to 16 Hz and with a minimum duration o f0.5 seconds.

- **Scoring of arousals according to AASM criteria**

Arousals were scored in accordance with the AASM 2012 criteria (47) which include:

- An abrupt shift in EEG rhythm to a higher frequency (alpha, theta, or beta)
- Minimum duration for the abrupt shift in EEG must be ≥ 3 s and < 15 s

- Preceded by at least 10 s of stable sleep

2.7.2 Measurement of vibration produced by the vibrotactile PT device

Vibration produced by the vibrotactile PT device was measured using a standard microphone which is typically used to measure snoring. The microphone was secured to the vibrotactile PT device and connected directly to the SOMNOscreen. The direct connection of the snore sensor to the SOMNOscreen allowed for accurate synchronisation with the EEG recordings (Figure 2.7).

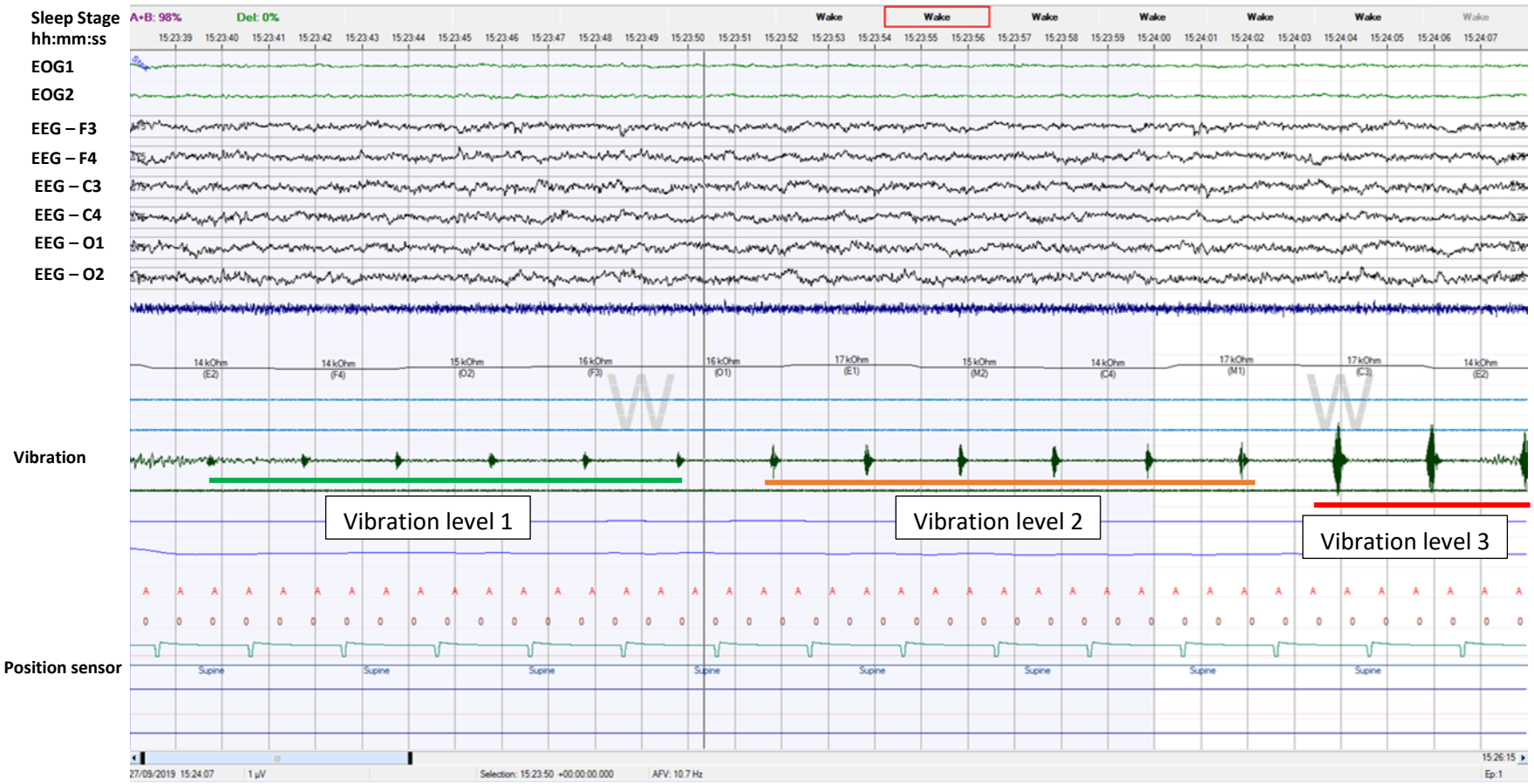


Figure 2.7: Measurement of vibration produced by the vibrotactile PT device using a snoring microphone synchronised with EEG

This figure shows a 30 s epoch in which the volunteer was set up with PSG while wearing a vibrotactile PT device. The vibrations in the vibration channel were recorded by a piezoelectric vibration sensor connected to the SOMNOscreen. As shown, three levels of vibration (underlined with green, orange, and red) are synchronised with the EEG recording. Note that there are six vibrations for vibration level one (green), six vibrations for level 2 (orange), and three vibrations for level 3 (red). Note the increasing intensity with each subsequent level of vibration.

2.8 Novel Method for Analysis of Arousability and Sleep Recovery Following PT

As discussed in chapter 1, section 1.8, one of the concerns when using vibrotactile stimuli is the possibility of causing arousals or awakenings, and it is likely that response to this stimulus might differ among individuals. A discussion of different sleep phenotypes is presented in chapter 1, section 1.3. To investigate the impact of the vibrotactile stimuli on arousal, I developed a novel analytical method to indirectly measure arousability and sleep recovery. This method is based on the concept that the vibration produced by the vibrotactile PT device is considered an external stimulus which might lead to arousal and or awakening.

Once a sleeper moves into the supine position, the vibrotactile PT device starts vibrating, as can be seen in the vibration channel in figure 2.8. The beginning of the vibration (point A) to the point of changing position away from the supine position (point B) represents the duration to position change, which is represented by variable 2 in figure 2.8. I proposed that this duration can be used as an indirect measure of arousability.

I have also proposed the duration to return to sleep, to indirectly quantify sleep recovery from the external stimulus (vibration). This duration starts from the point of changing position (point B) to the beginning of the first scorable epoch of sleep (point C). To ensure that the sleeper was in stable sleep prior to the vibration, the two variables (variables 2 and 3) were only eligible to be scored if they were preceded by a scorable epoch of sleep in one of the two epochs preceding the stimulus.

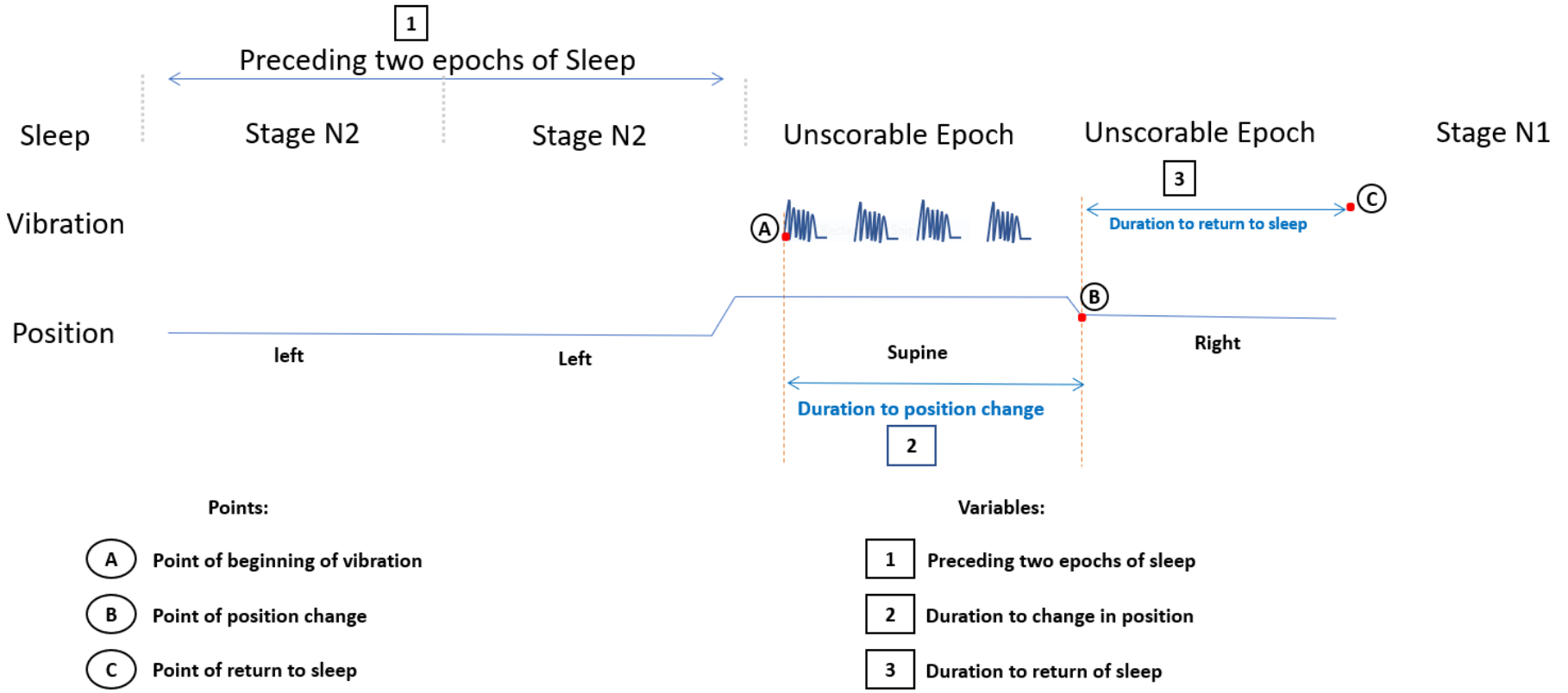


Figure 2.8: Novel method for analysis of indirect measures of arousability and sleep recovery

This figure shows the novel method analysis that was developed by the author of this thesis. It shows three channels: sleep stage, vibration, and position. To determine whether the sleeper has been aroused from sleep by the vibrotactile stimulus produced by the PT device, an indirect measure of arousability was developed. This measure is the duration to position change which extends from the beginning of the vibrotactile stimulus to the change in position away from the supine position (from point A to point B). In addition, an indirect measure of sleep recovery was developed: the duration to return to sleep. This extends from the point of position change away from the supine position to the first epoch of scorable sleep.

2.8.1 Statistical analyses

The statistical analyses specific to each study are described in their corresponding experimental chapter. Statistical analyses were performed using SPSS V.27.0 (IBM, Illinois, USA). Data were assessed for meeting parametric assumptions or not; this included testing for normality of distribution, homogeneity of variances, linearity, and independence. To test for normality of distribution, skewness and kurtosis were assessed. In addition, the Kolmogorov–Smirnov and Shapiro–Wilk tests were used. Histograms, P–P plots, and Q–Q plots were analysed as appropriate, and homogeneity of variance was checked using Leven's test.

In general, descriptive statistical analyses of the data were performed to present baseline characteristics and outcomes. If it met the parametric assumption, categorical data were presented as proportions, while continuous data were presented as means ± standard deviation (SD). If the data did not meet the assumption, they were presented as a median with interquartile range. Appropriate statistical tests were chosen based on meeting or not the assumption of parametric testing.

2.9 Data collection to Compare the Neck-Worn (Night Shift™) and Forehead-Secured (Somnibel™) Vibrotactile PT Devices

2.9.1 Background

The overall aim of the data collection was to compare the efficacy of the neck-worn and forehead-secured vibrotactile PT devices. The specific aims were to compare the devices in terms of the percentage of successful activations of vibration in response to supine position and the duration to start of vibration. It was hypothesised that the neck-worn device would demonstrate a higher percentage of successful activations of vibration in response to supine position when compared with the forehead-secured device. In addition, it was hypothesised that duration to start of vibration would be shorter in the neck-worn than the forehead-secured device.

These hypotheses were based on data from audiology literature, where it is well established that vibrotactile stimuli produced by a clinical bone vibrator can be transmitted via the forehead (frontal) bone to the ear via osseous conduction mechanisms (Sohmer, 2017). More recently, a clinical bone vibrator has been shown to transmit vibrotactile stimuli

through soft tissue (such as the tissue of the posterior neck) (Sohmer, 2017). The back of the neck is also a densely innervated area and is much closer to the vertebrae than the forehead. Therefore, both osseous and non-osseous soft tissue conduction mechanisms would favour the vibrotactile PT device being worn on the neck. However, the increased sensitivity of the back of the neck may result in more frequent arousals from sleep and sleep fragmentation.

2.9.2 Methods

- **Participants**

Healthy volunteers who were 18 years or older and who did not suffer from sleep disorders or other chronic diseases were invited to participate in this study. These healthy participants were comprised of staff recruited from Imperial College London or Imam Abdulrahman bin Faisal University in Dammam. Ethical approvals were obtained from both institutions and are found in appendix 19 and 20.

- **Procedures and measurements**

Two consecutive overnight PSG studies were performed in which the participant wore one vibrotactile PT device on each night. The order of the PT devices was randomly assigned using sealed envelopes. The PSGs were performed as described in section 2.4.1.

Vibrations were recorded using a microphone, as described in section 2.4.3. The duration to start of vibration was measured as described in section 2.7.2. Successful activation of vibration in response to the supine position was noted whenever the vibrotactile device detected the supine position and responded by activating vibration. Successful position change in response to vibration depended on whether vibration resulted in a position change away from the supine position or not. Duration to change in position and duration to return to sleep were noted based on the described novel analysis method in section 2.7.2.

- **Analyses**

Vibrotactile stimuli were analysed manually by counting the individual vibrations on the microphone channel. Sequential vibrations with similar intensity were counted as a single set, and scoring was done by author of this thesis. Blinding of the type of the PT device used was not possible because of the unique pattern of vibrations for each device.

The total number of supine events represents the total number of supine events that the participant experienced throughout the night. The total number of sets of vibrations represents the total number of vibrations activated throughout the night. The percentage of successful activations of vibration in response to supine position was calculated by dividing total sets of vibrations by the total number of supine events.

Descriptive statistics for the baseline characteristics were used to present outcome variables. Summary data are presented as mean ± SD, median (Q1, Q3), or median (min, max), as appropriate.

2.9.3 Results

Six participants completed the comparative study. Demographic data are shown in table 2.9. The mean age (years) was 36.7 ± 6.8, and the mean BMI (kg/m^2) was 25.3 ± 3.8.

Table 2.9: Demographic data of participants

Participant	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
1	M	29	163	88	33
2	M	31	168	68	24
3	M	36	182	76	23
4	F	42	175	75	24
5	M	35	164	62	23
6	M	47	188	90	25
Mean ± SD	-	36.7 ± 6.8	173.3 ± 10.2	76.5 ± 11	25.3 ± 3.8
M: male; F: female; SD: standard deviation; BMI: body mass index.					

- **Supine events and vibrations throughout the night**

Table 2.10 shows the total number of the supine events per night for the different devices for each participant. All participants experienced at least two supine events for both devices. In addition, the vibrotactile stimulus in response to the supine position is shown for each device.

Table 2.10: Total number of supine events throughout the night and total number of sets of vibrations between the neck-worn and forehead-secured device

Participants	Total supine events (event/night)		Total sets of vibrations (sets/night)	
	Neck-worn device	Forehead-secured device	Neck-worn device	Forehead-secured device
1	18	12	9	8
2	16	24	14	3
3	3	8	2	5
4	2	3	2	2
5	7	9	6	9
6	2	2	1	0
Median (Q1, Q3)	5 (2, 13.75)	8.5 (2, 11.25)	2 (1, 6)	4 (0, 7.25)

Q1: first quartile; Q3: third quartile; the reason for highlighting some numbers in grey is explained in the text.

- **Percentage of successful activations of vibration in response to supine position**

The group median percentage of successful activations of vibrotactile stimulus in response to supine position for the neck-worn vibrotactile PT device was 76.2% (50, 100) as compared with the forehead-secured vibrotactile PT device 64.6% (0, 100). This difference is mainly due to participant 2. This comparison is presented in figure 2.9.

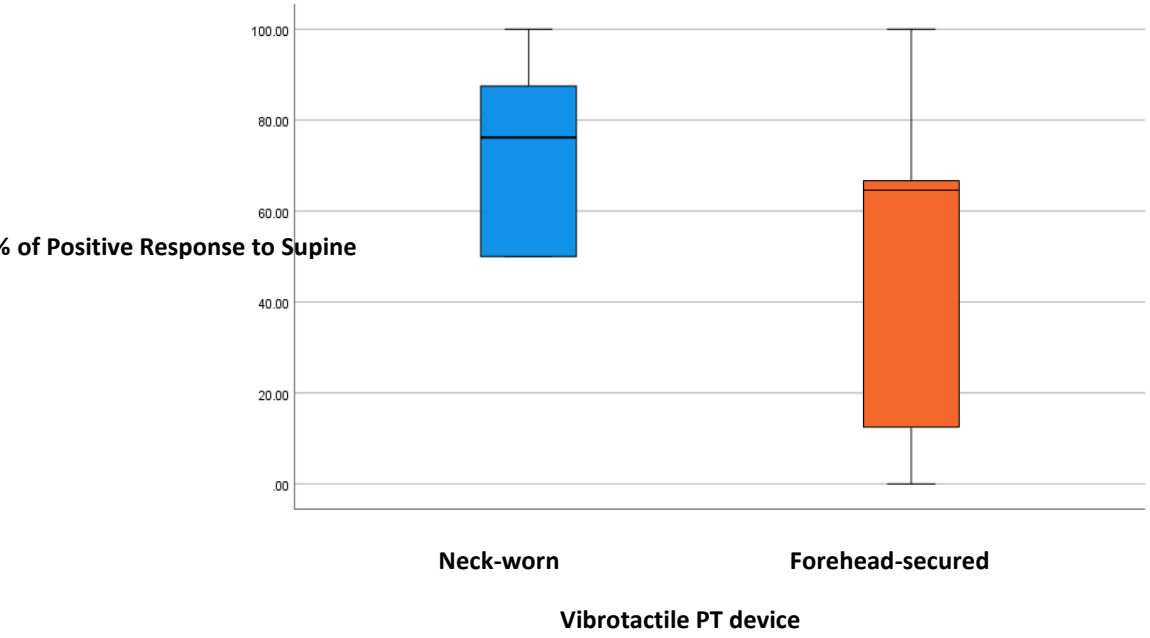


Figure 2.9: Median (min, max) percentage of successful activations of vibrotactile stimulus in response to supine position between neck-worn and forehead-secured vibrotactile PT devices

- **Duration to start of vibration**

Table 2.12 shows the median duration (Q1, Q3) to start of vibration, for each participant and each device. For the neck-worn device, the group median duration (Q1, Q3) to starting of the vibrotactile stimulus was 4.5 s (4, 5); for the forehead-secured device, the duration was 32 s (30, 98.5) (figure 2.10). It is important to note that the forehead-secured device uses a delay of 30-second to the start of the vibrotactile stimulus.

Table 2.11: Duration to start of vibration in the neck-worn and forehead-secured devices

Participants	Neck-worn device (seconds)	Forehead-secured device (seconds)
1	4.5	30.0
2	5.0	25.0
3	4.0	208.0
4	680.0	98.5
5	8.0	32.0
6	4.0	-
Median (Q1, Q3)	4.5 (4, 5)	32 (30, 98.5)
Q1: first quartile; Q3: third quartile.		

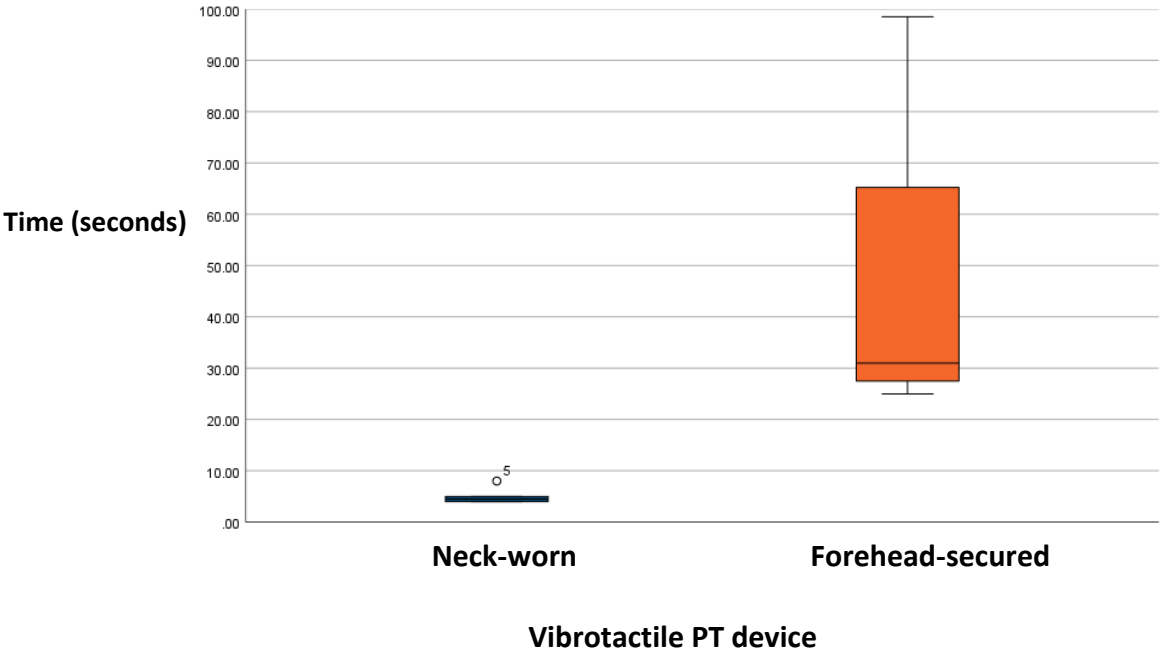


Figure 2.10: Median (Q1, Q3) duration to start of vibration between neck-worn and forehead-secured vibrotactile PT devices

2.9.4 Discussion

The main finding was that the neck-worn device performed better in detecting supine position and successfully activating the vibrotactile stimuli as compared with the forehead-secured device. In addition, the duration to starting of the vibrotactile stimulus was more consistent and shorter for the neck-worn device as compared with the forehead-secured device. Despite that the forehead-secured device uses a 30-second delay to the start of the

vibrotactile stimuli, the interquartile range for this device was wider (30 – 98.5, seconds) compared to the neck-worn device (4– 5, seconds).

A potential explanation for the forehead-secured device being less successful in detecting the supine position could be that movements of the head may not represent movements of the body. This might explain the values of participant 2 (table 2.10). This observation was noted during early testing trials of PT devices; the neck-worn device uses 45^{O} as the supine threshold angle. A similar observation was made in a study comparing the position of the forehead and of the trunk in 199 OSA patients (Van Kesteren *et al.*, 2011).

In this study, body position during sleep was measured by the SOMNOscreen built-in position sensor, which was located medially on the trunk, as described in section 2.4.1. However, the vibrotactile devices vibrated in response to their detection of supine position using built-in, three-dimensional accelerometers. Therefore, it is possible that while the trunk was in supine position the head and neck were not, and therefore the device did not produce vibrotactile stimulus.

Previous studies have investigated the position of the forehead vs the position of the trunk and the effect of these relative positions on OSA severity (van Kesteren & Hilgevoord, 2015; Van Kesteren *et al.*, 2011). It has been shown that rotation of the head to supine position significantly increased the AHI in about 31% of the study sample. (Zhu *et al.*, 2017) reported a similar observation in which the AHI dropped by about 10 events/hr when the head rotated from supine to lateral while the trunk was in supine position. In their study, the authors reported that in approximately 27% of the participants, OSA severity was essentially resolved by rotation of the head away from supine position while the trunk was in the supine position.

2.9.5 Summary

The neck-worn PT device activated vibrotactile stimulus in response to supine position more consistently compared with the forehead-secured PT device. Furthermore, the duration to starting of the vibrotactile stimulus was shorter in the neck-worn device as compared with the forehead-secured device. This is despite that the forehead-secured device uses a 30-second delay to start the vibrotactile stimuli. The following experimental chapters describe the effect of the neck-worn device on the AHI and daytime functioning (chapter 4), and

arousability (chapter 5). In chapter 3, a systematic review and meta-analysis were conducted to investigate the effect of vibrotactile PT devices on the AHI of patients with POSA.

CHAPTER 3: The Efficacy of Vibrotactile Positional Therapy Devices on Patients with Positional Obstructive Sleep Apnoea: a Systematic Review and Meta-Analysis

3.1 Introduction

As discussed in chapter 1, obstructive sleep apnoea (OSA) is a common sleep disorder affecting nearly one billion people worldwide (Benjafield *et al.*, 2019; Yingjuan *et al.*, 2019). Chapter 1, sections 1.5.4 and1.5.5 presented a review of how the supine sleep position is a risk factor for OSA (Cartwright, 1984), and when OSA occurs predominantly or exclusively in the supine position, it is referred to as positional obstructive sleep apnoea (POSA) (Frank *et al.*, 2015). Section 1.5.1 of chapter 1 includes a discussion on different definitions for POSA; the exact definition of POSA varies (Bignold *et al.*, 2011; Cartwright, 1984; Frank *et al.*, 2015; Levendowski *et al.*, 2018; Mador *et al.*, 2005; Marklund *et al.*, 1998), but it is often defined as an apnoea-hypopnoea index (AHI) in the supine position that is twice that of a non-supine AHI, with an overall AHI > 5 events/hr (Cartwright, 1984).

Chapter 1, section 1.5.3 discusses the clinical characteristics of patients with POSA. More than 50% of patients diagnosed with OSA have POSA (Lee *et al.*, 2017; Mo *et al.*, 2011; Oulhaj *et al.*, 2017; Ravesloot *et al.*, 2016). Patients with POSA are more likely to be male (Aarab *et al.*, 2009), young (Joosten *et al.*, 2014), have a lower BMI (Mo *et al.*, 2011), smaller neck and waist circumferences, and lower Mallampati scores (Yingjuan *et al.*, 2019), than those with non-positional OSA. OSA severity in patients with POSA tends to be milder, with a prevalence of POSA of 80% in mild-moderate OSA compared with 40% in severe OSA cases (Mo *et al.*, 2011).

PT has been proposed as an alternative treatment to continuous positive airway pressure (CPAP) for the treatment of POSA. As discussed in chapter 1, section 1.7. PT is any technique that prevents the patient from sleeping in the supine position (Yingjuan *et al.*, 2019). Traditional PT techniques use mechanical avoidance of the supine position and include the use of a bulky object (e.g., a tennis ball attached to the back of nightwear or a wedge-shaped pillow). These techniques are efficacious but are poorly tolerated (Bignold *et al.*, 2009; Loord & Hultcrantz, 2007; Oksenberg *et al.*, 2006), with low long-term compliance rates of around 10% (Bignold *et al.*, 2009). Traditional PT techniques, therefore, have not succeeded as a satisfactory routine treatment for POSA patients.

Vibrotactile PT devices are a relatively new development in the treatment of POSA. These devices are described in chapter 2, section 2.6. Briefly, these light-weight devices use position sensors to sense body position and small haptic motors (similar to those in a smartphone) to produce an incremental vibratory stimulus in response to movement to the supine position, thus encouraging a position change away from supine. In addition, the devices are capable of objectively monitoring usage and adherence data. Vibrotactile PT devices can be placed on different sites on the body, such as the back of the neck (Levendowski *et al.*, 2014), chest (Bignold *et al.*, 2011; van Maanen *et al.*, 2013), or the forehead (Armas *et al.*, 2019). These devices are shown in chapter 1, figure 1.7. Data comparing the efficacy of the neck-worn (figure 1.7, panel A) and forehead-secured (figure 1.7, panel D) vibrotactile PT devices are shown in chapter 2, section 2.9.

The primary aim of this systematic review and meta-analysis was to investigate the effect of vibrotactile PT devices on the AHI and the %Tsupine in patients with POSA, in comparison with the baseline. A secondary aim was to investigate the effect of vibrotactile PT devices on daytime sleepiness, daytime functioning, quality of life, sleep efficiency, and arousal from sleep.

3.2 Methods

A systematic review was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocol (PRISMA-P) and was registered on PROSPERO (CRD42020188617).

3.2.1 Inclusion criteria

- **Study type:** randomised parallel controlled and cross-over trials and prospective cohort studies.
- **Population:** studies that involved adult participants diagnosed with POSA.
- **Type of intervention:** studies that used vibrotactile PT devices.
- **Type of outcome:** primary outcomes were the AHI and %Tsupine. Both variables were measured objectively either by polygraphy or polysomnography (PSG) at a follow-up visit and compared with the baseline. In addition, the following secondary outcomes that assessed daytime functioning and quality of life outcomes, compared with the baseline, were extracted: Epworth Sleepiness Scale (ESS) scores (Johns, 1991),

Functional Outcomes of Sleep Questionnaire (FOSQ) global score (Weaver *et al.*, 1997), The 36-Item Short Form Health Survey (SF-36) scores (Jenkinson *et al.*, 1993). Secondary outcome measures included objectively measured sleep quality outcomes (sleep efficiency and arousal index).

3.2.2 Exclusion criteria

- Studies that were not in the English language.
- Studies that involved animals.
- Studies that used diagnostic modalities other than polygraphy or polysomnography.

3.2.3 Search strategy

To identify relevant research articles, an electronic search of articles up to September 10, 2021, of the following databases was performed: Medline (Ovid), Embase, Cochrane Library (CENTRAL). The search strategy was developed in consultation with an expert librarian. The following Medical Subject Headings (MeSH) terms, keywords, and combinations were used: obstructive sleep apnoea, obstructive sleep apnoea, obstructive sleep apnoea hypopnea syndrome, obstructive sleep apnoea hypopnoea syndrome, OSA, OSAHS, POSA, ePOSA, positional, position, posture, supine, supine-isolated, supine-predominant, supine-exclusive, dorsal, lateral, treatment, therapy, device, trainer. The search strategy for the electronic databases is included in the online supplement (appendix 9).

3.2.4 Search procedures

Searches were performed by AA and Dr Julia Kelly. All identified articles were imported into the COVIDENCE website (COVIDENCE systematic review software, Veritas Health Innovation, Melbourne, Australia) and duplicates were removed. For the assessment of eligibility, both reviewers (AA and JK) screened titles and abstracts of all identified research articles; ineligible articles were excluded. An additional manual search of the reference lists of the eligible articles as well as relevant systematic reviews was performed to capture articles that were not identified in the original electronic search. A search for ongoing clinical trials was also performed in the databases. Full-text review of all eligible articles was performed by two reviewers (AA and JK). Disagreement was resolved through discussion until a consensus was reached; where consensus could not be reached, the decision of a third reviewer (Dr C Turnbull, University of Oxford) was sought.

3.2.5 Data extraction

The following details were extracted from each research article and reviewed by two reviewers (AA and JK): research study characteristics, participant characteristics, intervention, and comparator characteristics. A standardised Microsoft Excel data extraction form was used. In case of missing data, the corresponding author was contacted by email. If data could not be obtained from the authors, calculation methods were used to determine the mean and standard deviation (Wan *et al.*, 2014). If data could neither be sourced from the authors or calculated by a standard method, then it was not included in the quantitative meta-analysis. If both per protocol and intention to treat data were available, then the data on the more conservative intention to treat were used. The two reviewers (AA and JK) independently judged each risk of bias for all included clinical trials. Disagreement was resolved through discussion until a consensus was reached; if consensus could not be reached, the decision of a third reviewer (Dr C Turnbull, University of Oxford) was sought. The 'Risk of Bias' tool in the Cochrane Collaboration RevMan 5.4 software (Review Manager [RevMan] software, The Cochrane Collaboration, Copenhagen) was used.

3.2.6 Data analysis

Synthesis of the results was aimed at clinically relevant outcomes including polygraphy or PSG-measured variables and daytime functioning measures. A meta-analysis was performed using RevMan 5.4 software (Review Manager [RevMan] software, The Cochrane Collaboration, Copenhagen). Results of continuous outcomes were expressed as a mean difference and 95% confidence interval. A random-effects model was used for the analysis of the effect of vibrotactile PT at follow-up and compared with the baseline. Heterogeneity among the included studies was assessed using prediction interval, I^2 statistics, and *p*-value. Subgroup meta-analyses based on the level of OSA severity were performed if I^2 was ≥ 50% and p-value < 0.1.

3.3 Results

The systematic search revealed 1015 articles of which 342 were duplicates. After title and abstract screening, 25 articles were assessed for eligibility for full-text reading. After exclusions, 18 studies were included in this review, of which ten were clinical trials (five parallel RCTs and five cross-over trials) and eight were cohort studies. The results of the

search are presented in a PRISMA flow chart (figure 3.1). This search also identified four ongoing, registered clinical trials which are available in appendix 10.

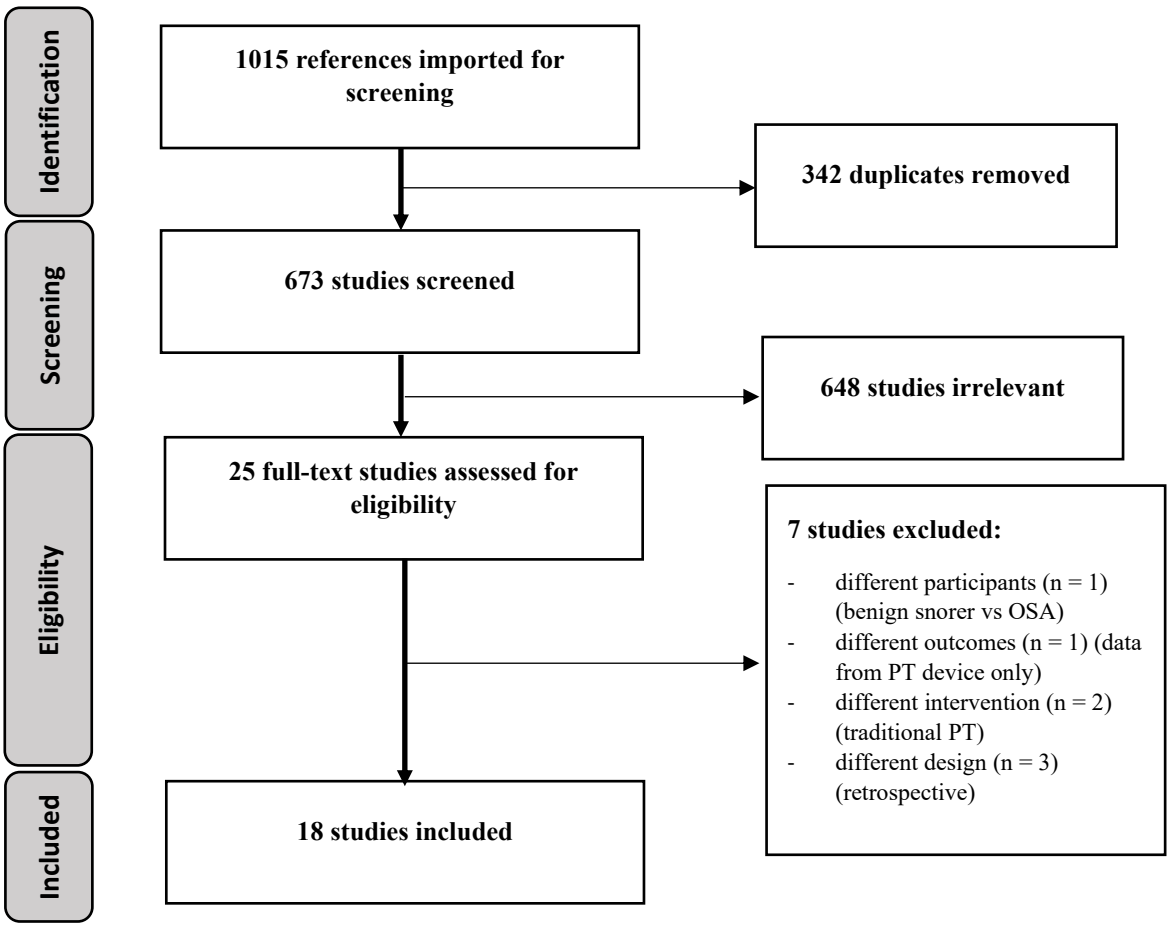


Figure 3.1: PRISMA Flow chart showing the screening process

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; OSA: obstructive sleep apnoea; PT: positional therapy.

Of the included studies, participant age (mean ± SD) ranged from 44 ± 11.2 to 64.8 ± 9.5 years. In all studies, the average BMI fell into the overweight category (25–30 kg/m^2). The studies tended to include participants across the OSA disease spectrum with no study limiting participants to a single OSA severity; therefore, the level of OSA severity for each study was based on the mean baseline AHI of the study: mild (4 studies: 2 clinical trials and 2 cohort studies), moderate (12 studies: 7 clinical trials and 5 cohort studies), and severe (2 studies: 1 clinical trial and 1 cohort study).

Most studies used chest-worn PT devices (6 clinical trials and 6 cohort studies), three used neck-worn devices (2 clinical trials and 1 cohort study), two studies used a forehead-secured PT device (1 clinical trial and 1 cohort study), and one study (1 clinical trial) used a prototype.

Across the ten clinical trials, the control group varied between inactive PT treatment (2 studies), no treatment (1 study), mandibular advancement device (MAD) (2 studies), tennis ball technique (TBT) (1 study) and auto-titrated positive airway pressure (APAP) (2 studies). One study used two different comparisons, MAD only and combined MAD and PT. One study used a comparison to no treatment and to inactive PT treatment.

The length of follow-up was different among the studies. In three studies, the length of follow-up was less than one week (2 clinical trials, 1 cohort study). In six studies the length of follow-up was between one week and one month (2 clinical trials and 4 cohort studies). In the remaining nine studies, the length of follow-up was between one and three months (4 clinical trials and 3 cohort studies). These studies are summarised in table 3.1 and table 3.2 for clinical trials and cohort studies, respectively.

Table 3.1: Summary of the baseline characteristics of the included clinical trials

Authors and Year	Type of Sleep Study	Design	Sample size	Intervention	Location and Name of Device	Control	Follow-up
Bignold et al., 2011 (Bignold *et al.*, 2011)	PG	Randomised crossover trial	n = 15	PT	Chest, BuzzPOD	Inactive treatment	3 weeks
van Maanen et al., 2012 (van Maanen *et al.*, 2012)	PSG	Randomised crossover trial	n = 30	PT	Neck, prototype	Inactive treatment	1 night with device on and 1 night off
Dieltjens et al., 2015 (Dieltjens *et al.*, 2015)	PSG	Randomised crossover trial	n = 20	PT	Chest, Night Balance	MAD only, PT + MAD	1 night intervention
Eijsvogel et al., 2015 (Eijsvogel *et al.*, 2015)	PSG	Parallel RCT	n = 55	PT	Chest, Night Balance	TBT	1 month
Benoist et al., 2017 (Benoist *et al.*, 2017)	PSG	Multicentre Parallel RCT	n = 99	PT	Chest, Night Balance	MAD	3 months
Laub et al., 2017 (Laub *et al.*, 2017)	PG	Parallel RCT	n = 101	PT	Chest, Night Balance	No treatment	2 months
Berry et al., 2019 (Berry *et al.*, 2019)	PSG	Multicentre randomised crossover trial	n = 117	PT	Chest, Night Balance	APAP	6 weeks
Mok et al., 2020 (Mok *et al.*, 2020)	PSG	Randomised crossover trial	n = 40	PT	Neck, Night Shift	APAP	8 weeks
Armas et al., 2021 (Hidalgo Armas *et al.*, 2021)	PSG	Parallel RCT	n = 128	PT	Forehead, Somnibel	No treatment, Inactive treatment	12 weeks
Suzuki et al., 2021 (Suzuki *et al.*, 2021)	PSG	Parallel RCT	n=160	PT	Neck, Night Shift	MAD	8 weeks

RCT: randomised controlled trial; n: sample size; PSG: polysomnography; PT: vibrotactile positional therapy; MAD: mandibular advancement device; TBT: tennis ball technique; APAP: auto-adjusting positive airway pressure; PG: polygraphy

Table 3.2: Summary of the baseline characteristics of the included cohort studies

Authors and Year	Type of Sleep Study	Design	Sample size	Intervention	Location and Name of Device	Follow-up
van Maanen et al., 2013 (van Maanen *et al.*, 2013)	PSG	Cohort study	n = 31	PT	Chest, Night Balance	1 month
van Maanen et al., 2014 (van Maanen & de Vries, 2014)	Polygraphy	Multicentre cohort study	n = 106	PT	Chest, Night Balance	6 months
Levendowski et al., 2014 (Levendowski *et al.*, 2014)	PSG	Cohort study	n = 30	PT	Chest, Night Balance	1 month
Scarlata et al, 2016 (Scarlata *et al.*, 2016)	PSG	Cohort study	n = 20	PT	Neck, Night Shift	3 days
Beyers et al, 2018 (Beyers *et al.*, 2018)	PSG	Cohort study	n = 79	PT	Chest, Night Balance	1 month
deRuiter et al., 2018 (de Ruiter *et al.*, 2018)	PSG	Cohort study	n = 99	PT	Chest, Night Balance	12 months
Armas et al., 2019 (Armas *et al.*, 2019)	PSG	Cohort study	n = 12	PT	Forehead, Somnibel	4 weeks
Beyers et al., 2019 (Beyers *et al.*, 2019)	PSG	Cohort study	n = 36	PT	Chest, Night Balance	12 months

n: sample size; PSG: polysomnography; PT: vibrotactile positional therapy; PSG: polysomnography.

3.3.1 Primary outcomes

- **AHI with vibrotactile PT at follow-up compared with the baseline**

Eighteen studies measured the total AHI at follow-up (with vibrotactile PT) as compared with the baseline (no vibrotactile PT). One study (van Maanen & de Vries, 2014) was excluded as mean (SD) data could not be calculated. Pooled analysis of 17 studies (n = 700) showed a statistically significant reduction in the total AHI at follow-up as compared with baseline (mean difference of -9.19 events/hr [95% CI: -11.68, -6.70; *p*-value < 0.001]) (figure 3.2).

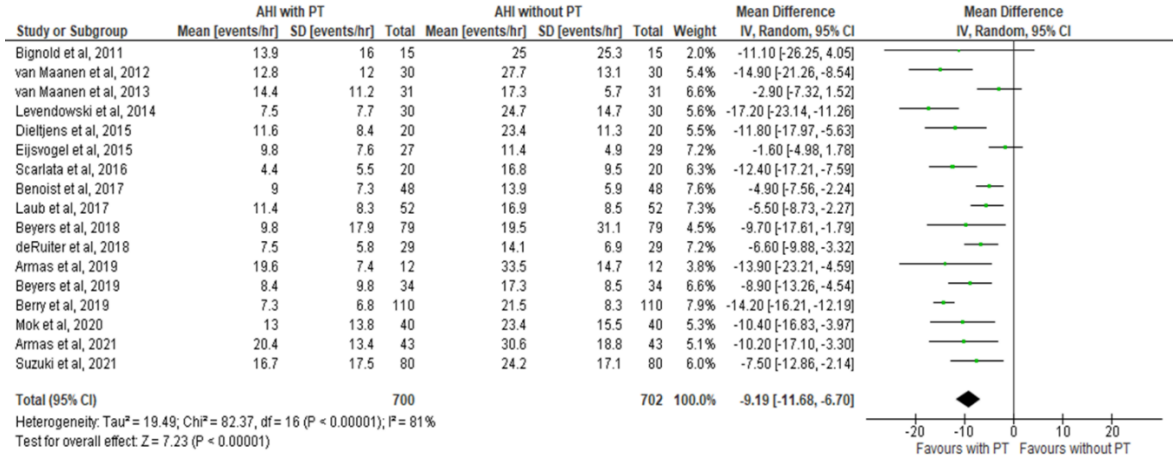


Figure 3.2: Forest plot of clinical trials and cohort studies comparing total AHI with and without vibrotactile PT (baseline)

AHI: apnoea hypopnea index; PT: positional therapy.

- **Percentage of time spent in the supine position (%Tsupine) with vibrotactile PT at follow-up as compared with the baseline**

Pooling of the results from 17 studies (n = 700) that compared mean %Tsupine at follow-up with the baseline showed a significant reduction in the mean %Tsupine (mean difference of -32.79% [95% CI: -38.75, -26.83; *p*-value < 0.001]) (figure 3.3).

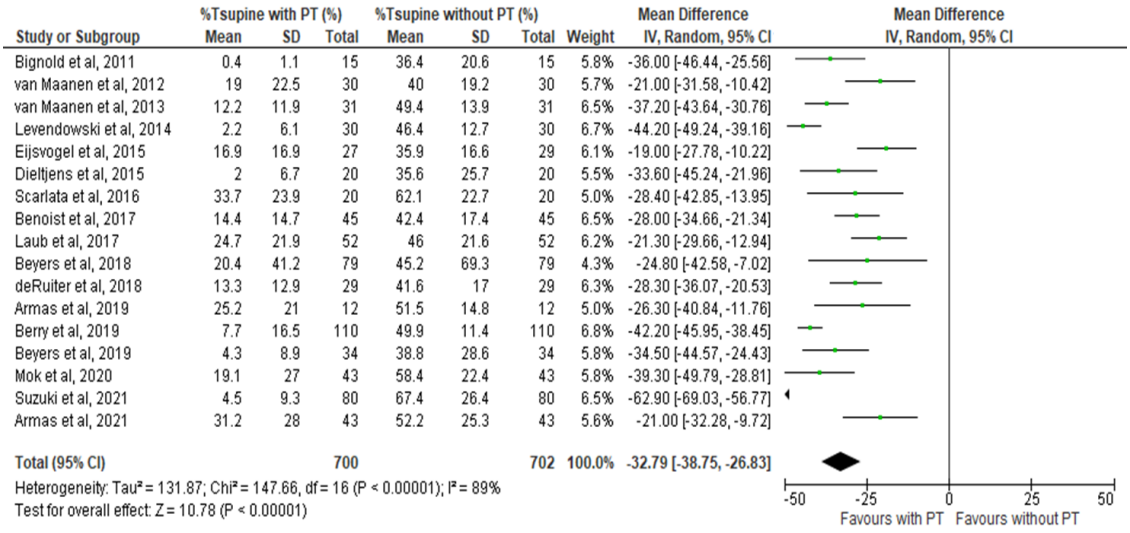


Figure 3.3: Forest plot of clinical trials and cohort studies comparing percentage of time spent in the supine position with and without vibrotactile PT (baseline)

%Tsupine: percentage of time spent in the supine position; PT: positional therapy.

3.3.2 Secondary outcomes

- **Epworth Sleepiness Scale (ESS)**

ESS data were available from nine studies (n = 411). There was a significant reduction in the mean ESS score at follow-up as compared with the baseline by a mean difference of -1.17 (95% CI: -1.75, -0.58; *p*-value < 0.001) (figure 3.4).

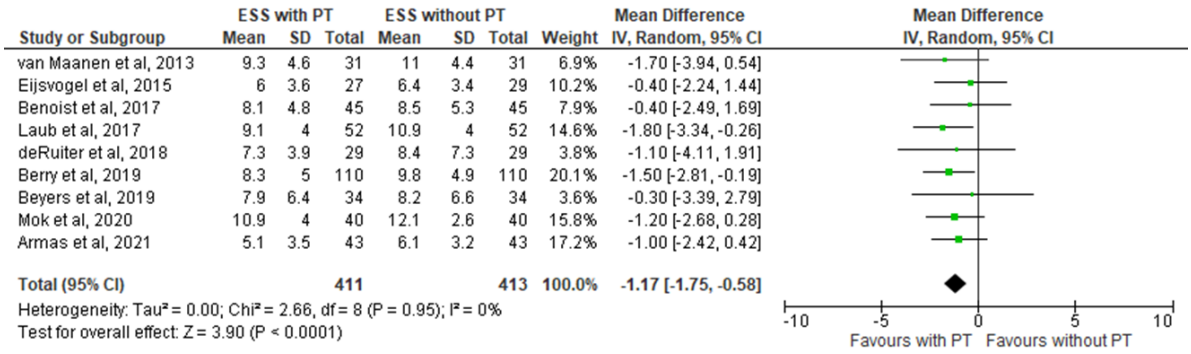


Figure 3.4: Forest plot of clinical trials and cohort studies comparing Epworth Sleepiness Scale with and without vibrotactile PT (baseline)

ESS: Epworth Sleepiness Scale; PT: positional therapy.

- **Quality of life (FOSQ global score and SF-36 Vitality score)**

FOSQ data were only available from four studies (n = 224). One other study (van Maanen & de Vries, 2014) was excluded as they used a version of FOSQ with a different FOSQ global score. The use of vibrotactile PT resulted in a significant increase in the mean global FOSQ score by a mean difference of +0.56 (95% CI: +0.12, +1.00; *p*-value = 0.01) (appendix 11).

SF-36 Vitality score data were available from only two studies (n = 150). The use of vibrotactile PT resulted in a significant increase in the mean vitality score by a mean difference of +6.72 (95% CI +2.52, +10.92; *p*-value = 0.002) (appendix 11).

- **Sleep efficiency**

Sleep efficiency data were available from 11 studies (n = 417). The use of vibrotactile PT did not result in a statistically significant difference in the mean sleep efficiency, with a mean difference of +0.74 (95% CI -0.63, +2.11; *p*-value = 0.29) (appendix 11).

- **Arousal index**

The arousal index data were available from 10 studies (n = 372). Pooling of these data showed that the use of vibrotactile PT resulted in a significant reduction in the mean arousal index, with a mean difference of -3.11 (95% CI -6.00, -0.21; *p*-value = 0.04) (appendix 11).

3.3.3 Sensitivity analyses

Because of the statistically significant heterogeneity in most of the results, subgroup analyses were performed for the primary outcome variables.

- **AHI with and without vibrotactile PT**

The result of the random-effects model of the AHI with and without PT showed that the heterogeneity was statistically significant with *p*-value <0.00001 and I^2 statistics of 78%. Therefore, predetermined subgroup analyses were run based on the level of OSA severity, which was determined based on the average baseline value of the AHI in each included study.

  - **Mild OSA:** three studies included 104 participants with mild OSA (average baseline AHI < 15 events/hr). Pooling of the results showed a 34% reduction in the AHI at follow-up as compared with the baseline (mean difference of -4.42

events/hr [95% CI: -7.10, -1.75; *p*-value = 0.001]) (appendix 12). The I^2 statistic in this model was higher, which may be explained by the presence of other factors that contributed to heterogeneity, such as length of follow-up.

- **Moderate and severe OSA:** fourteen studies included 596 participants with moderate and severe OSA (average baseline AHI ≥ 15 events/hr). The results showed that there was a significant reduction in the AHI of 46% at follow-up as compared with the baseline (mean difference of -10.50 events/hr [95% CI: -13.01, -7.99; *p*-value < 0.001]) (appendix 12).

- **Percentage of time spent in the supine position**

Heterogeneity results of the %Tsupine model were statistically significant, with *p*-value <0.00001 and I^2 statistics of 88%. Subgroup analyses were performed based on the OSA level of severity, as for AHI.

- **Mild OSA:** three studies included 101 participants with mild OSA and compared mean %Tsupine with and without vibrotactile PT. There was a significant reduction in the mean %Tsupine at follow-up as compared with the baseline (mean difference of -25.60 % [95% CI: -31.13, -20.07; *p*-value <0.001]) (appendix 12). The calculated percentage of change at follow-up compared to baseline was 64%.
- **Moderate and severe OSA:** fourteen studies included 599 participants with moderate and severe OSA and compared mean %Tsupine with and without vibrotactile PT. There was a significant reduction in the mean %Tsupine at follow-up as compared with the baseline (mean difference of -34.58% [95% CI: -41.08, -28.08; *p*-value < 0.001]) (appendix 12). The calculated percentage of change at follow-up compared to baseline was 71%.

3.4 Risk of Bias and Evidence Quality Assessment

The main reason for the increased risk of bias in the included studies is the difficulty to blind participants from interventions (APAP, MAD, TBT, or no device) (figure 3.5). However, this bias was not sufficiently large to decrease confidence in the estimated treatment effect. Additionally, the funnel plot (figure 3.6), showed some points outside the funnel and an absence of smaller studies, which is suggestive of publication bias. Imprecision was not

evident in this review because of the large sample size (n = 700), and the clinical decision would not be different if the true effect was at either side of the 95% CI. Moreover, the studies in this review showed consistent effect with overlap of the CIs. Finally, all studies directly compared the intervention of interest (vibrotactile PT) in the population of interest (POSA), and all reported the needed outcome (AHI). Therefore, according to the Grading Recommendations, Assessment, Development and Evaluations (GRADE) approach, the evidence to recommend the use of vibrotactile PT (compared to baseline) in patients with POSA to reduce OSA severity is moderate.

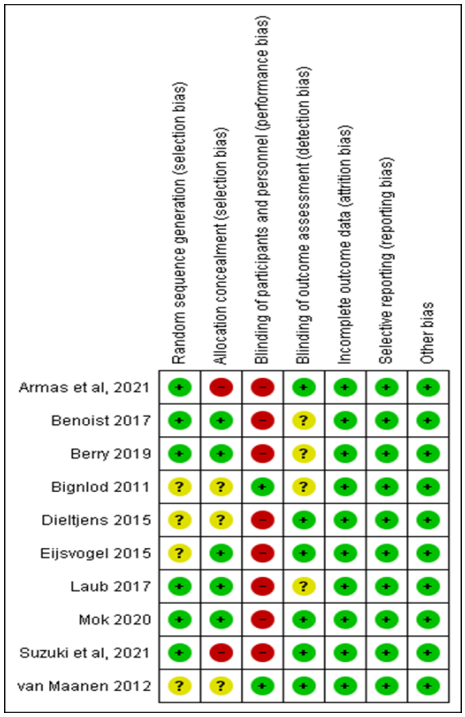


Figure 3.5: Risk of bias summary

Green circle with plus sign = low risk of bias; yellow circle with question mark = unclear risk of bias; red circle with minus sign = high risk of bias.

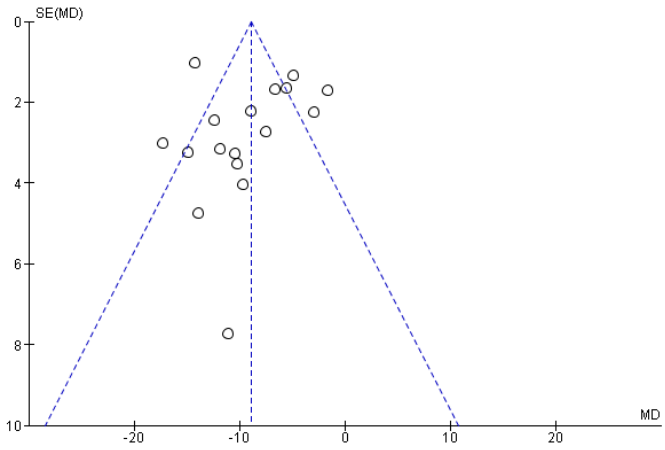


Figure 3.6: Funnel plot for detection of publication bias for the AHI

MD: mean difference; SE: standard error.

3.5 Discussion

The findings of this systematic review and meta-analysis suggest that vibrotactile PT is effective in reducing AHI and time spent in the supine position in patients with POSA. Pooled data showed a reduction in daytime sleepiness and a disease-specific quality of life score (FOSQ), but these secondary findings did not reach a clinically meaningful difference. Additionally, there were minimal improvements in sleep efficiency and arousal index. However, there were insufficient data to determine the effect of these vibrotactile PT devices on overall quality of life using generic questionnaires such as the SF-36.

Reductions observed in the primary outcomes AHI and %Tsupine corroborate with previous data. The recently published UK National Institute for Health and Care Excellence (NICE) guidelines (NG202) conducted a combined analysis of traditional and vibrotactile PT, stratified by disease severity, and concluded that both types of PT can be effective in reducing time spent in the supine position in mild and moderate OSA; PT was recommended as an alternative option if CPAP treatment was not suitable or not tolerable. In addition, the consensus opinion was that PT offered potential cost savings for the National Health Service (NHS) when compared with other available treatment options (NICE guidelines, 2021). In the recent European Respiratory Society guidelines for non-CPAP therapies in OSA patients, the evidence on the use of PT compared to CPAP (question no. 7) or MAD (question no. 8) was reviewed (Randerath *et al.*, 2021). Question no. 7 included five studies (n=221) and only one of them used vibrotactile PT and the remaining used traditional PT techniques. In question no. 8, one study was included (n=99) which used vibrotactile PT. The task force suggested that vibratory PT can be used for mild or moderate POSA as compared to MAD or CPAP. From an earlier meta-analysis that included seven studies using vibrotactile PT devices (4 clinical trials and 3 cohort studies), the reductions in the AHI and the time spent in the supine position were 54% and 84% respectively (Ravesloot *et al.*, 2017); in current review, the reductions were 43% and 70% respectively. The slightly lower efficacy observed in these findings may be attributed to the inclusion of more recent studies that tested the effect of vibrotactile PT on participants with higher baseline AHI.

The use of vibrotactile stimuli to encourage a position change from supine can be expected to cause arousal or awakening, thus leading to sleep fragmentation (discussed in chapter 5). However, in this systematic analysis, sleep efficiency and arousal index were not affected by vibrotactile PT.

Although there is convincing evidence that vibrotactile PT significantly reduces objective supine sleep, and therefore the severity of sleep apnoea in patients with POSA, there is less available subjective evidence to describe its effect on quality of life. This lack of available evidence is due in part to the variety of follow-up times and the different quality of life measures used across the studies. In this systematic analysis, the most frequently measured patient-reported outcome was the ESS (reported in nine studies). While the self-reported ESS was reduced with PT treatment, the reduction did not reach the clinically important difference of between 2, meaning that there may not be a meaningful change in daytime sleepiness (Crook *et al.*, 2019). Additionally, the FOSQ (a disease-specific quality of life questionnaire used to determine the impact of a sleep disorder on activities of everyday living) was used as a measure of quality of life in three studies, and again there was improvement observed with treatment but it did not reach the MCID of 2.2 (Weaver *et al.*, 2021). However, the follow-up in some studies was short and therefore may have missed important clinical changes in patient-centred outcomes.

The quality of life measure which is the most sensitive to OSA and its treatment is the vitality score questionnaire (SF-36) (Craig *et al.*, 2012; Wimms *et al.*, 2020). Only two of the studies included in the present review used the SF-36 in their assessment; however, there was an increase in vitality observed with PT treatment in both studies. Based on these findings it can be concluded that more trials focused on sensitive, patient-reported quality of life measures are needed; chapter 4 describes the POSA Trial (NCT04153240), which is an ongoing study that specifically addresses this demand.

The meta-analysis described in this chapter is the largest of its type to date (to my knowledge), including 18 studies were (10 clinical trials and 8 cohort studies) with over 700 patients. In a quickly progressing field, these results provide an update to the previous meta-analysis, which focused specifically on vibrotactile devices and included 7 studies (Ravesloot *et al.*, 2017). In comparison to the recent NICE and European Respiratory Society reviews, which compared both traditional and vibrotactile PT modalities to other available

treatment options, the current review used baseline and post-PT data, irrespective of the comparator; this enabled pooling of more data for analysis. (NICE guidelines, 2021; Randerath *et al.*, 2021).

3.5.1 Limitations

There are several limitations to consider in the interpretation of the results of this systematic analysis. The first are the heterogeneity among the definitions of POSA, the PT devices used, and the differences between the control groups of the included clinical trials. Two studies used inactive vibrotactile PT treatment, one study used no treatment, one study used MAD, one study used TBT, and two studies used APAP; the remaining two studies used multiple comparators or combined therapy as a control. Therefore, pooling of the results was only possible with vibrotactile PT at follow-up as compared with the baseline. However, with this approach I was able to include the large number of the studies. Moreover, in most of the studies, the follow-up times were short (3 months or less) and therefore the long-term effect of vibrotactile PT could not be investigated. This limitation highlights the need for large, blinded RCTs focused on investigating changes in patient-centred outcomes over longer follow-up periods. In addition, we were unable to pool data because adherence rates were defined differently between different studies.

3.6 Summary

Evidence suggests that vibrotactile PT reduces both the time spent in the supine position and AHI in patients with POSA, however the effect on self-reported daytime sleepiness is not clinically significant. More targeted outcomes for OSA, such as vitality, have limited data and follow-up periods were often short. The data from the clinical trial described in chapter 4 will help to fill these gaps in evidence.

CHAPTER 4: Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to Assess the Effect on Health and Well-Being (the POSA Trial)

4.1 Introduction

In the UK, it is estimated that at least eight million people have OSA (Benjafield *et al.*, 2019), and as mentioned in previous chapters, one of the risk factors associated with OSA is sleeping in the supine position (Cartwright, 1984). Further discussion on how sleeping in the supine position affects OSA can be found in chapter 1, sections 1.5.4 and 1.5.5.

4.1.1 Prevalence of POSA

As discussed in chapter one, section 1.5.2, more than 50% of patients diagnosed with OSA have POSA (Lee *et al.*, 2017; Mo *et al.*, 2011; Oulhaj *et al.*, 2017; Ravesloot *et al.*, 2016); however, the prevalence may vary according to disease severity. The prevalence of POSA in mild to moderate OSA may be as high as 80% (Mo *et al.*, 2011). In severe OSA, the prevalence of POSA is lower at about 40% (Mo *et al.*, 2011).

In chapter 1, section 1.6.1, highlights that the CPAP is considered the first line treatment for POSA. However, adherence is lower in mild compared with severe OSA (Jacobsen *et al.*, 2017; Wozniak *et al.*, 2014). PT has been proposed as an alternative therapy to CPAP for the treatment of POSA. It has been defined as any technique that prevents patients from sleeping in the supine position (Yingjuan *et al.*, 2019). As a result, vibrotactile PT devices were developed for the treatment of POSA. These devices are described in more detail in chapter 1, section 1.7.2. In summary, they contain position sensors for the determination of body position. Once supine position is detected, motors get activated to produce vibrotactile stimulus which encourage the sleeper to change position. All devices are capable of objectively monitoring usage and adherence data. The devices are lightweight and can be positioned at different bodily sites including the back of the neck (Levendowski *et al.*, 2014), chest (Bignold *et al.*, 2011; van Maanen *et al.*, 2013), or the forehead (Armas *et al.*, 2019) (see chapter 3, figure 3.1).

Number of clinical trials and cohort studies have been done to investigate the effect of vibrotactile PT in patients with POSA. In this thesis, chapter 3 presents a systematic review and meta-analysis on efficacy of the vibrotactile PT on patients with POSA. The main finding

of the review was that vibrotactile PT devices are effective in treating POSA (reducing both AHI and the percentage of time spent in the supine position). However, very few trials have investigated the effect of these devices on quality of life measures. In addition, none have investigated the effect on younger compared to older POSA patients.

4.1.2 Aims of this chapter

The primary aim of the POSA Trial, described in this chapter, is to evaluate the effect of 3-month of vibrotactile PT as compared with sham-vibrotactile PT on AHI at follow-up, adjusted for the baseline AHI, in patients with POSA. Secondary aims are to investigate the effect of vibrotactile PT as compared with sham-vibrotactile PT on quality of life and daytime functioning at follow-up, adjusted for baseline, in patients with POSA.

In this chapter the baseline data from the participants recruited at the Royal Brompton Hospital (RBH) are reported*. These data are compared with the findings of the systematic review presented in chapter 3.

*During the COVID-19 pandemic the POSA Trial was paused, which has resulted in the database remaining locked at the Oxford Respiratory Trials Unit (ORTU) until after all the patients have been recruited. Therefore, I am unable to present randomised data in this thesis. These data will be presented once all data have been collected. The POSA Trial has recently received an extension in National Institute for Health Research (NIHR) funding to Oct 2022.

4.2 Methods

4.2.1 Participants

Potential POSA Trial participants, who attended their local sleep clinic as part of their routine clinical care and who are CPAP naïve, were invited to participate in the trial. Patients were recruited via a Network of Respiratory Sleep centres, which included the RBH and six other participating centres (figure 4.1).

After obtaining informed consent, participants were screened, which included home polygraphy (type III sleep study; see section 4.2.6), to determine if they met the defining criteria of POSA (listed in table 4.1). The patients then took part in a ten-minute Night Shift run-in, to ensure that they could tolerate using the vibrotactile PT device.

Table 4.1: Inclusion and exclusion criteria for the POSA Trial

Inclusion criteria	Exclusion criteria
• Age ≥ 18 years • Ability and willingness to provide informed consent • AHI > 5 events/hr (American Academy of Sleep Medicine [AASM] 2012 scoring criteria) with events occurring at a frequency of 2:1 when supine compared with non-supine; total % supine sleep > 20% but < 90% of total sleep; central apnoeas < 20% of total apnoeas • Recording of ≥ 4 hr of analysable signals • Ability to fit and tolerate wearing the device around the neck during treatment demonstration and initiation	• Unstable cardiac disease • Cardiac arrhythmia with an artificial pacemaker • Supplemental oxygen • Secondary sleep pathology e.g., Periodic Limb Movement Syndrome, Narcolepsy, Circadian Disorder, Obesity Hypoventilation Syndrome • Physician concerns about sleepy driving or any other potentially dangerous symptoms • BMI ≥ 40 kg/m^2 • Inability to sleep in a non-supine position • Skin sensitivity or an open wound around neck • Tics or tremors of the head • Sleep with head in upright position • A female of child-bearing potential that is pregnant or intends to become pregnant • Previous usage of CPAP
AHI: apnoea hypopnoea index; BMI: body mass index.	

4.2.2 Study design

This is a prospective, three-month, multicentre, randomised, parallel, double-blind trial. The POSA Trial (ISRCTN51740863) includes seven nationwide participating UK sites (figure 4.1). The flowchart of the trial before and during the COVID-19 pandemic is shown in figure 4.2.

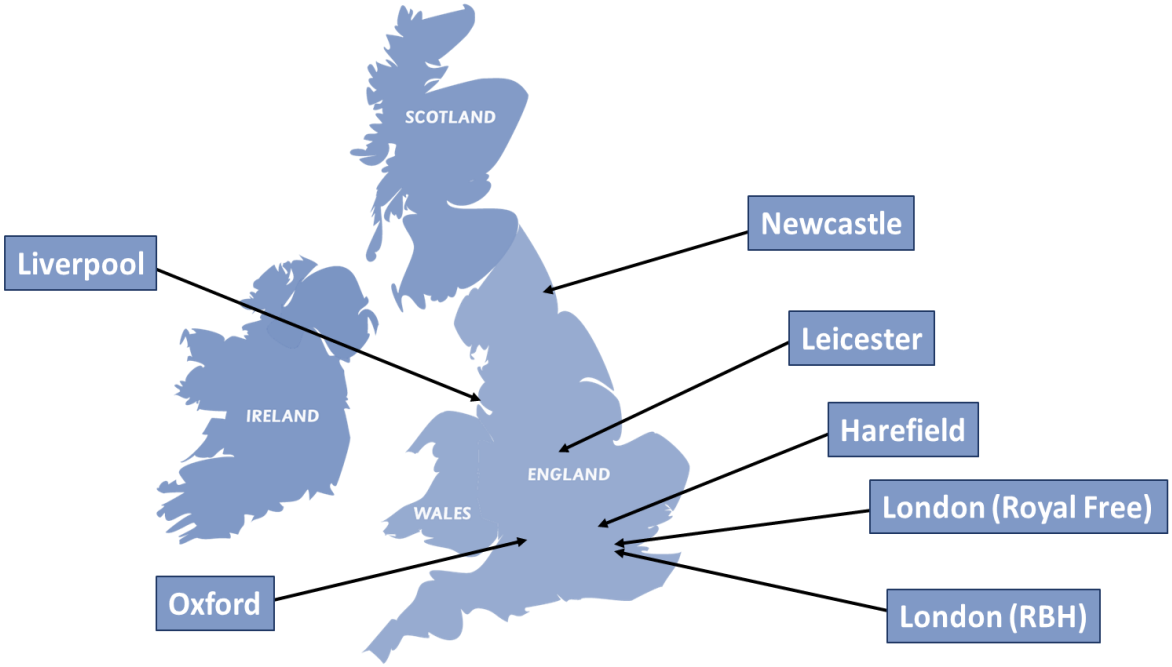


Figure 4.1: The UK Respiratory Sleep Research Network: sites participating in the POSA Trial

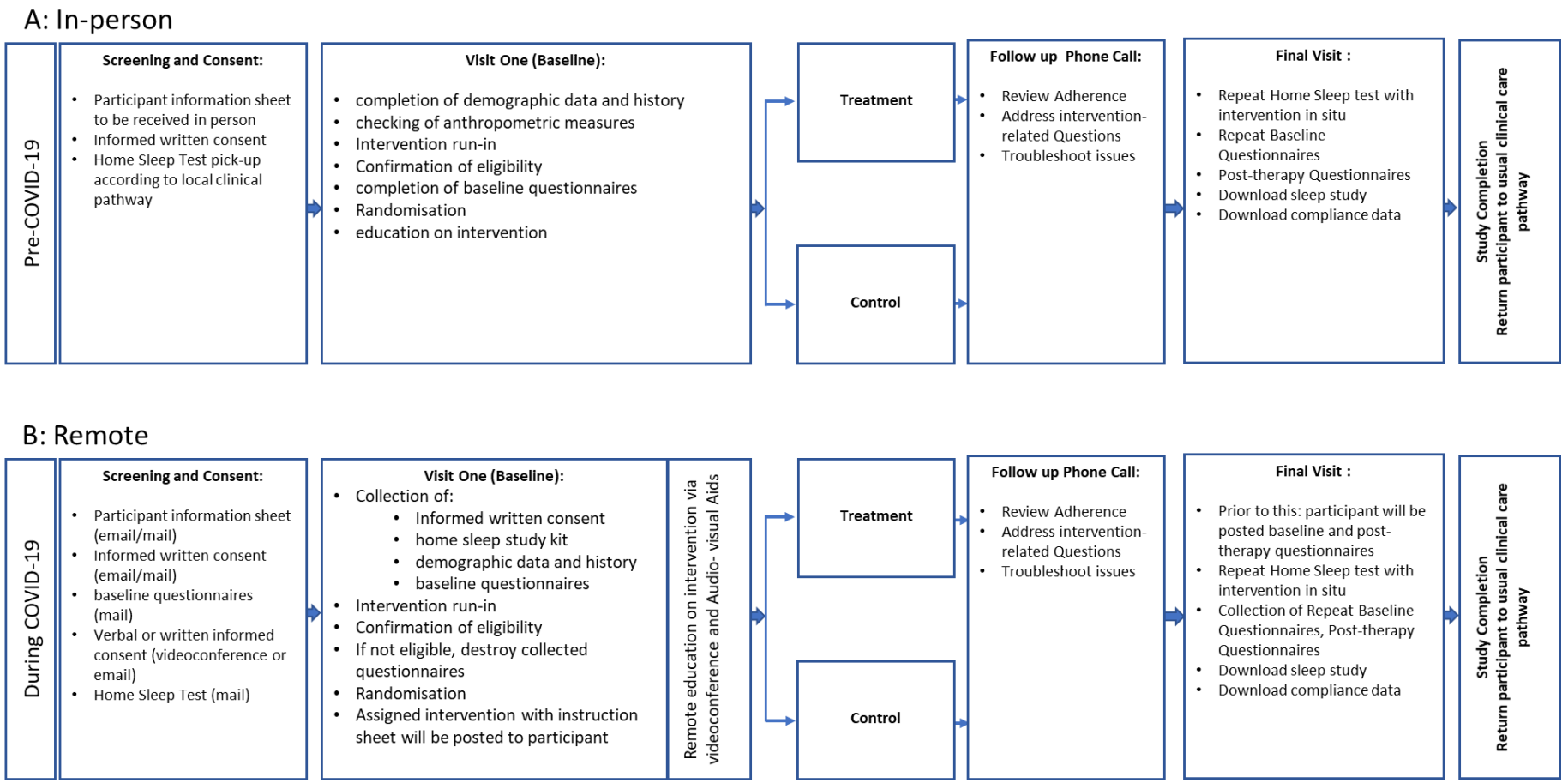


Figure 4.2: The POSA Trial flowchart

Panel A shows the in-person (pre-COVID-19) protocol. Panel B shows the remote (current) protocol.

4.2.3 Ethical approval

Ethical approval was granted by a central ethics committee (IRAS reference: 252494) (appendix 13) in July 2019. The ethical approval was granted pre COVID-19 and at this time the trial was carried out in person. An amendment to the original protocol was submitted during the COVID-19 pandemic to continue the trial in a semi-remote manner (appendix 14); the amendment was granted in September 2020. The amendments are embedded in the sections below and discussed in detail in the discussion (section 4.5).

4.2.4 Funding and sponsor

This study was funded by a Research for Patient Benefit grant (PB-PG-0817-20049) from the National Institute for Health Research (NIHR). My supervisor, Dr. Kelly, is the principal investigator. The POSA Trial was sponsored by the Royal Brompton and Harefield Trust (NHS Foundation Trust) (RBH & HT), now merged with the Guy's and St Thomas' NHS Foundation Trust. My role within the trial is described in section 4.3

4.2.5 Randomisation procedures

A web-based randomisation system (sortition system) was used to randomly allocate participants to either vibrotactile PT or sham-vibrotactile PT at a ratio of 1:1. To ensure the balance of both groups, minimisation based on AHI and age was used.

Each vibrotactile PT device was labelled with a trial asset number. In addition, the devices were pre-programed to either ‘monitoring mode’ (in which there is no vibrotactile stimulus or ‘trial mode’ (in which the device is set for one night of monitoring and the remaining nights with active vibrotactile stimulus). Both the researcher and the participants are blind to the mode of the device and can only identify the device number. This pre-programing is done in accordance with a random number that is generated by the ORTU and entered into the randomisation website. After completion of this randomisation process, the devices are packaged according to a list provided by the ORTU. They are then sent to each participating site.

4.2.6 Devices and measurements

Devices and measurements that are specific to the data presented in this study are detailed in this chapter. The generic methods and measurements are detailed in chapter 2.

- **Apnealink Air diagnostic polygraphy device and AirView diagnostic software**

The ApneaLink Air device (ResMed Ltd., Sydney, Australia) is a type III portable sleep study (polygraphy). Polygraphy is a widely used method in OSA diagnosis (53). The ApneaLink Air device (figure 4.3) is a portable device that includes a positional sensor to determine sleep position and an oximeter to measure oxygen saturation and pulse rate. It also includes a thoracic effort belt to measure respiratory effort, and nasal cannula to measure airflow and snoring (figure 4.3). This device was used at the baseline to determine participant eligibility and at the end of the trial to determine changes in sleep study parameters.

The AirView system (ResMed Ltd., Sydney, Australia) is web-based software used to program the ApneaLink Air device before delivery to a patient. Once the sleep study was completed and the patient returned their ApneaLink Air device, the AirView diagnostic system was used to automatically analyse the downloaded data using AASM 2012 scoring criteria (Berry *et al.*, 2012). In addition, the AirView diagnostic system was used to generate a sleep study report. No personal identifying information were used on this website, instead a trial identification number was assigned. Moreover, the AirView website is fully encrypted.

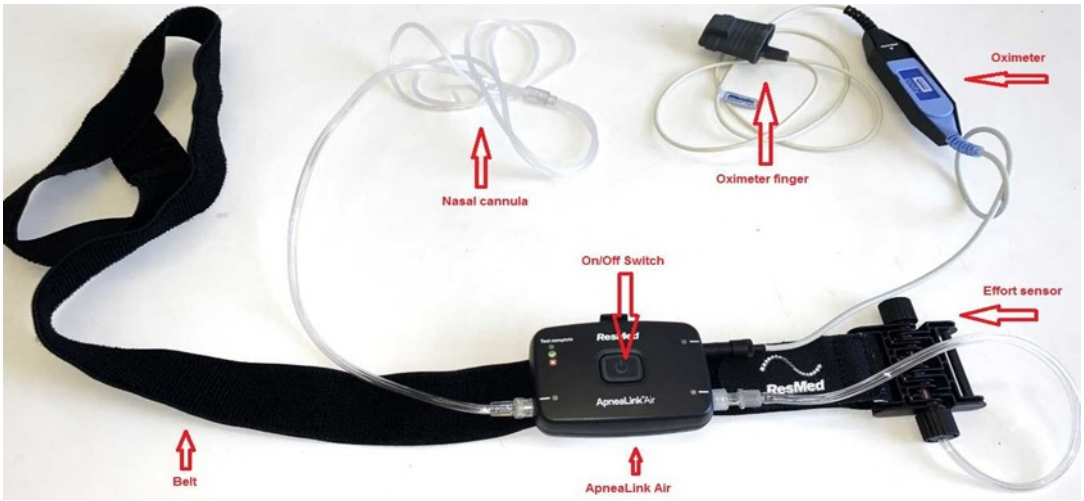


Figure 4.3: ApneaLink Air device (ResMed, Sydney, Australia)

This figure shows the ApneaLink Air recording channels, comprised of the nasal cannula (for airflow and snoring), pulse oximeter (to measure oxygen saturation and pulse rate), and thoracic effort sensor (to measure respiratory effort).

- **The vibrotactile PT device (Night Shift™)**

A neck-worn vibrotactile PT device (Night Shift™; Advanced Brain Monitoring, Carlsbad, CA, USA) was used in this study. A detailed description of this device can be found in chapter 2, section 2.6.

- **Questionnaires**

The questionnaires used in this trial are listed below and presented in appendix 15. The Epworth Sleepiness Scale (ESS) (Johns, 1991), Functional Outcomes of Sleep Questionnaire (FOSQ) (Weaver *et al.*, 1997), and 36-Item Short Form Health Survey (SF-36) (Jenkinson *et al.*, 1993) are discussed in detail in chapter 2, section 2.5.1. Other questionnaires used in this trial include the following:

  - **Pittsburgh Sleep Quality Index (PSQI)**

This questionnaire is widely used in sleep medicine to measure sleep disturbances and sleep quality over the span of one month (Buysse *et al.*, 1989). The questionnaire is composed of 19 items that pertain to seven domains, which are subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. In addition to these domains, the last five questions are about nocturnal sleep symptoms that can be noticed by the bed partner; these questions are not included in the final score. Scores for each item range from 0 to 3. Each domain has a total score, and the scores of these domains are added together to produce the overall possible score, which ranges from 0 to 21, where a higher score indicates better sleep quality. The PSQI questionnaire can be found in appendix 15.

  - **EuroQuol 5-Dimension Questionnaire (EQ-5D)**

This questionnaire measures generic health status (Rabin & de Charro, 2001). It consists of five domains which include mobility, self-care usual activities, pain and discomfort, anxiety, and depression. In each domain, the respondent is asked to rate their health problems from none to severe. The overall score is obtained by producing a five-digit number that represents the level of severity of each problem at each level of the five domains; the final total represents the health state. Many health states can be produced by this questionnaire and it can be used in many ways. One of the valuable outcomes of this questionnaire is that

the respondent's previous score can be converted to an index which can then be used to calculate costs associated with the underlying issues. The questionnaire also includes a Visual Analogue Scale (VAS) which ranges from 0 to 100, in which 0 indicates the worst imaginable health status and 100 indicates the best imaginable health status. This questionnaire can be found in appendix 15.

- **Townsend Disability Scale**

This questionnaire represents an index of activities that evaluate physical ability (McGee *et al.*, 1998). The questionnaire contains questions about the level of difficulty of performing nine physical activities; the respondent answers each question by indicating the level of difficulty of the activity, ranging from 0 to 2. Zero indicates no difficulty and no need for help to perform the activity, 1 indicates some difficulty, and 2 indicates inability to perform the activity and the need for help.

These questionnaires were given to participants and were completed during the first visit. Completion of the questionnaire was expected to take approximately one hour and it was repeated at the end of the study. An additional questionnaire and visual analogue scale about the vibrotactile PT device were completed at the end of the trial to assess the participant's experience with the Night Shift™ device.

4.2.7 Trial procedures

This section provides details of how the procedures and assessments were performed. A list of the procedures is provided in table 4.2.

- **Identification of POSA patients**

Figure 4.2 shows the POSA Trial flowchart. Patients with suspected OSA referred by their primary care physician to one of the participating sleep centres were considered for participation in this study.

The clinical team at the sleep centre discussed the POSA Trial with the patients. This occurred either during an in-person visit or remotely during the COVID-19 pandemic (via phone, videoconference, or email). The method of remote contact was dependent on the sleep centre's clinical guidelines. At this stage, written informed consent was obtained from participants who were physically present in the sleep centres; remote patients were sent

both the participant information sheet (appendix 16) and the informed consent document (appendix 17) either by mail or email. A designated researcher subsequently contacted the participant and obtained verbal informed consent. Signed and written informed consent documents were obtained by the researcher either by email, mail, or in-person, along with the baseline data package which included demographic data forms and the baseline questionnaire.

- **Screening for POSA**

A limited, type III sleep study was performed by the patients at their own homes using a portable sleep study kit (see section 4.2.6) to screen for POSA. Every participant received instructions on how to use the kit either at the sleep centre (see appendix 18) or remotely from the designated researcher. Participants either collected the device from sleep centres or received them by mail along with a prepaid envelope.

Participants returned the sleep kit to the sleep centre either in-person or by mail and prepaid envelope. The sleep study was downloaded from the device and uploaded to the AirView website for automated scoring. No identifying information was used on the AirView website, instead a trial number was assigned.

Once a sleep study report was downloaded, it was sent to the central trial site. If the participant fit the inclusion criteria they were invited for a first baseline visit either in-person or remotely. Those who were ineligible were given the opportunity to repeat the study; if they declined or remained ineligible they were informed of their exclusion from the study. Any data that were collected for the ineligible patients was destroyed.

- **POSA baseline visit**

Participants who visited centres in-person were given detailed instructions on how to charge, use, wear, and care for the neck-worn vibrotactile PT device. They were also given the chance to feel the vibrotactile stimulus produced by the device. In addition, they were shown how to adjust the rubber straps for appropriate fit around the neck. If this initial session was successful and the participant showed willingness to proceed, they were asked to complete demographic and self-reported medical history forms. They were subsequently randomised into either the vibrotactile PT or sham-vibrotactile PT device group.

Randomisation was performed by an online computer generation system (see section 4.2.5). Minimisation was performed based on age and OSA severity level.

Participants were instructed to use the vibrotactile PT device daily for the next three months. They were provided with written instructions on how to use the vibrotactile PT device and were given the researcher's contact information in case they needed to ask questions. To ensure appropriate usage of the device, a follow-up call was performed for each participant after four nights from the baseline visit.

Remote participants returned the portable sleep study kit and the completed baseline data package sent to them at the screening stage. This package included the demographic data forms and baseline questionnaires. In addition, they were asked to weigh themselves and measure their neck circumference. Once researchers confirmed their eligibility, participants were randomised to either the vibrotactile PT or sham-vibrotactile PT device group, as described in section 4.2.5. Subsequently, they were mailed the vibrotactile PT device with detailed written instructions. Moreover, they were asked to contact the researcher to confirm the receipt of the device so they could take part in an educational session on how to charge, use, wear, and care for the neck-worn vibrotactile PT device.

- **Usage monitoring and follow-up**

Once a participant had been randomised, the central sleep therapist received the participant's contact information via their NHS.net email. Participants who were contacted remotely for their baseline visits were asked to contact the central sleep therapist prior to their first night using the device. In addition, all participants were contacted following four nights of usage; this contact addressed the participant's experience with the device and troubleshooting for related issues.

- **Three-month follow-up visit**

The three-month visit represented the final visit and was conducted either in-person or in a remote manner in accordance with the local sleep centre guidelines. Before this visit, each participant was mailed the portable sleep study kit, including the vibrotactile PT device, for repetition of the final sleep study. In addition, participants were sent all the questionnaires that were used at the beginning of the trial with the addition of an in-house bespoke

questionnaire that was developed to assess the participant's experience with the PT device, and a prepaid envelop. In remote cases, participants were asked to return the sleep kit, questionnaires, and the vibrotactile PT device by mail. For in-person cases, participants were asked to either return the items by mail using the prepaid envelope or to return them to a safe location. At this visit, the final sleep study and vibrotactile PT device data were downloaded, and questionnaires were checked for completeness.

At this stage, the participation in the trial was complete. Participants were given the choice to either continue to use the vibrotactile PT device, or not with the supervision of the clinical team.

Table 4.2: Summary of trial-related assessments

Stage of assessment	Type of assessment
Screening assessment	• In-home baseline sleep study • Baseline demographics including BMI and neck circumference • Physician concern about sleepy driving or any other potentially dangerous symptom • Informed consent
Baseline assessment	• Medical history • Questionnaires • Tolerance of the vibrotactile PT device
Assessment at the four-day follow-up (monitoring) contact	• Experience and tolerance of the vibrotactile PT device
Final assessment	• Questionnaires • Vibrotactile PT device questionnaire • In-home final sleep study • Vibrotactile PT device data downloaded
PT: Positional Therapy; BMI: body mass index.	

4.2.8 Outcome measures

This section details the primary and secondary outcome measures for the POSA Trial. It also demonstrates how these outcomes measures have been modified for the data presented in this thesis.

- **Primary outcome**

The primary outcome for this trial was improvement in the AHI at follow-up after 3 months of using the vibrotactile PT device, adjusted for the baseline AHI and compared with the sham-vibrotactile PT.

- **Secondary outcomes**

Secondary outcomes included outcomes derived from the sleep study, the questionnaires, and the vibrotactile PT device (table 4.3).

Table 4.3: Secondary outcomes derived from the sleep study, questionnaires, and vibrotactile PT device data

Derived from	Secondary outcomes
Sleep study	• Improvement at follow-up after 3 months of vibrotactile PT device use, adjusted for the baseline in: o Oxygen desaturation index o Supine AHI o Average overnight oxygen saturation (SpO2) o % time with SpO2 ≤ 90%
Questionnaires	• Improvement at follow-up after 3 months of vibrotactile PT use, adjusted for the baseline in: o Short Form-36 with focus on vitality score o Functional Outcomes of Sleep Questionnaire o Epworth Sleepiness Scale o The Pittsburgh Sleep Quality Index o Hospital Anxiety and Depression Scale o Health Utilisation Questionnaire o Visual Analogue Scale of comfort and tolerance of the device o EuroQol EQ-5D o Independent Functioning (Townsend Disability Scale) and Rate of Accidents
Vibrotactile PT device (Night Shift)	o % sleep time in supine o Number of supine attempts o Number of vibrotactile events o % sleep time snoring > 50 dB
PT: positional therapy; AHI: apnoea-hypopnoea index; SpO2: oxygen saturation (measured by pulse oximetry).	

Due to the extended time needed to complete this trial, the COVID-19 pandemic (suspension of the trial), and the subsequent inability to unlock the trial database prematurely, the baseline data for participants recruited at RBH are reported in this thesis. Specifically:

- **Sleep study:**
  - AHI
  - %Tsupine
- **Questionnaires:**
  - SF-36 Vitality score
  - FOSQ global score
  - ESS scores

4.2.9 Statistical plan

- **Sample size calculation**

Based on a mean difference of five events/hrs (Ravesloot *et al.*, 2017) and assuming a standard deviation of 9.05 events/hr, 155 patients are needed to achieve a statistical power of 0.90 at 5% significance level. This sample will allow detection of superiority of the vibrotactile PT compared to sham-vibrotactile PT after three months of therapy. This sample size assumed a dropout rate of 10%.

- **Statistical Analysis**

Data were assessed for meeting of parametric assumptions; this included testing for normality of distribution, homogeneity of variances, linearity, and independence.

Descriptive statistics for the baseline characteristics were used to present outcome variables. Summary data were presented based on the type of data (categorical data presented as a proportion, and numerical data as mean ± standard deviation [SD] or median with interquartile range [IQR]).

The primary outcome for this study was the AHI, which was analysed using regression analysis with adjustment for the baseline AHI and age. The influence of age was tested as a continuous variable. All statistical tests were two-sided, and significance was determined if $p < 0.05$. SPSS software was used for statistical analysis.

4.2.10 Quality assurance and data management

- **Data collection tools**

Case Report Forms (CRFs) and self-completed questionnaires were used for the collection of data. The CRFs were developed and inspected by the trial's central site team in conjunction with the ORTU. Data were entered clearly and legibly using a ball-point pen. If errors were noted, the investigator made a single line that crossed through the erroneous entry, leaving the error clearly readable. The investigator then initialled and dated the correction.

In the case of self-completed questionnaires, participants were instructed to write their responses legibly with a ball-point pen according to the corresponding instructions in each questionnaire. The investigator then confirmed the completeness of the responses.

- **Data handling**

Collected data, including the CRFs, self-completed questionnaires, and sleep study reports, were scanned and sent through secure a NHS.net email to the ORTU. Each participating site was responsible for checking the correctness and completeness of the data. In addition, the ORTU was responsible for confirming the correctness and completeness of the data. Moreover, the ORTU was responsible for entering the data into a secure database; this database is hosted on a server provided by University of Oxford and serviced by the university medical IT centre. Only designated, trained individuals from the ORTU had access to the trial database, and this access was controlled by individualised user accounts, which were password-protected. All activities on the database were logged and can be retraced if necessary.

- **Data storage and confidentiality**

Paper-based data, which included the CRFs, self-completed questionnaires, and sleep study reports, as well as the Trial Master File (TMF), were kept at each participating site. Data that included identifying information, such as the informed consents documents, were kept in a locked cabinet in an access-controlled room.

Data from the sleep studies were accessed from the AirView server using a trial identification number. No personal identifying information was available on this server. In addition, the website was secure and fully encrypted and was compliant with UK national

data privacy laws and EU 95/46/EC. Access to this server was based on individualised password-protected accounts, which were granted only to designated and trained investigators at each participating site. All activities on the database were logged and can be retraced if necessary.

The data were transformed to electronic version by the ORTU. These electronic data were kept in a secure database and managed by the ORTU. The database was hosted on a server provided by the University of Oxford and serviced by the university medical IT centre. Only designated, trained individuals from the ORTU had access to the trial database, and this access was controlled by individualised password-protected users accounts.

- **Data archiving**

Each participating site retained the corresponding study documents (CRFs, informed consents, and TMF) for minimum of five years. The sponsor site was responsible for managing the TMF. All paper documents that were sent to the ORTU and the database were sent back to the sponsor for appropriate archiving. The electronic data were secured on the RBH internal computer network for a minimum of five years.

- **Training of researchers**

To provide quality assurance across the participating seven sites, training was performed by the central trial team. These training sessions were completed during site initiation visits (SIVs). Standardised operating procedures (SOPs) for all trial-related procedures were developed by the central trial team in conjunction with the ORTU. During each SIV, the designated researchers were trained on the study protocol via power point presentation, which was developed by the central team in conjunction with the ORTU. Sessions were followed by a question-and-answer session to ensure appropriate understanding of the trial protocol. In addition, researchers from each site were trained on each trial-related procedure according to the pre-developed SOPs. The central trial team provided on-call support for all sites. In-person support visits were completed at the beginning of recruitment at each participating site, in which a researcher from the central site supervised the first recruitment and helped with any issues. Further in-person support visits were subsequently made as needed while conforming to local COVID-19 pandemic guidelines.

4.2.11 My Role in the POSA Trial

My role included the development and the delivery of the trial. In both phases, I had the opportunity to gain clinical, research, and management skills.

In the development phase of the trial, my role involved working on the POSA trial protocol, CRFs, and standardised operating procedures, and the preparation for ethical application and subsequent ethical amendments. I was responsible for the testing and troubleshooting of diagnostic equipment and software (Apnealink-Air devices, Airview Software). In addition to the diagnostic equipment, I was also responsible for the NightShift device and software management. An important aspects of my involment in the trial were the site initation visits and the training of investigators and researchers, both in-person and remotely.

During the delivery of the trial I was involved in the recruitment of participants in the RBH and provided in-person and remote assistance to other sites. I was also responsible for providing centralised clinical follow-up and support for trial participants across all other sites. Moreover, I supported the centralised management of trial diagnostics, treatment equipment, and data management. I was also part of the Trial Management Group.

4.3 Results

4.3.1 Update on the ongoing recruitment of the POSA Trial

The target sample size in the POSA Trial is 155 participants. Before the trial was suspended due to the start of the COVID-19 pandemic (March 2020), the overall number of participants recruited across all sites was 13. Suspension continued until September 2020, and we were ready to recruit again in November 2020. At the time of writing of this chapter (November 2021), the number of participants recruited was 64, of which 7 were recruited from the RBH. The updated recruitment chart is shown in figure 4.4.

An extension to the trial to October 2022 has recently been granted. The projected completion date of the target sample size recruitment is by July 2022. Data analysis and dissemination of the results is expected to be completed by October 2022.

The following sections (4.4.2 and 4.4.3) present the demographic data for the POSA Trial participants recruited from the RBH (henceforth referred to as ‘RBH POSA Trial participants’ or ‘RBH participants’). In addition, the baseline data of these participants are discussed and

compared with the data obtained from the systematic review (chapter 3). Furthermore, the anticipated follow-up results for RBH POSA Trial participants are calculated based on the data obtained from chapter 3.

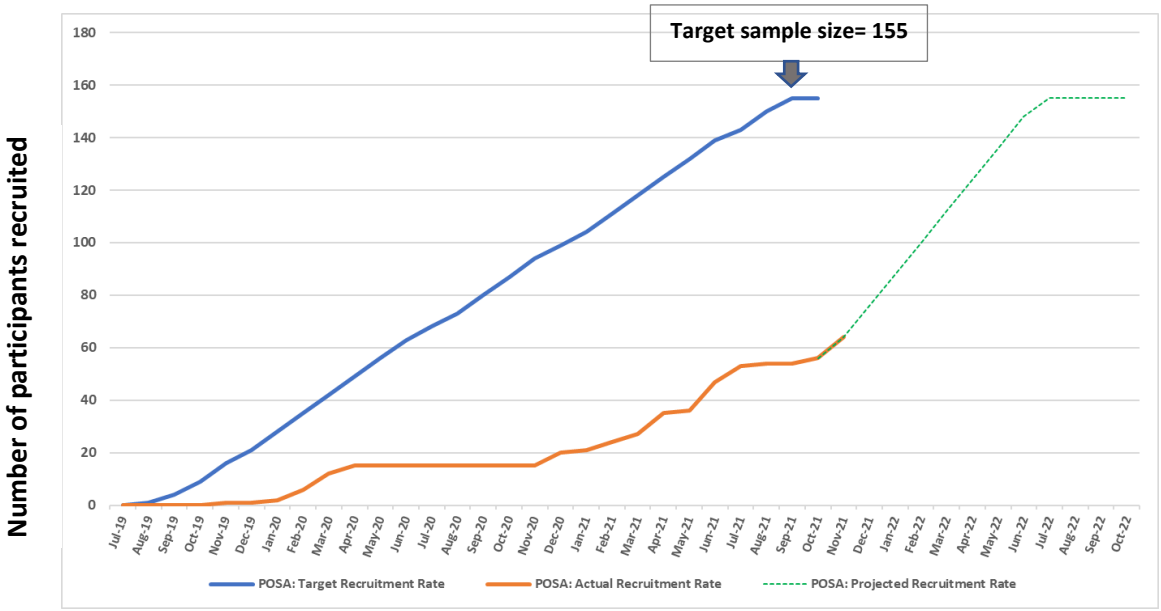


Figure 4.4: Targeted compared to actual and projected recruitment rate of the POSA Trial

4.3.2 Demographics and baseline data from RBH POSA Trial participants

The demographic data for the RBH participants are shown in table 4.4. Most participants were male. The BMI is also reported and is within the overweight category (25–30 kg/m^2), which is a common feature of POSA participants.

Table 4.4: Demographic data of the RBH POSA Trial participants

Participant number (n = 7)	Age (years)	Gender	BMI (kg/m^2)
A107	64	M	24.5
A108	42	M	29.0
A109	48	M	35.4
A110	39	M	30.5
A111	67	M	18.3
A112	63	F	22.0
A113	46	M	28.5
Mean (SD)	**52.7 ± 11.6**	**-**	**26.9 ± 5.7**

SD: standard deviation; M: Male; F: female; BMI: Body mass index; n: sample size.

Table 4.5 presents the baseline characteristics for participants recruited from the RBH. The mean (SD) baseline AHI was 11.6 ± 5.9 events/hr, indicating that the participants were in the mild OSA category. The mean baseline supine and non-supine AHI were 21.8 ± 13.4 and 4.3 ± 5.1, respectively**.** In addition, these participants spent a mean of 52.1 ± 26.1% time in the supine position.

The participant-centred outcomes obtained from the RBH participants at baseline are also shown in table 4.5, which includes baseline SF-36 Vitality scores, FOSQ global scores, and ESS scores. The mean baseline SF-36 Vitality score was 45 ± 13.8, the mean FOSQ global score was 15.2 ± 4.2, and the mean ESS score was 8.4 ± 4.8.

Table 4.5: Baseline results of the RBH POSA Trial participants

Participant number (n=7)	Baseline AHI (events/hr)	Baseline Supine AHI (events/hr)	Baseline non-supine AHI (events/hr)	Baseline %Tsupine (%)	Baseline SF-36 Vitality score	Baseline FOSQ global score	Baseline ESS score
A107	23.0	40.3	14.1	34.9	55	6.2	15
A108	7.4	9.5	0.7	76.1	35	17.6	5
A109	11.0	MISSING	MISSING	MISSING	30	16.5	15
A110	6.8	21.0	2.6	23.1	35	18.2	4
A111	12.8	17.6	0.8	70.6	45	14.5	8
A112	6.2	7.2	2.0	79.8	45	15.3	4
A113	13.7	35.0	5.4	28.1	70	18.0	8
Mean (SD)	**11.6 ± 5.9**	**21.8 ± 13.4**	**4.3 ± 5.1**	**52.1 ± 26.1**	**45 ± 13.8**	**15.2 ± 4.2**	**8.4 ± 4.8**

AHI: apnoea hypopnoea Index; SD; standard deviation; hr: hour; %Tsupine: percentage of time spent in the supine position; SF-36: 36-Item Short Form Survey; FOSQ: Functional Outcomes of Sleep Questionnaire; ESS: Epworth Sleepiness Scale.

4.3.3 Comparison of baseline data between RBH participants and the systematic review

AHI values from the RBH POSA Trial participants and data from the systematic review (chapter 3) are compared in table 4.6. In the systematic review, the mean (SD) baseline AHI was 21.2 ± 6.1 events/hr, and in the mild OSA subgroup the mean AHI was 13.1 ± 1.5 events/hr; the mild OSA subgroup AHI values are more similar to the RBH participants. Comparison of the percentage of time spent in supine position between the systematic review and the RBH POSA Trial participants is shown in table 4.6. In the systematic review, the mean (SD) baseline percentage of time spent in supine position (%Tsupine) was 47 ± 9.3%, and in the mild OSA subgroup the mean %Tsupine was 40 ± 3.5%. Therefore, the time spent in supine position for the whole group was more similar when compared to the RBH participants, despite the AHI being lower.

Table 4.6: Comparison of the AHI and %Tsupine at baseline between the systematic review and the RBH POSA Trial participants

	Systematic Review (overall; n = 700) Mean (SD)	Systematic Review (mild OSA subgroup; n = 104) Mean (SD)	RBH POSA Trial participants (n = 7) Mean (SD)
Baseline AHI (events/hr)	21.2 ± 6.1	13.1 ± 1.5	11.6 ± 5.9
Follow-up AHI (events/hr)	11.6 ± 4.4	8.8 ± 1.2	-
Baseline %Tsupine (%)	47.0 ± 9.3	40.0 ± 3.5	52.1 ± 26.1
Follow-up %Tsupine (%)	14.8 ± 10.3	14.9 ± 1.8	-
n: sample size; AHI: apnoea hypopnoea Index; hrs: hours.			

- **Comparison of participant-centred outcomes**

Comparison of the participant-centred outcomes obtained from participants recruited at the RBH and the systematic review are shown in table 4.7. In the systematic review, the mean baseline SF-36 Vitality Score was 47 ± 2.9. In the RBH POSA trial participants, the mean baseline SF-36 Vitality Score was 45 ± 13.8.

In addition, the mean baseline FOSQ global score in the systematic review was 16.6 ± 1.3. In the RBH POSA trial participants, the mean baseline FOSQ global score was 15.2 ± 4.2.

Moreover, the mean baseline ESS score in the systematic review was 9 ± 2.1. In the RBH POSA trial participants, the mean baseline 8.4 ± 4.8.

Table 4.7: Comparison of patient-centred outcomes at baseline between the systematic review and the RBH POSA Trial participants

	Systematic Review Mean (SD)	POSA Trial Participants (n = 7) Mean (SD)
Baseline SF-36 Vitality Score (points)	47.0 ± 2.9	45 ± 13.8
Follow-up SF-36 Vitality Score (points)	53.2 ± 4.7	-
Baseline FOSQ Global Score (points)	16.6 ± 1.3	15.2 ± 4.2
Follow-up FOSQ Global Score (points)	17.0 ± 1.4	-
Baseline ESS Score (points)	9.0 ± 2.1	8.4 ± 4.8

Follow-up ESS Score (points)	8.0 ± 1.7	-
SF-36: 36-Item Short Form Survey; FOSQ: Functional Outcomes of Sleep Questionnaire; ESS: Epworth Sleepiness Scale; n: sample size; SR: systematic review; SD; standard deviation.		

4.4 Discussion

The aim of this chapter was to describe the POSA Trial and to present the baseline data obtained from the RBH participants. The main findings were that the mean baseline AHI for RBH participants was in the mild OSA category, compared with the mean baseline AHI data obtained from the systematic review (chapter 3, section 3.3.3). However, the RBH participants spent more time in the supine position as compared with the patients with mild OSA in the systematic review.

4.4.1 Comparison of participant-centred outcomes

Participant-centred outcomes (SF-36 Vitality score, FOSQ global score, and ESS scores) obtained from the RBH participants were compared with data obtained from the systematic review in chapter 3. These comparisons showed that it is likely that the SF-36 Vitality score would be improved following vibrotactile PT. However, the FOSQ global score and ESS may improve less based on extrapolation of the baseline data, and the improvements will not by clinically significant (22)(23). These results are in line with previously published trials in which patient-centred outcomes did not improved following treatment (23, 24). It remains to be seen if the SF-36, ESS, and FOSQ are clinically improved following 12 weeks of vibrotactile PT in the POSA Trial.

4.4.2 Relationship of baseline data to NICE Guidelines

Vibrotactile PT devices have been introduced as an alternative to traditional PT techniques such as the tennis ball technique, which was associated with significant discomfort (Bignold *et al.*, 2009; Loord & Hultcrantz, 2007; Oksenberg *et al.*, 2006). Vibrotactile PT devices have the advantages of being small, easy to use, and work by producing gentle vibrotactile stimulus (see chapter 1, section 1.7.2). Recent National Institute for Healthcare Excellence (NICE) guidelines (NG202) suggest that vibrotactile PT devices can be effective in reducing AHI and time spent in supine position (NICE guidelines, 2021). The guidelines also recommend the use of these devices as an alternative treatment modality if other

treatments like CPAP are not successful or not tolerable, especially in patients with mild and moderate OSA (NICE guidelines, 2021). The systematic review findings presented in chapter 3 showed that vibrotactile PT devices were effective in reducing AHI and time spent in supine position. However, there was a paucity of data on sensitive patient-centred outcomes such as SF-36 Vitality scores. *It is anticipated that the findings of the POSA Trial will address this evidence gap and may provide the evidence needed for future guidelines to support inclusion of PT for patients with OSA.*

4.4.3 Learning points from modifications of the POSA Trial protocol

The POSA Trial protocol was modified during the COVID-19 pandemic to occur in a semi-remote manner. The modifications made to the trial protocol are detailed below and some of the methodological and ethical issues that were encountered are highlighted. I have reported the key challenges and their solutions, which could inform and support other research studies conducted during the COVID-19 pandemic.

The impact of the COVID-19 pandemic on healthcare provision highlighted the importance of the POSA Trial, as it offers a potential alternative treatment for OSA in a time when airborne aerosol generation is considered a specific risk factor for COVID-19 (1). Recent NICE guidelines (NG202) suggest the vibrotactile PT devices can be effective in reducing AHI and time spent in supine position; these devices are also presented as a potential alternative therapy if treatment modalities like CPAP are not successful or not tolerable (NICE guidelines, 2021).

The POSA Trial was originally designed to fit within existing clinical care pathways for patients undergoing investigation and treatment of OSA, using an established Respiratory Sleep Research Network across different regions of the UK (2, 3). However, the onset of the pandemic led to changes in elective care pathways (4); healthcare providers modified these pathways to minimise the risk of COVID-19 transmission for patients and staff, frequently utilising remote care and digital platforms (5, 6). Research trials also had to develop modifications in line with these clinical changes.

- **Remote screening to enhance patient recruitment**

Screening for recruitment into the POSA Trial was carried out pre-pandemic using overnight home polygraphy. Home sleep testing equipment was collected and returned by the patient to the local sleep centre. COVID-19 modifications to the trial protocol have enabled us to deliver the overnight polygraphy equipment from the local sleep centre to the patient's home via postal services. Remote pick-up procedures, such as locker systems, have also been utilised. Patient instructions have been provided in both written and digital forms (e.g., YouTube videos). Cleaning of the equipment has followed local infection control guidelines.

- **Remote data collection**

Remote patient consultations were introduced to replace face-to-face clinic visits during the COVID-19 pandemic, in line with changes in local clinical care pathways. This change required the consent from patients to be sought through contact by either phone, email, or teleconference, and the patients' preferences for contact method and timing were also considered.

During remote consultations, patients were asked to provide their own measurements for anthropometric data (weight, neck circumference, etc.). These data would normally have been collected by delegated researchers following standard operating procedures; however, we have found that clear, simple instructions have enabled our patients to successfully provide these data. Concerns about the impact of self-reporting and the accuracy of different measurements are offset by benefit of being able to continue the trial and the fact that anthropometric data are not a primary outcome.

Prior to the COVID-19 pandemic, the self-administered, subjective symptom questionnaires were completed during clinic visits at baseline and end-of-study. COVID-19 modifications to the trial protocol resulted in the patients being asked to complete the questionnaires remotely; this enabled the patients to complete the data collection at a time and place that were most comfortable for them. Additionally, the potential bias introduced by the presence of a researcher was removed. However, remote completion of questionnaires has increased the risk of returning incomplete questionnaire items, possibly due to misunderstanding of questions. This issue was addressed by introducing an inspection of the

questionnaires as soon as they were returned, and a rapid follow-up phone call or videoconference with the participant for clarification.

The implementation of remote data collection necessitated the repurposing of the trial funding (i.e., patient transport funds were reallocated to fund additional postage costs). To save on postage fees and to minimise the infection risks associated with the sending and receipt of multiple parcels, participants were provided with a 'data collection pack' which included: polygraphy equipment, subjective symptom questionnaires, instruction sheets, and prepaid envelopes.

The increased demand on remote data collection formats led to concerns of potential breaches of confidentiality. Therefore, ensuring the transfer of anonymised data only, using properly encrypted and approved digital platforms (e.g., Skype, Attend Anywhere), and maintaining up-to-date internet security were critical.

- **Remote therapy set-up**

In the modified protocol, the non-invasive PT device was sent to the patient with written instructions and information on how to contact the researcher prior to use. To avoid incorrect use of the device, remote education was provided with visual instruction of its application either by teleconference or by videolink. Further education on how to use the device was necessary to ensure ongoing safe and appropriate use of the intervention.

- **Remote communication and patient education using multimedia platforms**

Communication between healthcare professionals and patients is paramount in developing professional relationships. The use of digital platforms offers patients more flexibility and can be a more cost effective and time efficient for both researchers and patients (e.g., travel time is reduced). However, implementation of digital communications can be challenging for participants with poor internet access and those who are less familiar with technology. Ensuring technological support and providing alternatives (e.g., phone calls or mail) have been major factors in making the switch to delivering the POSA Trial remotely (7).

The POSA Trial is an NIHR Research for Patient Benefit-funded trial, and patient education is an important deliverable of the project. Moreover, the UK sleep network has found that patient education and engagement are key factors in the successful completion of a clinical

trial (2,3). In modifying the POSA Trial protocol, we focused on communication and patient understanding to address the need for patients to take on more trial-related responsibilities such as remote data collection. The POSA Trial protocol uses remote education and instructions available in multiple forms, including visual demonstration (i.e., via video-teleconferences), carefully written instruction sheets with pictorial representations, and step-by-step audio-visual aids such as online videos. *These have been the single most important part of our COVID-19 pandemic modifications.*

4.4.4 Limitations of the data presented in this chapter

The data presented in this chapter were associated with number of limitations. The sample size for the baseline data included in this chapter was limited; however, I was able to show that these baseline data were comparable to data obtained from the systematic review (chapter 3). It was not possible to include any follow-up data to illustrate the changes resulting from the use of vibrotactile PT as compared with the baseline. At the time of writing this chapter, the POSA Trial aims to complete recruitment by July 2022.

4.4.5 Implications and future directions

As shown in the systematic review presented in chapter 3, vibrotactile PT devices were effective in reducing the AHI and time spent in the supine position in patients with POSA. Recent NICE guidelines (NG202) suggest that vibrotactile PT can be an alternative treatment for patients who are unable to tolerate established treatments such as CPAP (NICE guidelines, 2021). However, the guidelines also highlighted lack of evidence on patient-centred outcomes.

The National Health Service (NHS) currently does not offer vibrotactile PT treatment for OSA patients; well-designed clinical trials, such as the POSA Trial, will need to be completed to fill these evidence gaps. The POSA Trial will provide evidence for decision makers to review the use of this simple and easy treatment in the NHS.

The use of vibrotactile stimuli to encourage a position change from supine might not be suitable for all POSA patients; some patients might be too sensitive to the vibrotactile stimuli, resulting in arousal or awakening. Therefore, further physiological studies are needed to determine phenotypic arousal responses to the vibrotactile stimuli produced by

the PT device. These studies could help to personalise vibrotactile PT to appropriate POSA patients.

CHAPTER 5: Arousability and Sleep Recovery Responses in Healthy Individuals Using Vibrotactile Positional Therapy

5.1 Introduction

Vibrotactile PT is delivered via a small, non-invasive, watch-like device, see chapter 1, section 1.7.3. It works by producing a gentle vibrotactile stimulus to urge patients to avoid sleeping in the supine position and the devices can be worn in different positions on the body, e.g. on the back of the neck or on the chest, see chapter 1, section 1.7.2. The evidence for the use of vibrotactile PT is systematically reviewed in chapter 3; the results of this analysis show that vibrotactile PT is an effective treatment for patients with POSA, although there was minimal evidence for patient-centred outcomes. The results of the POSA trial (described in chapter 4) are awaited; the data will inform the evidence base for vibrotactile PT by focusing on the patient-centred outcomes.

When considering the clinical application of vibrotactile PT, it is important to remember that the vibrotactile stimulus urging patients to avoid sleeping in the supine position may also cause arousal from sleep. Arousal is a brief transition from a state of sleep to wakefulness (8). The cortical arousal is defined by the AASM as "*an abrupt shift in EEG to a higher frequency, including alpha, theta, or beta, for at least 3 seconds with at least 10 seconds of stable sleep preceding the change"*(Berry *et al.*, 2012). The sensitivity of the arousal response to the vibrotactile stimuli may vary within individuals across the night, e.g. in different sleep stages and between individuals. It has been previously shown that spontaneous cortical arousals vary greatly between individuals (Azarbarzin *et al.*, 2015). Specifically, when external stimuli, such as sound and flow limitations, are used to induce arousal, the magnitude of the arousal response varies (Amatoury *et al.*, 2016; Jordan *et al.*, 2003; Jordan *et al.*, 2004).

Arousability has also been reported as different between males and females (Jordan *et al.*, 2003). Studies in humans (and animals) have shown that females seem to be more resilient to arousability compared to males (Bixler *et al.*, 2009; Jordan *et al.*, 2003; Jordan *et al.*, 2004; Koehl *et al.*, 2006; Vgontzas *et al.*, 2004). These differences are also evident when comparing the objective and subjective sleep quality between males and females. Females tend to report poorer subjective sleep quality (Berg *et al.*, 2009) despite having better

objective sleep quality than males (Bixler *et al.*, 2009; Redline *et al.*, 2004; Walsleben *et al.*, 2004). Understanding these differences in arousability and the impact on daytime symptoms is important for the personalisation of therapeutic options in sleep medicine.

A detailed discussion on gender differences in sleep quality is included in chapter 1, section 1.9.2. It is speculated that some people may be more sensitive to the vibrotactile stimuli and thus respond faster to the stimulus, whereas others might take longer to respond. Whether those who are more sensitive also suffer from sleep fragmentation and poor daytime subjective sleep quality due to frequent vibrotactile stimuli is not known. Such differentiation could support treatment tolerability and adherence. It may also be important for tailoring treatment according to the individual physiology.

5.1.1 Aims of the chapter

This study was observational and hypothesis generating. The primary aim of the study was to evaluate the arousability and sleep recovery responses to the vibrotactile stimulus in healthy individuals.

The secondary aims of this study were to evaluate whether:

5- Arousability and sleep recovery responses are influenced by gender
6- Arousability and sleep recovery responses are sleep state dependent
7- Subjective sleep quality is influenced by gender
8- There are different arousability and sleep recovery phenotypes

I tested the hypothesis that females are more resilient to arousability compared to males.

5.2 Method

This section discusses the methods specific to this chapter, including eligibility criteria, recruitment process, phenotyping method, and statistical analyses. The reproducibility and representation of the data is also tested. For details about the general methodology of measuring objective sleep, see chapter 2, section 2.4.

5.2.1 Participants and patient recruitment information

Participants were invited to take part in this study if they met the following eligibility criteria:

- Age of 18 years or older
- Healthy volunteers who do not suffer from physician-diagnosed sleep disorders or other chronic diseases and have not used medications known to influence sleep
- The absence of signs that are indicative of high suspicion of OSA, such as witnessed apnoea and choking during sleep
- Ability to tolerate wearing the vibrotactile PT device
- Sleep primarily in the supine position
- Absence of abnormality to prevent sleeping in any sleep position
- Willingness and ability to give written informed consent

The participants were recruited from both Imperial College London and the Kingdom of Saudi Arabia, specifically from Imam Abdulrahman bin Faisal University in Dammam or King Abdullaziz University and Hospital in Jeddah. This was due to the lockdown imposed by the COVID-19 pandemic and the repatriation of Saudi citizens to the Kingdom of Saudi Arabia. Participants studied in the UK after the repatriation of the author were completed with the help of Ms Alexis Perkin.

5.2.2 Sample size calculation

The sample size was calculated based on the hypothesis that females are more resilient to arousability compared to males. A mean difference between males and females was estimated using the AASM criteria for scoring arousal, which states that the duration of arousal can be from 3 to 15 seconds (Berry *et al.*, 2012). Therefore, I chose the maximum of 15 seconds as a hypothesised mean difference between males and females. In addition, the standard deviation was estimated based on a 95% range of values (3 to 15 seconds) divided by four to give a standard deviation of 12 (Schumm *et al.*, 2017).

Assuming the mean difference between males and females will be 15 seconds and the pooled standard deviation will be 12 seconds, the study would require a sample size of 22 participants (11 in each group) to achieve a power of 80% and a level of significance of 5% (two sided).

A PSG failure rate is reported in previous studies to be between 4% and 8%, and one study reported 20% (Bruyneel *et al.*, 2015; Bruyneel *et al.*, 2011; Campbell & Neill, 2011; Douglas *et al.*, 2017; Iber *et al.*, 2004; Portier *et al.*, 2000). Therefore, assuming for a PSG failure rate of 10%, an additional two participants are needed. Therefore, a total sample size of 24 participants was needed.

5.2.3 Ethical approval

This was a physiological study, performed in both Imperial College London, Royal Brompton Hospital campus, and Imam Abdulrahman Bin Faisal University. Ethical approvals were received from both institutions with ethical approval no. ICREC 20IC5874 and no. IRB-2020-04-275 for Imperial College London and Imam Abdulrahman Bin Faisal University, respectively (appendices 19 and 20). Participants were given patient information sheets (PIS) prior to participation in the study. Copies of each PIS can be found in appendix (21). Written informed consent was obtained from each participant. The written informed consent form can be found in appendix (22).

5.2.4 Study design

In this physiological study, healthy participants carried out an overnight PT while wearing the neck-worn PT device and completed an in-house subjective sleep quality questionnaire before and after the sleep study. Figure 5.1 show the flow chart of the study.

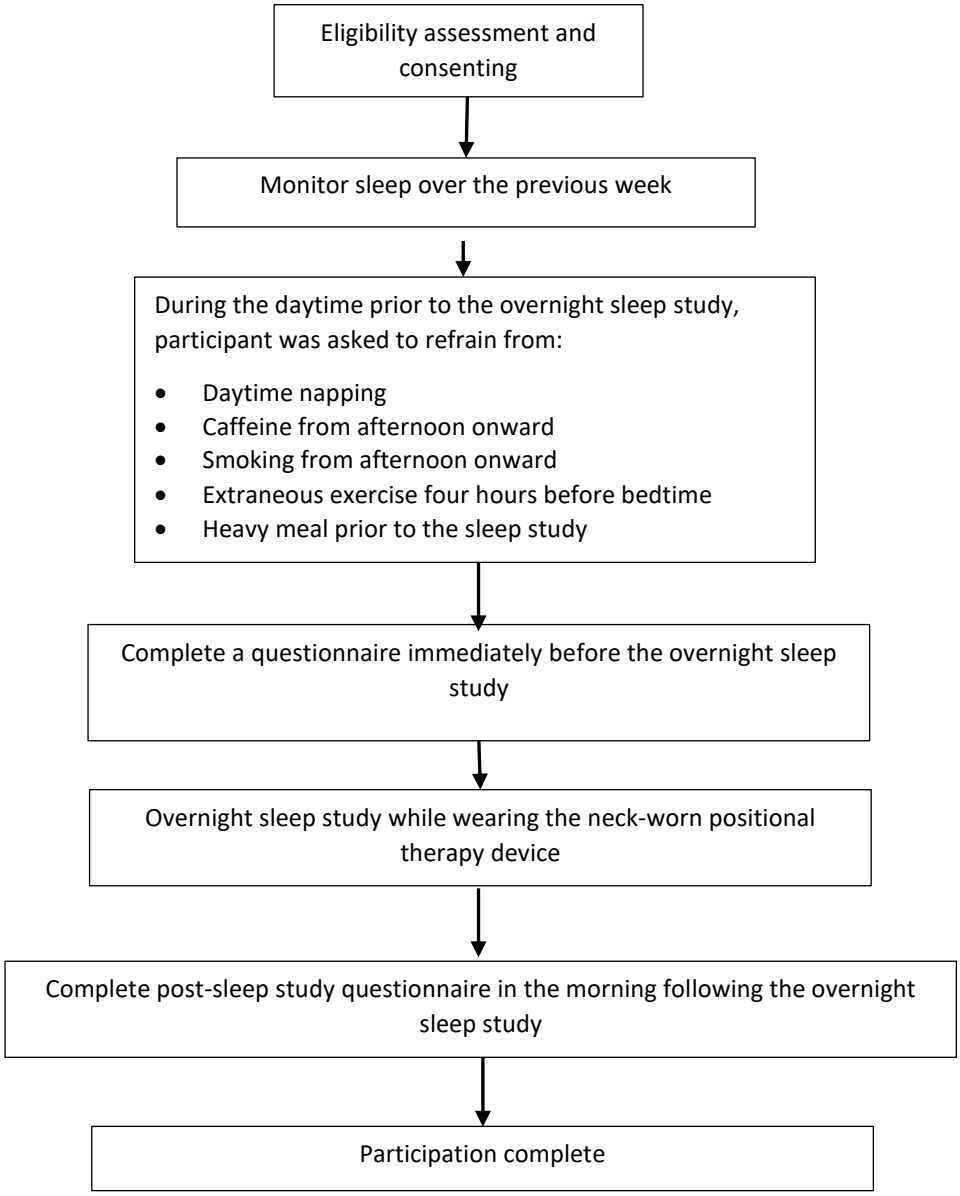


Figure 5.1: Flow chart of the study recruitment process

5.2.5 Method used for the measurement of objective sleep

A type II overnight portable sleep study was performed as described in chapter 2, section 2.4.1. Briefly, prior to the overnight home sleep study, participants were instructed to maintain a consistent overnight sleep pattern for at least one week prior to the study. On

the night of the study, participants were asked to prepare for their usual bedtime sleep routine. The author visited the participants at their own home at least two hours prior to their usual sleeping time. The sleep study data collection was carried out while the participant was wearing the neck-worn vibrotactile PT. PSG setup was performed in accordance with the AASM 2012 criteria (Berry *et al.*, 2012).

5.2.6 Method used for the measurement of subjective sleep quality

A bespoke questionnaire was developed using a visual analogue scale to assess sleep quality and the patient experience with the vibrotactile PT device. Details about this questionnaire can be found in chapter 2, section 2.5.2. Briefly, the items of this bespoke questionnaire focused on sleep quality, the ease of falling asleep, daytime functioning and disturbance of sleep due to vibrotactile stimulus. Responses were based on VAS with a 100 mm horizontal line anchored by two statements (see below).

Sleep quality: This question was used to assess subjective sleep quality while the participant was wearing the vibrotactile PT device. The question was "*Overall, how do you rate your sleep quality last night?".* Response ranged from worst ever (0 mm) to best ever (100 mm).

Easiness of falling asleep: This question was used to assess the easiness of falling asleep on the night of the sleep study while wearing the vibrotactile PT device. The question was *"on average, how easy did you find falling asleep while wearing the positional therapy device over the last night?*" Responses ranged from very easy (0 mm) to very difficult (100 mm).

Daytime functioning: This question was used to evaluate the daytime function on the day following the sleep study. The question was "*overall, how fresh and well rested did you feel when you woke up today?*" Responses ranged from worst ever (0 mm) to best ever (100 mm).

Disturbance of sleep: This question was used to evaluate sleep disturbance on the night of the sleep study while the participant was wearing the vibrotactile PT device. The question was *"If applicable, how much did the vibrations of positional therapy device disturb your bed partner's sleep over the last night?"* Responses ranged from not at all (0 mm) to very much (100 mm).

These questions were also used to investigate if males and females differed on subjective sleep quality compared to objective measures of sleep.

5.2.7 Neck-worn vibrotactile positional therapy device (Night Shift™ device)

The Night Shift™ (Advanced Brain Monitoring, Carlsbad, CA, USA) was used in this study. The Night Shift™ contains a vibrotactile motor to produce a vibrotactile stimulus as well as a position sensor that uses a three-dimensional digital accelerometer to detect sleep position. A description of this device, its components, and its mechanism of action can be found in chapter 2, section 2.6.1.

5.2.8 Measurement of vibration produced by the vibrotactile PT device

Vibration produced by the vibrotactile PT device were measured using the standard microphone. This is fully described in chapter 2, section 2.7.2

5.2.9 Representation and reproducibility of the data

- **Inter-scorer reliability**

Six sleep studies were carried out in London and 22 in Saudi Arabia. All studies were performed using the same equipment and the same standardised procedures. The data from the London studies were analysed to determine the inter-scorer reliability of the novel analysis method. The scoring of these studies was done twice: by the author and by Ms Alexis Perkins. Agreement between the two scorers was determined.

- **Reproducibility of the arousability and sleep recovery variables over time**

To check the reproducibility of the novel analysis method, a sleep study was repeated on one healthy volunteer twice. The first study was carried out in August 2020, and the second was in June 2021. The two studies were analysed using the novel analysis method.

- **A case study of a patient with POSA**

One study was completed on a patient with POSA. This study was carried out to determine the feasibility of the protocol in a patient population. The study was carried out in London by Dr Kelly. The analysis of the data was carried out by the author. It was not possible to complete further studies due to the COVID-19 pandemic.

5.2.10 Data analysis

- **Analysis of the PSG**

Sleep scoring was completed in accordance with the AASM 2012 criteria (Berry *et al.*, 2012) and is described in detail in chapter 2, section 2.7.1

- **Novel method for the analysis of arousability and sleep recovery**

A novel analysis method was developed for this study (chapter 2, section 2.8). Briefly, the analysis was based on the duration to position change and the duration to return to sleep. The first serves as a marker of arousability, and the second serves as a marker of sleep recovery. The duration to change position extended from the beginning of the vibrotactile stimulus to the change in position away from the supine position. The duration of the return to sleep extended from the position change (away from the supine position) to the first epoch of scorable sleep. Throughout the results section, data were "paired": this means that both a response to vibrotactile stimulus (position change away from the supine) and a subsequent return to sleep occurred.

- **Phenotyping of arousability and sleep recovery**

An attempt to classify participants according to their arousal response was carried out. A 10-second criterion was used as cut-off value to differentiate between phenotypes. This criterion was chosen based on the AASM criteria for scoring arousal, which requires that 10 seconds of stable sleep occur preceding an arousal from sleep (Berry *et al.*, 2012).

- **Inter-scorer reliability**

The novel analysis method (described above) was used to analyse the duration to change position and the duration to return to sleep. The analyses were carried out by the author and Ms Alexis Perkins. Each scorer identified the interventions and scored the sleep blinded to the results of the other scorer.

- **Reproducibility of the arousability and sleep recovery variables over time**

The two studies described in (section 5.2.8) were analysed using the novel analysis method.

- **A case study of a patient with POSA**

The sleep data from the patient with POSA patient were analysed using the novel analysis method.

- **Statistical analyses**

Statistical analyses were performed with a commercial software (SPSS V.27.0, IBM, Illinois, USA). Data were assessed for meeting parametric assumptions. This included testing for the normality of distribution, homogeneity of variances, linearity, and independence. Data that were not normally distributed (duration to change position and duration to return to sleep) were transformed using Log transformation. Log transformation (log10) was used to deal the positively skewed distribution.

Descriptive statistics for the data were performed to present baseline characteristics and outcomes. If met the parametric assumptions, categorical data were presented as proportion, whereas continuous data were presented as mean ± standard deviation (SD). If parametric assumptions were not met, data were presented using a median with an interquartile range (Q1, Q2). Data were presented in tables, boxplots, and bar graphs as appropriate.

To investigate if males and females where significantly different in term of age or BMI, the Mann–Whitney U test was used.

To determine the impact of gender and sleep stages and the interaction between them on the duration to change position and the duration to return to sleep, factorial ANOVA was used.

To investigate whether gender influenced subjective sleep quality, the Independent Sample Test or the Mann–Whitney U test were used as appropriate.

To determine if the difference between the phenotypes was statistically significant, the Kruskal–Wallis H test was used.

To investigate inter-rater reliability among two scorers, for the six studies that were scored twice, the intraclass correlation coefficient (ICC) was used. The absolute agreement between the scorers (the author and Ms Alexis Perkins) was determined using the single measure, two-way mixed effects model. The level of agreement was interpreted according to Portney & Watkins (Koo & Li, 2016). An ICC of less than 0.5 is considered poor agreement,

0.5 to 0.75 is considered moderate agreement, more than 0.75 to 0.90 is good agreement, and more than 0.90 indicates excellent reliability.

To investigate the reproducibility of the arousability and sleep recovery variables over time in one participant, descriptive data (mean and SD) were used to show the difference between the two times of scoring. However, the coefficient of variation was not possible to calculate.

In all statistical tests, the 2-sided significance was considered statistically significant if p was less than 0.05.

5.3 Results

5.3.1 Study participants

A total of 67 healthy participants (55 from Saudi Arabia and 12 from London) were screened for eligibility (figure 5.2). Thirty-nine participants completed the subjective questionnaire and had an overnight sleep study while wearing the neck-worn vibrotactile PT device. Twelve participants were excluded from the analysis. Seven participants had less than two paired events (supine events with position change in response to vibrotactile stimulus *and* return to sleep), three recordings failed because of technical issues, one participant had a short recording time (less than four hours) and one had an AHI of > 5 events/hr. Twenty-seven participants were included in the statistical analysis.

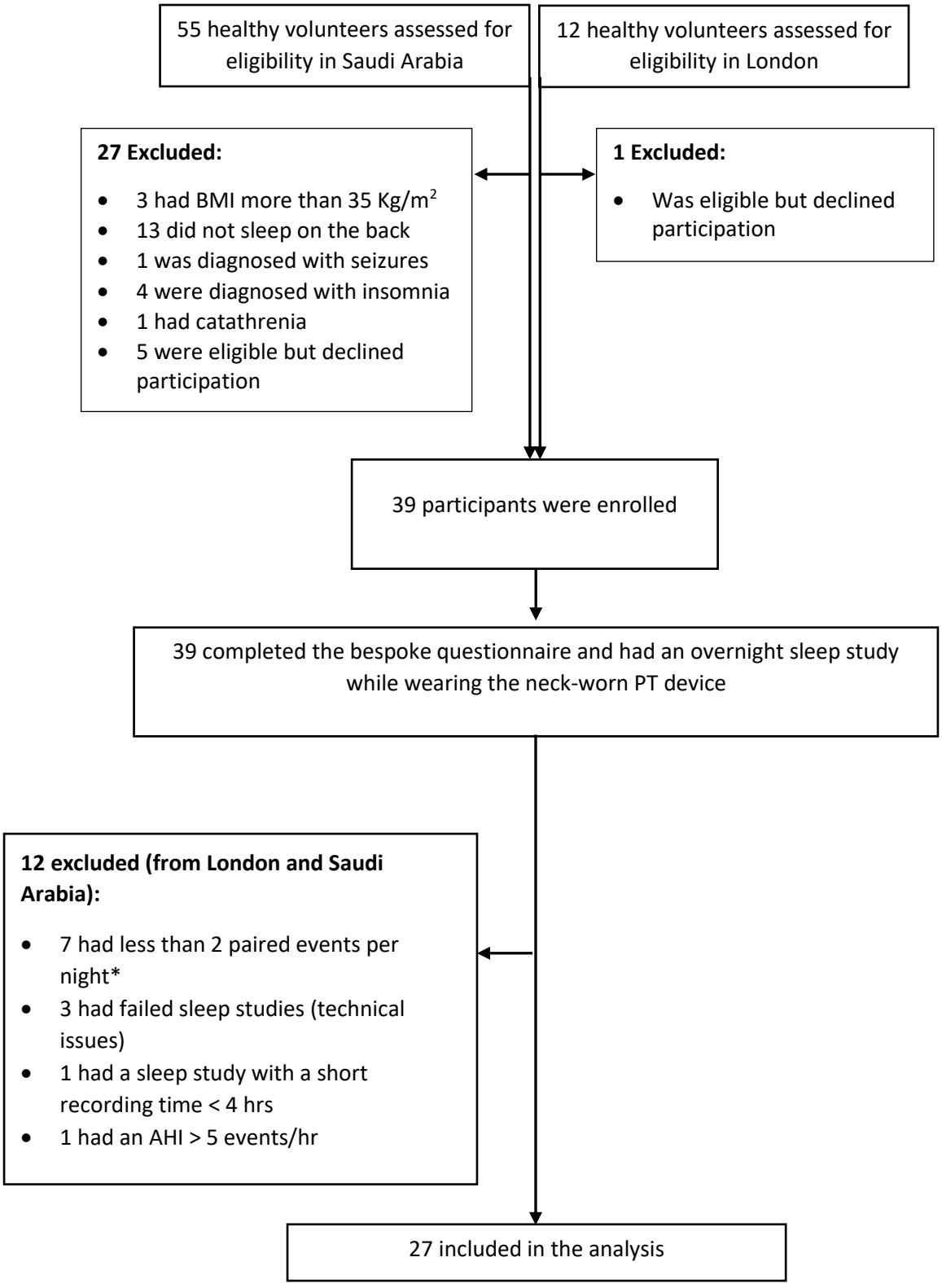


Figure 5.2: Study CONSORT flow diagram

*Flow diagram shows the recruitment process. *A paired event is the presence of a supine event and a change in position due to vibrotactile stimulus (arousal) as well as return to sleep.*

Participants' baseline characteristics are shown in table 5.1. The data are ordered according to age. The group median (Q1, Q3) age was 36 (28, 43.5) years, and the group mean (SD) BMI was 24 ± 2 kg/m^2. Male participants represented 44% of the sample, with a median (Q1, Q3) age of 35.5 (28.7, 36.7) years and a mean (SD) body mass index (BMI) of 24 ± 4 kg/m^2. Female participants represented 56% of the sample, with a median (Q1, Q3) age of 36.0 (27.0, 46.5) years and a BMI of 24 ± 3 kg/m^2. The female participants were older than males; however, this difference was not statistically significant (p=0.82)

Table 5.1: Participants baseline characteristics

Subject	Gender	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)
14	M	23	163	55	21
8	M	24	165	54	20
27	M	28	169	69	24
4	M	29	163	88	33
15	M	33	177	77	25
5	M	35	164	62	23
13	M	36	182	76	23
11	M	36	194	82	22
22	M	36	179	85	27
9	M	39	176	58	19
3	M	47	188	90	25
19	M	78	-	-	-
	Males (n=12)	35.5 (28.8, 36.8)	172 ± 13	71 ± 14	24 ± 4
10	F	23	-	-	-
2	F	24	-	-	-
20	F	24	152	52	23
7	F	26	-	-	-
16	F	28	157	52	21
23	F	28	167	68	24
12	F	30	155	50	21
17	F	36	170	72	25
25	F	41	162	53	20
1	F	42	175	75	24
18	F	45	163	73	27
6	F	48	-	-	-
26	F	49	156	60	25
21	F	50	159	64	25
24	F	57	160	66	26
	Females (n=15)	36.0 (27.0, 46.5)	162 ± 7	62 ± 9	24 ± 2
	Total (n=27)	**36.0 (28.0, 43.5)**	**168 ± 11**	**67 ± 12**	**24 ± 3**

Data are presented in mean (SD) or median (Q1, Q3); n=sample size, cm: centimetre; kg: kilogram; m^2 : squared metre; BMI: body mass index

5.3.2 Are arousability and sleep recovery responses influenced by gender?

All except two participants had 3 to 17 paired data points (i.e. an arousal and return to sleep). The two participants in question (no. 1 and 13) had two paired data points. Figure 5.3 shows the group arousability and sleep recovery responses. The group median (Q1, Q3) arousability was 32.6 (20.7, 71.0) seconds, and the sleep recovery was 27.3 (17.4, 44.1) seconds.

5.3.3 Gender influence on arousability and sleep recovery responses

Figures 5.3 also shows the effect of gender on arousability and recovery responses. Female participants took longer to arouse, with a longer duration to change position (median [Q1, Q2]: 40.7 [29.3, 132.9] seconds) compared to male participants (median [Q1, Q2]: 24.3 [14.7, 32.7] seconds). The duration to change position was not normally distributed (appendix 24); therefore, a log transformation was applied (see appendix 25). Factorial ANOVA of the log transformed arousability showed a statistically significant effect of gender on duration to change position, p <0.001.

The female participants had similar duration to return to sleep compared to males (median (Q1, Q2): females, 27.3 (18.4, 43.7) seconds; males, 28.5 (15.5, 44.3) seconds). The return to sleep was not normally distributed (appendix 26); therefore, a log transformation was applied (see appendix 27). Factorial ANOVA of the log transformed duration to return to sleep showed no statistical difference in the main effect of the gender on the duration to return to sleep p=0.780.

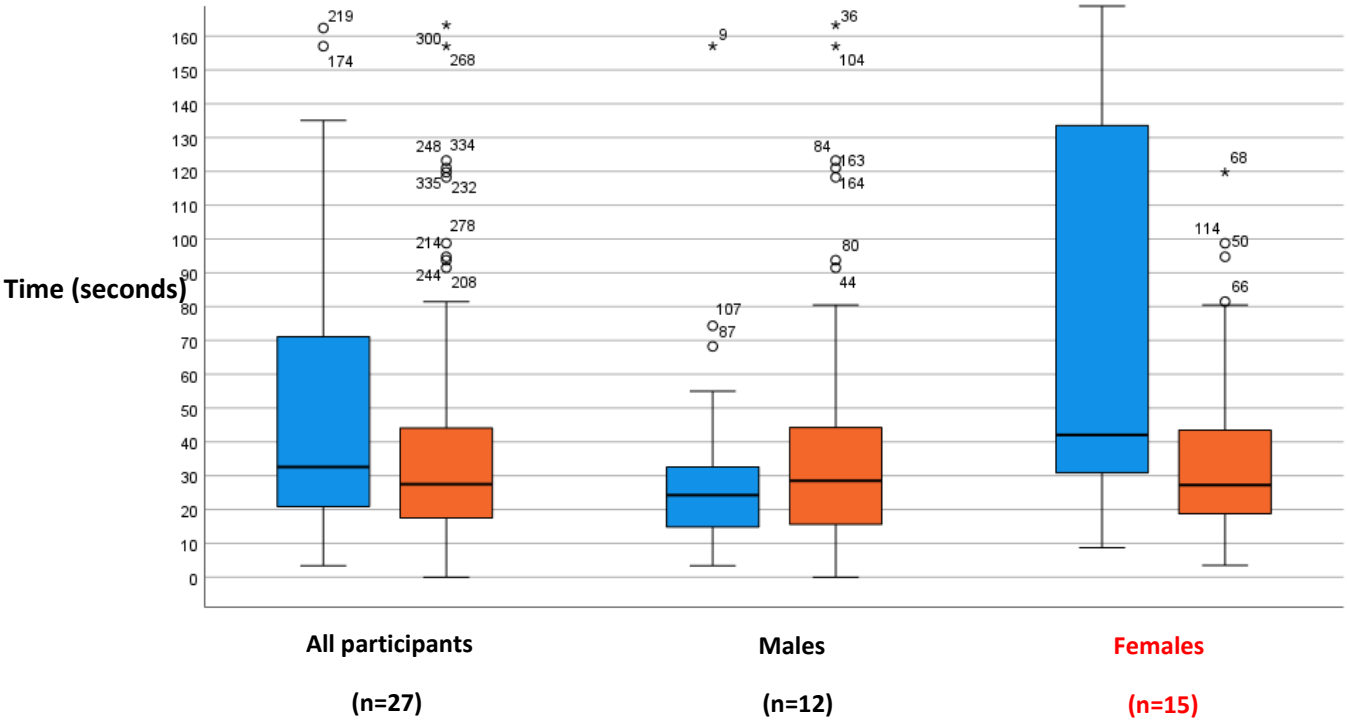


Figure 5.3: The relationship between median duration to position change (arousability) and the median duration to return to sleep (sleep recovery) during the use of a neck-worn vibrotactile positional therapy device in all participants, and also categorised for males and females

"n" represents the number of participants.

Duration to change in position: *Defined as the duration from the start of the initial vibration to the change in position away from the supine position*

Duration to return to sleep: *Defined as the duration from the moving to a new position to the first scorable epoch of sleep*

5.3.4 Are arousability and sleep recovery responses sleep stage dependent?

Figure 5.4 shows the effect of sleep stage on arousability and recovery response. The number of paired events per participant is given in appendix 28. The duration to position change was similar across all sleep stages. The factorial ANOVA of the sleep stage and log transformed duration to position change showed no statistically significant main effect of sleep stage on duration to position change, p=0.93.

The duration to return to sleep was also similar across sleep stages, and the factorial ANOVA of the sleep stage and log transformed duration to return to sleep showed no statistically significant main effect of sleep stage on duration to change position, p=0.15

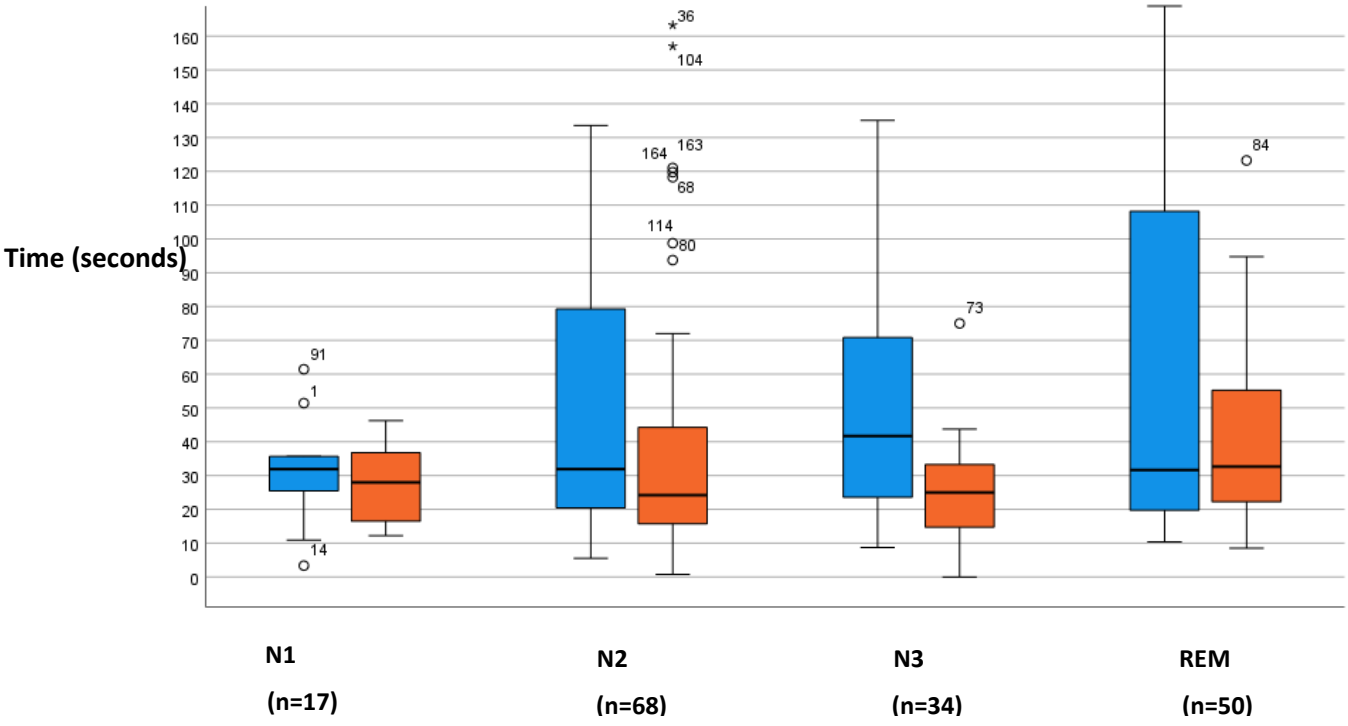


Figure 5.4: Relationship between median duration to position change and median duration to return to sleep during the use of a neck-worn vibrotactile positional therapy device categorised on sleep stage

"n" represents the number of paired events.

Duration to change in position: *Defined as the duration from the start of the initial vibration to the change in position away from the supine position*

Duration to return to sleep: *Defined as the duration from the moving to a new position to the first scorable epoch of sleep*

5.3.5 Interaction of gender and sleep stage and their influence on arousability and sleep recovery responses

The factorial ANOVA showed that there was no significant interaction effect between the gender and sleep stage on the log transformed duration to position change, p=0.76. In addition, there was no significant interaction effect between the gender and sleep stage on log transformed duration to return to sleep, p=0.5. These data suggest that the main factor was gender and that depth of sleep did not influence arousability and recovery responses.

5.3.6 Is subjective sleep quality influenced by gender?

Figure 5.5 shows the subjective sleep quality for all participants, also categorised by female and male: perceived sleep quality on the night of the sleep study (Panel A), ease of falling asleep (Panel B), and daytime restfulness (Panel C).

The female participants reported poor perceived sleep quality on the night of the sleep study (mean [SD]: 49.8 [22.6] mm) compared to male participants (mean [SD] 58.4 [22.5] mm). However, this difference was not statistically significant, p=0.35.

The female participants also reported difficulty in falling asleep on the night of the sleep study compared to the male participants; however, again, the differences were not statistically significant (mean [SD]: females 33.5 [25.4] mm, males 48.7 [28.0] mm; p=0.166).

Furthermore, the female participants reported worse daytime restfulness on the day following the sleep study; however, again, the difference was not statistically significant (mean [SD]: females 54.9 [24.9] mm, males 62.6 [28.5] mm p=0.464).

Figure 5.6 shows the reported sleep disturbance on the night of the sleep study. Females reported more sleep disturbance compared to males (median [Q1, Q2]: females 59.0 [39.8, 75.0] mm, males 41.0 [24.8, 56.8] mm); this difference was not statistically significant, p=0.08.

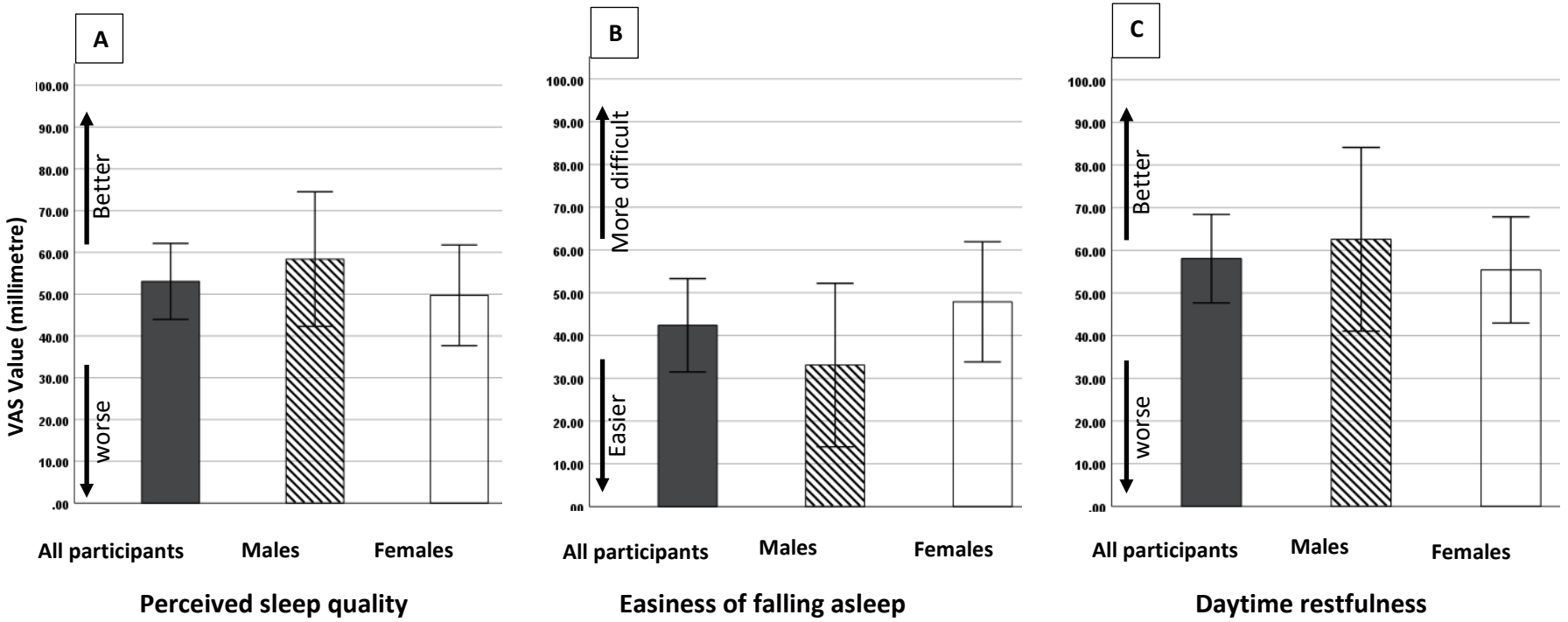


Figure 5.5: The perceived sleep quality, daytime restfulness, and easiness of falling asleep between males and females

(error bar=95% CI)

Panel A: Perceived sleep quality on the night of the sleep study while wearing the PT device; the corresponding questionnaire item was "Overall, how do you rate your sleep quality last night?"

Panel B: Easiness of falling asleep on the night of the sleep study while wearing the PT device; the corresponding questionnaire item was "On average, how easy did you find falling asleep while wearing the positional therapy device over the last night?"

Panel C: Daytime restfulness on the night of the sleep study while wearing PT device; the corresponding questionnaire item was "Overall, how fresh and well rested you feel when you woke up today?"

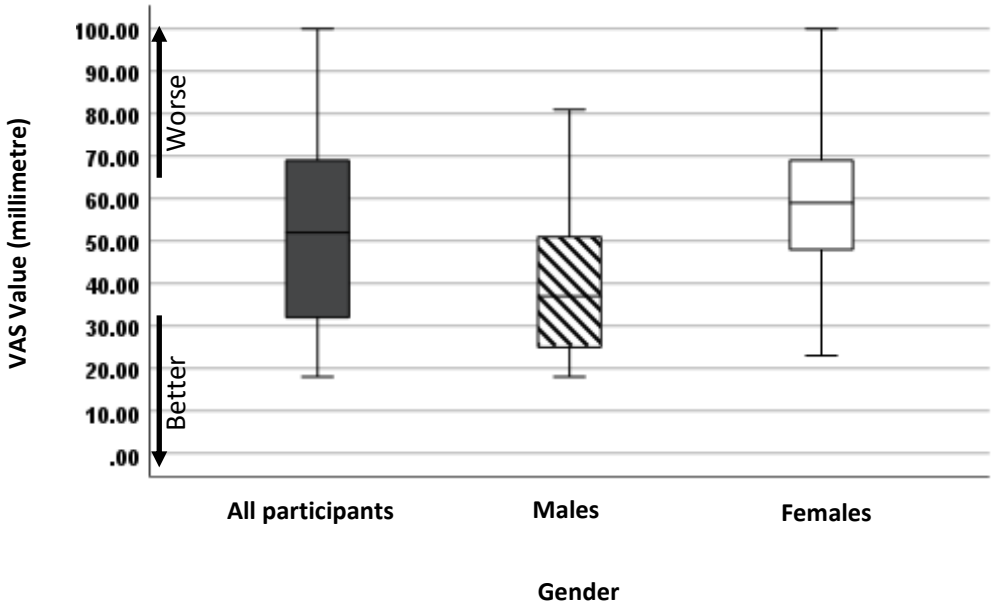


Figure 5.6: The reported sleep disturbance by vibrotactile PT device in all participants, and also categorised by male and female on the night of sleep study

5.3.7 Are there different arousability and sleep recovery phenotypes?

Figure 5.7 shows that there was variability in arousability (duration to position change) and sleep recovery (duration to return to sleep). This variability can be described as three 'physiological phenotypes':

Phenotype 1 (n=10): Short duration to change position (median [Q1, Q3]: 24.8 [15.6, 32.6] seconds) with the duration of the return to sleep being 22.3 (14.0, 33.3) seconds.

Phenotype 2 (n=7): Intermediate duration to change position (median [Q1, Q3]: 35.7 [24.8, 51.5] seconds) with the duration of the return to sleep being 32.0 (21.6, 60.4) seconds.

Phenotype 3 (n=10): Long duration to change position (median [Q1, Q3]: 134.0 [51.8, 577.6] seconds) with the duration of the return to sleep being 32.5 (19.5, 52.1) seconds.

The arousability was statistically significant between the three phenotypes for duration to change position (p <0.001) and duration to return sleep (p=0.001). There was a significant difference on the duration to change position between phenotypes 1 and 2 (p=0.006), 1 and 3 (p <0.001), and 2 and 3 (p <0.001). However, the duration to return to sleep was only significant between phenotypes 1 and 2 (p=0.014) and phenotypes 1 and 3 (p=0.003).

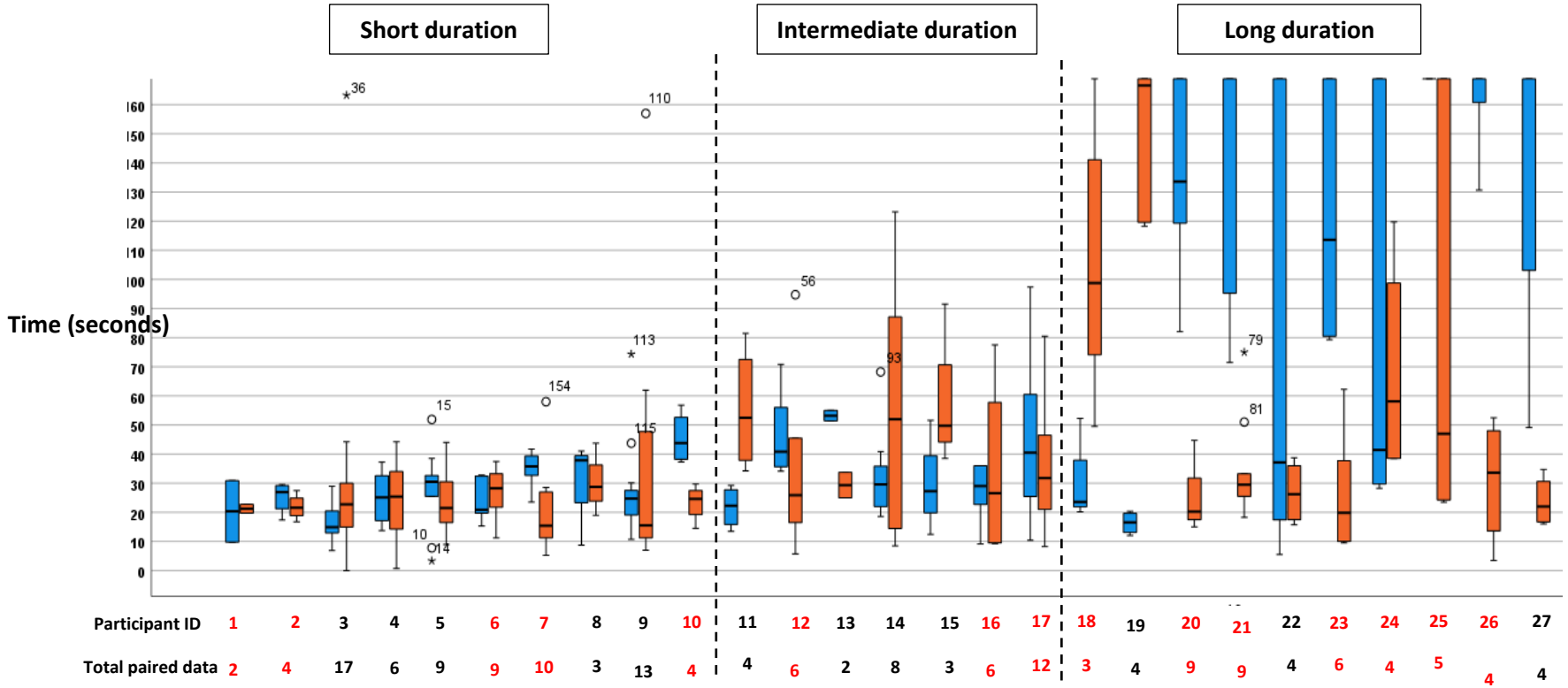


Figure 5.7: Phenotypes of arousability and sleep recovery

Duration to change in position: *Defined as the duration from the start of the initial vibration to the change in position away from the supine position*

Duration to return to sleep: *Defined as the duration from the moving to a new position to the first scorable epoch of sleep*

Males (black text) and females (red text). *Data are presented in ascending order based on the median duration of position change and duration to sleep return*

5.3.8 Representation and reproducibility of the data

- **Inter-scorer reliability**

The baseline characteristics for the six participants investigated in this analysis are shown in table 5.1 (participant no: 2, 3, 6, 7, 10, and 19). Excellent reliability was found between the two scorers for the duration to position change (ICC [95% *CI*] 0.98 [0.89 to 0.98] and a $p <$ .001). There was also good reliability between the two scorers for the duration to return to sleep (ICC [95% *CI*] 0.83 [0.80 to 0.98] p=.015).

- **Reproducibility of the arousability and sleep recovery variables over time**

The baseline characteristics for the participant who was studied twice are shown in table 5.1 (participant no: 3). The first study was carried out in August 2020 (n=9 paired interventions), whereas the second study was carried out in June 2021 (n=6 paired interventions).

During the first study, the mean (SD) duration to change position was 16.4 (6.5) seconds, and the return to sleep was 22.2 (13.9) seconds. During the second study, the data were similar, with the mean (SD) duration to change position being 16.4 (4.7) seconds, and the return to sleep being 22.9 (9.7) seconds.

- **A case study of a patient with POSA**

A patient with POSA was studied in August 2021. The patient was 64 years, with a BMI of 24.5 kg/m^2 and a total AHI of 23 events/hr. The supine and non-supine AHI were 40 events/hr and 14 events/hr, respectively. In addition, the ESS was 15 points. The duration to change position (arousability) and duration to return to sleep (sleep recovery) are shown for three paired data in table 5.2. These data were in the same range as those reported in healthy people (see Fig 5.7) and falls within the short duration phenotype.

Table 5.2: Data for one patient with POSA

Order	Duration to change in position (arousability) (seconds)	Duration to return to sleep (sleep recovery) (seconds)
1	16.7	13.0
2	17.9	21.3
3	18.2	23.0

5.4 Discussion

The main finding of this study was that there was a wide range of arousal responses to the vibrotactile stimulus in healthy participants. In addition, females took longer to arouse and change position compared to male participants. Females also tended to report poor subjective sleep quality compared to males. The arousability and recovery responses were not sleep stage dependent.

The findings of this study may indicate that females are more resilient to an external arousal stimulus, such as the vibrotactile stimulus, compared to males. A number of stressors have been used in previous studies to assess gender differences on arousability during sleep. In an animal model, Koehl *et al.* found that female mice were more resilient to an external stressor compared to males (Koehl *et al.*, 2006). In humans, Bixler *et al.* examined gender differences towards an external stressor in 66 healthy participants (Bixler *et al.*, 2009). They found that male participants' sleep was more disturbed than that of females. Vgontzas *et al.* investigated the effect of sleep restriction on inflammatory markers (TNFalpa) and cortisol levels in males and females (Vgontzas *et al.*, 2004). They found that women were more resilient to sleep restriction, with the TNFalpa elevated in males but not females. In addition, they found that the reduction in the peak cortisol level compared to baseline was significantly greater in males compared to females. Jordan et al examined the ventilatory response and peripheral vasoconstriction responses to spontaneous and tone-induced arousal in healthy males and females (Jordan *et al.*, 2003). They found that both ventilatory and peripheral vasoconstriction responses following induced arousals were significantly greater in males compared to females. In another study, Jordan *et al.* examined the gender differences on the ventilatory response to arousal that was induced by tone or by CPAP drops in patients with OSA (Jordan *et al.*, 2004). They found that a ventilatory response following arousal was greater in males compared to females. In a more recent animal study, it was found that when applying an external stimulus on male and female mice, the males immediately increased the NREM delta power; however, the females showed a weak response or no response (Choi *et al.*, 2021).

Taken together, these studies indicate that female participants are more resilient in their response to arousal stimuli compared to male participants. The results of the present study strengthen this notion because females were more resilient to the vibrotactile stimulus,

taking longer to change position. The underlining mechanism(s) of such a finding is not well understood. It has been suggested that pathways responsible for the regulation of the sympathetic nervous system (the sympatho-adrenal pathway) may be more sensitive to inhibitory stimuli and less sensitive to excitatory stimuli in females compared to males (Hinojosa-Laborde *et al.*, 1999). This could mean that in females, the activation of the sympathoadrenal pathway is attenuated or that the inhibition of the sympathoadrenal pathway is augmented.

Another potential explanation of the finding that females took longer to change position is that they have more sleep spindles. A recent large study, which characterised sleep spindles in a sample of more than eleven thousand individuals, found that females had more spindles than males (Purcell *et al.*, 2017). One of the many roles of sleep spindles is to act as a protective "gate" for the processing of nociceptive stimuli (Fernandez & Lüthi, 2020). If sleep spindles act as a protective mechanism for arousability, they could mediate the longer duration to position changes in females. This possibility would need further studies to fully investigate.

The role of hormone differences between males and females must also be considered in the interpretation of these data. Higher levels of estrogen and or progesterone may be protective against the development of OSA in females at an early age (Lin *et al.*, 2008) as well as when postmenopausal females (without hormone replacement therapy) were compared to premenopausal females they were at higher (approximately four-fold) risk of having OSA (Bixler *et al.*, 2001). Similar findings were found in 589 females who were enrolled in the Wisconsin Sleep Cohort, in which postmenopausal females were at much higher risk of developing OSA, compared to premenopausal females (Young *et al.*, 2003). More recently, a study investigated longitudinal data on menopausal status and sleep found that in females who were in the perimenopausal period, each additional year was associated with a 4% higher AHI (Mirer *et al.*, 2017). This observation was independent of aging and body habitus changes.

Although these examples of hormones being protective in females are interesting, the exact mechanism that leads to a difference in arousability is not known. In the study presented in this chapter, information about hormonal cycles was not gathered.

5.4.1 Gender influence on subjective and objective sleep quality

The data discussed in the previous section are also consistent with reports that have shown that females have better objective sleep quality compared to males (Basoglu & Tasbakan, 2017; Bixler *et al.*, 2009; Redline *et al.*, 2004; Walsleben *et al.*, 2004; Zhou *et al.*, 2021). These studies, and the findings of this chapter seem contrary to the finding that females have poor subjective sleep quality, including more insomnia complaints, compared to males (Fatima *et al.*, 2016; Hung *et al.*, 2013). In the present study, when females were asked about sleep quality, ease of falling asleep, sleep disturbance due to the vibrotactile PT, and daytime restfulness, they reported worse results compared to male participants. Therefore, gender seems to influence subjective sleep quality because females report poorer subjective sleep quality.

In the present study, there were no statistically significant differences in the arousability between different sleep stages. These data are consistent with the published findings. Amatoury *et al.* reported that sleep stage did not influence the arousal intensity (Amatoury *et al.*, 2016), and Jordan *et al.* did not find differences between different sleep stages with spontaneous or tone-induced arousals (Jordan *et al.*, 2003).

5.4.2 Phenotypes of arousability and sleep recovery

Using the duration to change position as an indirect marker of arousability and the duration to return to sleep as an indirect marker of sleep recovery, three arousability phenotypes have been proposed.

In previous studies, Azabarzin *et al.* categorised spontaneous arousals from sleep (based on EEG) into nine categories, ranging from low to high arousal intensity (Azarbarzin *et al.*, 2015). They found that these arousal intensities were widely variable among healthy participants but stable within-participant. Amatoury *et al*. induced cortical arousals by dropping CPAP levels (Amatoury *et al.*, 2016) and using the same arousal categories as Azabrarzin *et al.*, who found that the physiological responses to arousal varied according to the arousal intensity. People with high arousal intensity showed a greater ventilatory response and greater upper airway muscle activity compared to people who had a lower arousal intensity. The findings of the present study are consistent with the results of these published studies. The duration to change position after a vibrotactile stimulus (a marker of

indirect arousability) varied significantly between participants. In addition, the reproducibility data in one participant showed that the duration to change position did not change, even after one year. These findings may indicate that arousability is a distinct physiological trait.

5.4.3 Study strengths and limitations

This study has several strengths. The data analysis was reliable with excellent agreement on the scoring of the arousability and good agreement on sleep recovery. The novel analysis method was easy to apply to data collected during a routine sleep study. Standardising the measurement of arousability may be helpful in evaluating the treatment response to a range of therapy options for OSA. In the present study, data from one patient with OSA was examined. This needs to be replicated on larger studies. To my knowledge, arousability and sleep recovery have not yet been investigated in response to vibrotactile PT devices.

This study was carried out during the COVID-19 pandemic. Applying strict precautionary measures to prevent the transmission of infection, data were collected in both the UK and Saudi Arabia, with no transmission of infection three weeks after the sleep study.

Several limitations of this study are acknowledged. The sample size is relatively small for a study of phenotyping. A larger study would need to take into consideration the time-consuming nature of manual sleep scoring. The automation of scoring arousability may facilitate a larger study.

An additional limitation is the use of the non-validated bespoke subjective sleep questionnaire. However, the findings of this questionnaire seem to corroborate with studies that used validated questionnaires, in which females reported worse subjective sleep quality. The reason that these difference in subjective sleep quality were not statistically significant could be because of the small sample size.

5.4.4 Implications and future directions

In summary, the findings of this study show that healthy participants responded differently to the vibrotactile stimulus, and females are resilient to arousal compared to males. It is possible that a better understanding of arousability phenotypes could inform the clinical

response vibrotactile PT. Repeating these findings in POSA patients will be an important next step.

CHAPTER 6: General Discussion

6.1 Summary of Thesis Aims

POSA is prevalent among patients with OSA. It usually occurs within the mild and moderate spectrum of OSA, and it is known that patients with these severity levels are less adherent to CPAP treatment. In addition, traditional PT techniques are effective in treating POSA; however, their use is linked with significant discomfort and low adherence. Therefore, the relatively new vibrotactile PT devices were developed to deliver gentle vibrotactile stimuli to patients in supine position to encourage them to change position. Although such stimuli are effective in causing movement, there are concerns that it may lead to arousal from sleep, with daytime symptoms. This thesis has evaluated the effectiveness of vibrotactile PT devices as a treatment for POSA, specifically focusing on patient centred outcomes and possible approaches to assist with therapy personalisation to improve treatment success rates.

The overall aim of this thesis was to investigate the effect of vibrotactile PT devices on arousal from sleep in patients with POSA. To achieve this aim, three experimental studies were carried out.

In chapter 3, data from a systematic review and meta-analysis are presented. The aims of this study were to investigate the effect of vibrotactile PT devices on AHI, percentage of time spent in the supine position (%Tsupine), and patient-centred outcomes in patients with POSA compared to baseline.

In chapter 4, the protocol for a prospective three-month, multicentre, randomised, parallel, and double-blind trial (The POSA Trial, ISRCTN51740863) is presented. This study was developed to investigate the effect of vibrotactile PT on AHI, quality of life, and daytime functioning at follow-up adjusted for the baseline in patients with POSA compared to sham-vibrotactile PT. Baseline data (AHI, quality of life and daytime functioning) were obtained from the participants recruited at the RBH and compared to data obtained from the systematic review.

In chapter 5, data from an observational physiological study are presented. This was a hypothesis generating study that aimed to explore the effect of the vibrotactile stimulus on arousability from sleep in healthy people using a novel analysis method developed to measure arousability. This study specifically investigated the influence of gender and sleep stage on arousability and sleep recovery. A comparison of objective measures of arousal from sleep to subjective measures of sleep quality was also carried out. The study tested the hypothesis that females are more resilient to arousability compared to males.

6.2 Summary of the Findings

The findings for each individual study are summarised below.

In chapter 3, the systematic review and meta-analysis, including 16 studies, showed vibrotactile PT was effective in reducing AHI and time spent in the supine position. The ESS and FOSQ global score were minimally improved, and these changes did not reach clinically important differences. In addition, the results on the sensitive quality of life (SF-36) vitality score were promising; however, data on this measure were limited.

In chapter 4, the POSA randomised controlled trial is ongoing; 64 POSA participants have been recruited, comprising 41% of the total sample size (n = 155), and the trial has been extended to October 2022. Baseline data (i.e. AHI, quality of life, and daytime functioning) obtained from the participants recruited at the RBH (n = 7) were compared to data obtained from the systematic review presented in chapter 3 (n = 700, POSA patients). The mean baseline AHI for RBH participants was in the mild OSA category, which was comparable to that of the patients in the mild subgroup in the systematic review. A higher baseline %Tsupine was found among RBH participants compared to the baseline data in the mild OSA subgroup in the systematic review.

The RBH participants baseline patient-centred outcomes were comparable to those found in the systematic review. Specifically, the mean baseline SF-36 vitality score for RBH participants was comparable to that found in the systematic review. In addition, the mean baseline FOSQ global score was comparable to what was found in the systematic review. The mean baseline ESS score in the RBH participant was comparable to what was found in the systematic review. Based on the observed percentage of improvement in the systematic

review improvement (–13%), it is possible the ESS score in the RBH participant will be reduced by 1.1 points in the POSA trial. Interestingly, this is below the minimum clinically important difference which is reported to be 2 points (Crook *et al.*, 2019).

In chapter 5, the observational physiological study showed a wider range of arousal responses to the vibrotactile stimulus in healthy people. Specifically, the female participants took longer to arouse from sleep following the stimuli compared to male participants. However, the duration of return to sleep (i.e. sleep recovery) was comparable between males and females. There were small differences observed in the subjective measurements of sleep quality between males and females; however, these differences did not reach statistical significance, possibly because of the small sample size. Through exploring all the data points, three arousal phenotypes were identified based on a prior criterion, (a 10-second difference in arousability, and sleep recovery). The phenotypes were a short, intermediate, and long duration of arousability and sleep recovery. How representative these phenotypes, are needs to be further explored with a larger sample. The clinical relevance of the wide range of arousal responses also needs to be further explored.

6.2.1. Overall Thesis Findings

The overall findings of the Thesis were that vibrotactile PT is effective in reducing the AHI and time spent in the supine position. However, there is an evidence gap of how vibrotactile PT affects patient-centred outcomes. The POSA trial results will address this gap, and since the baseline data of POSA participants recruited from the RBH are consistent with data from the published literature, therefore, it is expected that after 12 weeks of vibrotactile PT, there will be a significant reduction in AHI and time spent in the supine position.

One concern when prescribing vibrotactile PT is that it may cause arousal from sleep in some individuals, with worsening daytime symptoms (e.g. an increased daytime sleepiness). Variability in the arousability responses to the vibrotactile stimulus was found among healthy participants. Specifically, there were differences in the arousability between males and females, with females being less arousable by the vibrotactile stimuli. These findings need to be further explored with a larger sample of healthy people and patients with POSA.

6.3 Future Directions

Vibrotactile PT devices have been introduced as a treatment for POSA, potentially replacing the traditional PT techniques, such as the tennis ball to prevent sleeping on the back. The vibrotactile PT devices are small and easy to use. They work by producing a gentle vibrotactile stimulus.

The data presented in this thesis have shown the new vibrotactile PT devises are effective in reducing time spent in the supine position and respiratory events in patients with POSA. These findings were similar to those presented in the recent NICE guideline (NG202), which show that the vibrotactile PT devices can be effective in reducing AHI and time spent in the supine position (NICE guidelines, 2021). The guidance recommended vibrotactile PT as an alternative treatment for patients with POSA if other treatments (e.g. CPAP) were not successful or tolerable, especially for patients with mild or moderate OSA. However, as shown in this Thesis there was a paucity of data on patient-centred outcomes. It is anticipated that the results of the (ongoing) POSA Trial will address this evidence gap and could provide the much needed data for future guidelines, to potentially support the provision of PT therapy for patient with POSA.

COVID-19 occurred during data collection for the studies presented in this thesis, including the POSA trial. The pandemic has caused many changes in health-care provision. It has accelerated the use of technology for the diagnosis and treatment of OSA. The simplicity of vibrotactile PT devices, which can be remotely initiated and monitored, meant they were acceptable to patients as a potential treatment during the pandemic. This feature was utilised during the modification of the trial to enable work to continue in a semi-remote manner. Our patients have informed us that the POSA trial is user-friendly, and we are proud that we have been able to continue the trial, although recruitment has inevitably been impacted.

Despite the major advantages of the vibrotactile PT treatment, it also has the potential limitation to cause arousal from sleep. The development of a novel analysis method, which enabled a standardised measurement of the induced arousal, has shown that there is variability in arousability responses to vibrotactile stimuli among healthy participants.

Some participants aroused easily, but others took a longer time to be aroused and to move in response to the stimuli. These differences may highlight the need for a more personalised approach for the management of patients with POSA. Although a larger study is needed to verify the three possible phenotypes. It may be that with a larger group of patients the three phenotypes will become a continuous spectrum of responses. Never-the-less, it is possible to speculate that some patients will likely benefit more from the vibrotactile PT without concurrent sleep fragmentation compared to others. Any future studies will also need to compare the physiological differences with the subjective impact of the stimuli on symptoms of daytime sleepiness.

The physiological study has also highlighted that females may be more resilient to being aroused from sleep than males. This, potentially, means that the vibrotactile PT is a treatment option that maybe preferred by females especially if they do not have disturbance of sleep. Females tend to show a discrepancy between subjective and objective sleep quality. The females tended to report poorer subjective sleep despite having better objective sleep quality than male participants. Understanding the underlying mechanisms that cause these differences is important for better personalisation of treatment. It is also important that any future studies are powered to account for confounding influences such as age, and even childcare responsibilities.

6.4 Conclusion

The aim of this thesis was to investigate the effect of vibrotactile PT devices on arousal from sleep among patients with POSA. Although the vibrotactile PT was effective in treating POSA, there were limited data on sensitive patient-centred outcomes, such as the vitality score. This gap in evidence is expected to be addressed by the results of the POSA trial. Such data are of paramount importance for the future development of guidelines, which may support the inclusion of PT for patients with POSA. The variability in arousability responses to vibrotactile stimuli highlights the need for further research that may support a personalised approach to the diagnosis and management of POSA.

CHAPTER 7: References

Aarab, G., Lobbezoo, F., Hamburger, H. L., & Naeije, M. (2009). Variability in the Apnea-Hypopnea Index and Its Consequences for Diagnosis and Therapy Evaluation. *Respiration, 77*(1), 32-37. doi:10.1159/000167790

Amatoury, J., Azarbarzin, A., Younes, M., Jordan, A. S., Wellman, A., & Eckert, D. J. (2016). Arousal Intensity is a Distinct Pathophysiological Trait in Obstructive Sleep Apnea. *Sleep, 39*(12), 2091-2100. doi:10.5665/sleep.6304

Anttalainen, U., Saaresranta T Fau - Kalleinen, N., Kalleinen N Fau - Aittokallio, J., Aittokallio J Fau - Vahlberg, T., Vahlberg T Fau - Polo, O., & Polo, O. (2007). CPAP adherence and partial upper airway obstruction during sleep. *Sleep and Breathing, 11*(3), 171-176.

Armas, L. H., Turino, C., Cordero-Guevara, J., Manjón, J. L., Durán-Carro, J., Barbé, F., . . . Durán-Cantolla, J. (2019). A new postural device for the treatment of positional obstructive sleep apnea. A pilot study. *Respiratory Medicine, 151*, 111-117. doi:10.1016/j.rmed.2019.02.005

Avraam, J., Dawson, A., Rochford, P. D., Brazzale, D. J., O'Donoghue F, J., Trinder, J., & Jordan, A. S. (2019). The effect of sex and body weight on lung volumes during sleep. *Sleep*. doi:10.1093/sleep/zsz141

Azarbarzin, A., Ostrowski, M., Hanly, P., & Younes, M. (2014). Relationship between Arousal Intensity and Heart Rate Response to Arousal. *Sleep, 37*(4), 645-653. doi:10.5665/sleep.3560

Azarbarzin, A., Ostrowski, M., Younes, M., Keenan, B. T., Pack, A. I., Staley, B., & Kuna, S. T. (2015). Arousal Responses during Overnight Polysomnography and their Reproducibility in Healthy Young Adults. *Sleep, 38*(8), 1313-1321. doi:10.5665/sleep.4916

Basoglu, O. K., & Tasbakan, M. S. (2017). Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. *Sleep and Breathing, 22*(1), 241-249.

Benjafield, A. V., Ayas, N. T., Eastwood, P. R., Heinzer, R., Ip, M. S. M., Morrell, M. J., . . . Malhotra, A. (2019). Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. *Lancet Respiratory Medicine, 7*(8), 687-698. doi:10.1016/s2213-2600(19)30198-5

Bennett, L. S., Barbour, C., Langford, B., Stradling, J. R., & Davies, R. J. (1999). Health status in obstructive sleep apnea: relationship with sleep fragmentation and daytine sleepiness, and effects of continuous positive airway pressure treatment. *Am J Respir Crit Care Med, 159*(6), 1884-1890. doi:10.1164/ajrccm.159.6.9808107

Benoist, L., de Ruiter, M., de Lange, J., & de Vries, N. (2017). A randomized, controlled trial of positional therapy versus oral appliance therapy for position-dependent sleep apnea. *Sleep Med, 34*, 109-117. doi:10.1016/j.sleep.2017.01.024

Berg, J. F. v. d., Miedema Hm Fau - Tulen, J. H. M., Tulen Jh Fau - Hofman, A., Hofman A Fau - Neven, A. K., Neven Ak Fau - Tiemeier, H., & Tiemeier, H. (2009). Sex differences in subjective and actigraphic sleep measures: a population-based study of elderly persons. *Sleep, 32*(10).

Berry, R. B., Brooks, R., Gamaldo, C. E., Harding, S. M., Marcus, C., & Vaughn, B. V. (2012). The AASM manual for the scoring of sleep and associated events: Rules, Terminology and Technical Specifications. *176*.

Berry, R. B., Budhiraja, R., Gottlieb, D. J., Gozal, D., Iber, C., Kapur, V. K., . . . Tangredi, M. M. (2012). Rules for scoring respiratory events in sleep: update of the 2007 AASM Manual for the Scoring of Sleep and Associated Events. Deliberations of the Sleep Apnea Definitions Task Force of the American Academy of Sleep Medicine. *J Clin Sleep Med, 8*(5), 597-619. doi:10.5664/jcsm.2172

Berry, R. B., Uhles, M. L., Abaluck, B. K., Winslow, D. H., Schweitzer, P. K., Gaskins, R. A., Jr., . . . Emsellem, H. A. (2019). NightBalance Sleep Position Treatment Device Versus Auto-Adjusting Positive Airway Pressure for Treatment of Positional Obstructive Sleep Apnea. *Journal of Clinical Sleep Medicine, 15*(7), 947-956. doi:10.5664/jcsm.7868

Beyers, J., Dieltjens, M., Kastoer, C., Opdebeeck, L., Boudewyns, A. N., De Volder, I., . . . Vanderveken, O. M. (2018). Evaluation of a Trial Period With a Sleep Position Trainer in Patients With Positional Sleep Apnea. *Journal of Clinical Sleep Medicine, 14*(4), 575-583. doi:10.5664/jcsm.7048

Beyers, J., Vanderveken, O. M., Kastoer, C., Boudewyns, A., De Volder, I., Van Gastel, A., . . . Dieltjens, M. (2019). Treatment of sleep-disordered breathing with positional therapy: long-term results. *Sleep & breathing, 23*(4), 1141-1149. doi:https://dx.doi.org/10.1007/s11325-019-01792-9

Bignold, J. J., Deans-Costi, G., Goldsworthy, M. R., Robertson, C. A., McEvoy, D., Catcheside, P. G., & Mercer, J. D. (2009). Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. *Journal of Clinical Sleep Medicine, 5*(5), 428-430.

Bignold, J. J., Mercer, J. D., Antic, N. A., McEvoy, R. D., & Catcheside, P. G. (2011). Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. *Journal of Clinical Sleep Medicine, 7*(4), 376-383. doi:10.5664/jcsm.1194

Bignold, J. J., Mercer Jd Fau - Antic, N. A., Antic Na Fau - McEvoy, R. D., McEvoy Rd Fau - Catcheside, P. G., & Catcheside, P. G. Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device. (1550-9397 (Electronic)).

Bixler, E. O., Papaliaga, M. N., Vgontzas, A. N., Lin, H. M., Pejovic, S., Karataraki, M., . . . Chrousos, G. P. (2009). Women sleep objectively better than men and the sleep of young women is more resilient to external stressors: effects of age and menopause. *J Sleep Res, 18*(2), 221-228. doi:10.1111/j.1365-2869.2008.00713.x

Bixler, E. O., Vgontzas, A. N., Lin, H. M., Ten Have, T., Rein, J., Vela-Bueno, A., & Kales, A. (2001). Prevalence of sleep-disordered breathing in women: effects of gender. *American journal of respiratory and critical care medicine, 163*(3 Pt 1), 608-613.

Bonnet, M. H., & Arand, D. L. (2003). Clinical effects of sleep fragmentation versus sleep deprivation. *Sleep Med Rev, 7*(4), 297-310.

Boulos, M. I., Jairam, T., Kendzerska, T., Im, J., Mekhael, A., & Murray, B. J. (2019). Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis. *Lancet Respir Med, 7*(6), 533-543. doi:10.1016/s2213-2600(19)30057-8

Brownell, L., Perez-Padilla, R., West, P., & Kryger, M. H. (1983). The role of protriptyline in obstructive sleep apnea. *Bulletin Européen de Physiopathologie Respiratoire, 19*(6), 621-624.

Bruyneel, M., Libert, W., Ameye, L., & Ninane, V. (2015). Comparison between home and hospital set-up for unattended home-based polysomnography: a prospective randomized study. *Sleep Med, 16*(11), 1434-1438. doi:10.1016/j.sleep.2015.04.006

Bruyneel, M., Sanida, C., Art, G., Libert, W., Cuvelier, L., Paesmans, M., . . . Ninane, V. (2011). Sleep efficiency during sleep studies: results of a prospective study comparing home-based and in-hospital polysomnography. *J Sleep Res, 20*(1 Pt 2), 201-206. doi:10.1111/j.1365-2869.2010.00859.x

Bucks, R. S., Olaithe, M., & Eastwood, P. (2013). Neurocognitive function in obstructive sleep apnoea: a meta-review. *Respirology, 18*(1), 61-70. doi:10.1111/j.1440-1843.2012.02255.x

Buysse, D. J., Reynolds, C. F., 3rd, Monk, T. H., Berman, S. R., & Kupfer, D. J. (1989). The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. *Psychiatry Res, 28*(2), 193-213. doi:10.1016/0165-1781(89)90047-4

Campbell, A. J., & Neill, A. M. (2011). Home set-up polysomnography in the assessment of suspected obstructive sleep apnea. *J Sleep Res, 20*(1 Pt 2), 207-213. doi:10.1111/j.1365-2869.2010.00854.x

Caples, S. M., Rowley, J. A., Prinsell, J. R., Pallanch, J. F., Elamin, M. B., Katz, S. G., & Harwick, J. D. (2010). Surgical modifications of the upper airway for obstructive sleep apnea in adults: a

systematic review and meta-analysis. *Sleep, 33*(10), 1396-1407. doi:10.1093/sleep/33.10.1396

Carberry, J. C., Jordan, A. S., White, D. P., Wellman, A., & Eckert, D. J. (2016). Upper Airway Collapsibility (Pcrit) and Pharyngeal Dilator Muscle Activity are Sleep Stage Dependent. *Sleep, 39*(3), 511-521.

Carter, R., 3rd, & Watenpaugh, D. E. (2008). Obesity and obstructive sleep apnea: or is it OSA and obesity? *Pathophysiology, 15*(2), 71-77. doi:10.1016/j.pathophys.2008.04.009

Cartwright, R. D. (1984). Effect of sleep position on sleep apnea severity. *Sleep, 7*(2), 110-114. doi:10.1093/sleep/7.2.110

Chapman, J. L., Vakulin, A., Hedner, J., Yee, B. J., & Marshall, N. S. (2016). Modafinil/armodafinil in obstructive sleep apnoea: a systematic review and meta-analysis. *Eur Respir J.*(1399-3003 (Electronic)). doi:10.1183/13993003.01509-2015

Choi, J., Kim, S. J., Fujiyama, T., Miyoshi, C., Park, M., Suzuki-Abe, H., . . . Funato, H. (2021). The Role of Reproductive Hormones in Sex Differences in Sleep Homeostasis and Arousal Response in Mice. *Frontiers in Neuroscience*(1662-4548 (Print)).

Ciscar, M. A., Juan, G., Martínez, V., Ramón, M., Lloret, T., Mínguez, J., . . . Basterra, J. (2001). Magnetic resonance imaging of the pharynx in OSA patients and healthy subjects. *European Respiratory Journal, 17*(1), 79-86.

Craig, S. E., Kohler, M., Nicoll, D., Bratton, D. J., Nunn, A., Davies, R., & Stradling, J. (2012). Continuous positive airway pressure improves sleepiness but not calculated vascular risk in patients with minimally symptomatic obstructive sleep apnoea: the MOSAIC randomised controlled trial. *Thorax, 67*(12), 1090-1096. doi:10.1136/thoraxjnl-2012-202178

Crook, S., Sievi, N. A., Bloch, K. E., Stradling, J. R., Frei, A., Puhan, M. A., & Kohler, M. (2019). Minimum important difference of the Epworth Sleepiness Scale in obstructive sleep apnoea: estimation from three randomised controlled trials. *Thorax, 74*(4), 390-396. doi:10.1136/thoraxjnl-2018-211959

D'Ambrosio, C., Bowman, T., & Mohsenin, V. (1999). Quality of life in patients with obstructive sleep apnea: effect of nasal continuous positive airway pressure--a prospective study. *Chest, 115*(1), 123-129. doi:10.1378/chest.115.1.123

de Ruiter, M. H. T., Benoist, L. B. L., de Vries, N., & de Lange, J. (2018). Durability of treatment effects of the Sleep Position Trainer versus oral appliance therapy in positional OSA: 12-month follow-up of a randomized controlled trial. *Sleep Breath, 22*(2), 441-450. doi:10.1007/s11325-017-1568-4

Dieltjens, M., Vroegop, A. V., Verbruggen, A. E., Wouters, K., Willemen, M., De Backer, W. A., . . . Vanderveken, O. M. (2015). A promising concept of combination therapy for positional obstructive sleep apnea. *Sleep Breath, 19*(2), 637-644. doi:10.1007/s11325-014-1068-8

Dorsey, A., de Lecea, L., & Jennings, K. J. (2021). Neurobiological and Hormonal Mechanisms Regulating Women's Sleep. *Frontiers in Neuroscience*(1662-4548 (Print)).

Douglas, J. A., Chai-Coetzer, C. L., McEvoy, D., Naughton, M. T., Neill, A. M., Rochford, P., . . . Worsnop, C. (2017). Guidelines for sleep studies in adults - a position statement of the Australasian Sleep Association. *Sleep Med, 36 Suppl 1*, S2-s22. doi:10.1016/j.sleep.2017.03.019

Dunietz, G. A.-O., Shedden, K., Schisterman, E. F., Lisabeth, L. D., Treadwell, M. C., & O'Brien, L. M. (2018). Associations of snoring frequency and intensity in pregnancy with time-to-delivery. *Paediatric and Perinatal Epidemiology, 32*(6), 504-511.

Duran-Cantolla, J., Barbe, F., Rigau, J., Oreja, D., Martinez-Null, C., & Santaolalla, C. E. (2013). A new vibratory postural device for the treatment of positional obstructive sleep apnea (OSA). A pilot study. *Sleep Med, 14*, e111. doi:https://doi.org/10.1016/j.sleep.2013.11.244

Eckert, D. J. (2018). Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. *Sleep Medicine Reviews*(1532-2955 (Electronic)).

Eckert, D. J., & Wellman, A. (2015). Physiological phenotypes. *European Respiratory Society Monograph, 67*, 9-23. doi:10.1183/2312508x.10005414

Eckert, D. J., White, D. P., Jordan, A. S., Malhotra, A., & Wellman, A. (2013). Defining Phenotypic Causes of Obstructive Sleep Apnea. Identification of Novel Therapeutic Targets. *American journal of respiratory and critical care medicine, 188*(8), 996-1004. doi:10.1164/rccm.201303-0448OC

Eckert, D. J., & Younes, M. K. (2013). Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *Journal of Applied Physiology, 116*(3), 302-313. doi:10.1152/japplphysiol.00649.2013

Eckert, D. J., & Younes, M. K. (2014). Arousal from sleep: implications for obstructive sleep apnea pathogenesis and treatment. *J Appl Physiol (1985), 116*(3), 302-313. doi:10.1152/japplphysiol.00649.2013

Edwards, B. A., Sands Sa Fau - Eckert, D. J., Eckert Dj Fau - White, D. P., White Dp Fau - Butler, J. P., Butler Jp Fau - Owens, R. L., Owens Rl Fau - Malhotra, A., . . . Wellman, A. (2012). Acetazolamide improves loop gain but not the other physiological traits causing obstructive sleep apnoea. *J Physiol, 590*(5), 1199–1211.

Edwards, B. A., Sands, S. A., Owens, R. L., White, D. P., Genta, P. R., Butler, J. P., . . . Wellman, A. (2014). Effects of hyperoxia and hypoxia on the physiological traits responsible for obstructive sleep apnoea. *The Journal of physiology, 592*(20), 4523-4535. doi:10.1113/jphysiol.2014.277210

Eijsvogel, M. M., Ubbink, R., Dekker, J., Oppersma, E., de Jongh, F. H., van der Palen, J., & Brusse-Keizer, M. G. (2015). Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. *Journal of Clinical Sleep Medicine, 11*(2), 139-147. doi:10.5664/jcsm.4460

Elshaug, A. G., Moss Jr Fau - Southcott, A. M., Southcott Am Fau - Hiller, J. E., & Hiller, J. E. (2007). Redefining success in airway surgery for obstructive sleep apnea: a meta analysis and synthesis of the evidence. *Sleep, 30*(4).

Fatima, Y., Doi, S. A., Najman, J. M., & Mamun, A. A. (2016). Exploring Gender Difference in Sleep Quality of Young Adults: Findings from a Large Population Study. *Clin Med Res, 14*(3-4), 138–144.

Fernandez, L. M. J., & Lüthi, A. (2020). Sleep Spindles: Mechanisms and Functions. *Physiol Rev, 100*(2), 805-868. doi:10.1152/physrev.00042.2018

Finn, L., Young, T., Palta, M., & Fryback, D. G. (1998). Sleep-disordered breathing and self-reported general health status in the Wisconsin Sleep Cohort Study. *Sleep, 21*(7), 701-706.

Floras, J. S. (2018). Sleep Apnea and Cardiovascular Disease. *Circulation Research, 122*(12), 1741-1764. doi:doi:10.1161/CIRCRESAHA.118.310783

Frank, M. H., Ravesloot, M. J. L., van Maanen, J. P., Verhagen, E., de Lange, J., & de Vries, N. (2015). Positional OSA part 1: towards a clinical classification system for position-dependent obstructive sleep apnoea. *Sleep and Breathing, 19*(2), 473-480. doi:10.1007/s11325-014-1022-9

Gabbay, I. E., & Lavie, P. (2012). Age- and gender-related characteristics of obstructive sleep apnea. *Sleep and Breathing, 16*(2), 453-460.

Gottlieb, D. J., & Punjabi, N. M. (2020). Diagnosis and Management of Obstructive Sleep Apnea: A Review. *Jama, 323*(14), 1389-1400.

Gray, E. L., McKenzie, D. K., & Eckert, D. J. (2017). Obstructive Sleep Apnea without Obesity Is Common and Difficult to Treat: Evidence for a Distinct Pathophysiological Phenotype. *J Clin Sleep Med, 13*(1), 81-88.

Hanzel, D. A., Proia Ng Fau - Hudgel, D. W., & Hudgel, D. W. (1991). Response of obstructive sleep apnea to fluoxetine and protriptyline. *Chest, 100*(2), 416-421.

Heinzer, R., Petitpierre, N. J., Marti-Soler, H., & Haba-Rubio, J. (2018). Prevalence and characteristics of positional sleep apnea in the HypnoLaus population-based cohort. *Sleep Med, 48*, 157-162. doi:10.1016/j.sleep.2018.02.011

Heinzer, R., Vat, S., Marques-Vidal, P., Marti-Soler, H., Andries, D., Tobback, N., . . . Haba-Rubio, J. (2015). Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. *Lancet Respir Med, 3*(4), 310-318. doi:10.1016/s2213-2600(15)00043-0

Hernandez, L., Ballester, E., Farre, R., Badia, J. R., Lobelo, R., Navajas, D., & Montserrat, J. M. (2001). Performance of nasal prongs in sleep studies : spectrum of flow-related events. *Chest, 119*(2), 442-450. doi:10.1378/chest.119.2.442

Hidalgo Armas, L., Ingles, S., Vaca, R., Cordero-Guevara, J., Duran Carro, J., Ullate, J., . . . Spanish Sleep, N. (2021). New forehead device in positional obstructive sleep apnoea: a randomised clinical trial. *Thorax, 76*(9), 930-938. doi:https://dx.doi.org/10.1136/thoraxjnl-2020-216167

Hidalgo Armas, L., Turino, C., Cordero-Guevara, J., Manjón, J. L., Durán-Carro, J., Barbé, F., . . . Durán-Cantolla, J. (2019). A new postural device for the treatment of positional obstructive sleep apnea. A pilot study. *Respiratory Medicine, 151*, 111-117. doi:10.1016/j.rmed.2019.02.005

Hinojosa-Laborde, C., Chapa, I., Lange, D., & Haywood, J. R. (1999). Gender differences in sympathetic nervous system regulation. *Clin Exp Pharmacol Physiol, 26*(2), 122-126. doi:10.1046/j.1440-1681.1999.02995.x

Hung, H. C., Yang Yc Fau - Ou, H.-Y., Ou Hy Fau - Wu, J.-S., Wu Js Fau - Lu, F.-H., Lu Fh Fau - Chang, C.-J., & Chang, C. J. (2013). The association between self-reported sleep quality and metabolic syndrome. *PLoS ONE, 8*(1).

Iber, C., Redline, S., Kaplan Gilpin, A. M., Quan, S. F., Zhang, L., Gottlieb, D. J., . . . Smith, P. (2004). Polysomnography performed in the unattended home versus the attended laboratory setting--Sleep Heart Health Study methodology. *Sleep, 27*(3), 536-540. doi:10.1093/sleep/27.3.536

Jacobsen, A. R., Eriksen, F., Hansen, R. W., Erlandsen, M., Thorup, L., Damgård, M. B., . . . Hansen, K. W. (2017). Determinants for adherence to continuous positive airway pressure therapy in obstructive sleep apnea. *PLoS ONE, 12*(12), e0189614. doi:10.1371/journal.pone.0189614

Jenkinson, C., Coulter, A., & Wright, L. (1993). Short form 36 (SF36) health survey questionnaire: normative data for adults of working age. *BMJ, 306*(6890), 1437-1440. doi:10.1136/bmj.306.6890.1437

Johns, M. W. (1991). A new method for measuring daytime sleepiness: the Epworth sleepiness scale. *Sleep, 14*(6), 540-545.

Joosten, S. A., Edwards, B. A., Wellman, A., Turton, A., Skuza, E. M., Berger, P. J., & Hamilton, G. S. (2015). The Effect of Body Position on Physiological Factors that Contribute to Obstructive Sleep Apnea. *Sleep, 38*(9), 1469-1478. doi:10.5665/sleep.4992

Joosten, S. A., O'Driscoll, D. M., Berger, P. J., & Hamilton, G. S. (2014). Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Medicine Reviews, 18*(1), 7-17. doi:10.1016/j.smrv.2013.01.005

Joosten, S. A., O'Driscoll, D. M., Berger, P. J., & Hamilton, G. S. (2014). Supine position related obstructive sleep apnea in adults: pathogenesis and treatment. *Sleep Med Rev, 18*(1), 7-17. doi:10.1016/j.smrv.2013.01.005

Joosten, S. A., Sands, S. A., Edwards, B. A., Hamza, K., Turton, A., Lau, K. K., . . . Hamilton, G. S. (2015). Evaluation of the role of lung volume and airway size and shape in supine-predominant obstructive sleep apnoea patients. *Respirology, 20*(5), 819-827. doi:10.1111/resp.12549

Jordan, A. S., Eckert, D. J., Catcheside, P. G., & McEvoy, R. D. (2003). Ventilatory response to brief arousal from non-rapid eye movement sleep is greater in men than in women. *Am J Respir Crit Care Med, 168*(12), 1512-1519. doi:10.1164/rccm.200302-150OC

Jordan, A. S., & McEvoy, R. D. (2003). Gender differences in sleep apnea: epidemiology, clinical presentation and pathogenic mechanisms. *Sleep Med Rev, 7*(5), 377-389.

Jordan, A. S., McEvoy, R. D., Edwards, J. K., Schory, K., Yang, C. K., Catcheside, P. G., . . . White, D. P. (2004). The influence of gender and upper airway resistance on the ventilatory response to arousal in obstructive sleep apnoea in humans. *J Physiol, 558*(Pt 3), 993-1004. doi:10.1113/jphysiol.2004.064238

Jordan, A. S., McSharry, D. G., & Malhotra, A. (2014). Adult obstructive sleep apnoea. *Lancet, 383*(9918), 736-747. doi:D - NLM: NIHMS524777

Jubran, A. (2015). Pulse oximetry. *Crtical Care, 19*(1).

Kaplan, K. A., Hirshman, J., Hernandez, B., Stefanick, M. L., Hoffman, A. R., Redline, S., . . . Zeitzer, J. M. (2017). When a gold standard isn't so golden: Lack of prediction of subjective sleep quality from sleep polysomnography. *Biol Psychol, 123*, 37-46. doi:10.1016/j.biopsycho.2016.11.010

Koehl, M., Battle, S., & Meerlo, P. (2006). Sex differences in sleep: the response to sleep deprivation and restraint stress in mice. *Sleep, 29*(9), 1224-1231. doi:10.1093/sleep/29.9.1224

Koo, T. K., & Li, M. Y. (2016). A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *Journal of Chiropractic Medicine, 15*(2), 155-163.

Kraiczi, H., Hedner J Fau - Dahlöf, P., Dahlöf P Fau - Ejnell, H., Ejnell H Fau - Carlson, J., & Carlson, J. (1999). Effect of serotonin uptake inhibition on breathing during sleep and daytime symptoms in obstructive sleep apnea. *Sleep, 22*(0161-8105 (Print)), 61-67.

Lai, V., Carberry, J. C., & Eckert, D. J. J. J. D. S. M. (2019). Sleep apnea phenotyping: implications for dental sleep medicine. *6*(2).

Laub, R. R., Tønnesen, P., & Jennum, P. J. (2017). A Sleep Position Trainer for positional sleep apnea: a randomized, controlled trial. *J Sleep Res, 26*(5), 641-650. doi:10.1111/jsr.12530

Lee, S. A., Paek, J. H., Chung, Y. S., & Kim, W. S. (2017). Clinical features in patients with positional obstructive sleep apnea according to its subtypes. *Sleep Breath, 21*(1), 109-117. doi:10.1007/s11325-016-1379-z

Levendowski, D. J., Oksenberg, A., Vicini, C., Penzel, T., Levi, M., & Westbrook, P. R. (2018). A systematic comparison of factors that could impact treatment recommendations for patients with Positional Obstructive Sleep Apnea (POSA). *Sleep Med, 50*, 145-151. doi:10.1016/j.sleep.2018.05.012

Levendowski, D. J., Seagraves, S., Popovic, D., & Westbrook, P. R. (2014). Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea. *Journal of Clinical Sleep Medicine, 10*(8), 863-871. doi:10.5664/jcsm.3956

Levendowski, D. J., Seagraves, S., Popovic, D., & Westbrook, P. R. (2014). Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea. *J Clin Sleep Med, 10*(8), 863-871. doi:10.5664/jcsm.3956

Levendowski, D. J., Veljkovic, B., Seagraves, S., & Westbrook, P. R. (2015). Capability of a neck worn device to measure sleep/wake, airway position, and differentiate benign snoring from obstructive sleep apnea. *J Clin Monit Comput, 29*(1), 53-64. doi:10.1007/s10877-014-9569-3

Lin, C. M., Davidson, T. F., & Ancoli-Israel, S. (2008). Gender differences in obstructive sleep apnea and treatment implications. *Sleep Med Rev, 12*(6), 481-496.

Lindberg, E., Bonsignore, M. R., & Polo-Kantola, P. (2020). Role of menopause and hormone replacement therapy in sleep-disordered breathing. *Sleep Med Rev, 49*. doi:10.1016/j.smrv.2019.101225

Loord, H., & Hultcrantz, E. (2007). Positioner--a method for preventing sleep apnea. *Acta Oto-Laryngologica, 127*(8), 861-868. doi:10.1080/00016480601089390

Lowe, A. A., Ono, T., Ferguson, K. A., Pae, E. K., Ryan, C. F., & Fleetham, J. A. (1996). Cephalometric comparisons of craniofacial and upper airway structure by skeletal subtype and gender in patients with obstructive sleep apnea. *Am J Orthod Dentofacial Orthop, 110*(6), 653-664. doi:10.1016/s0889-5406(96)80043-6

Mador, M. J., Kufel, T. J., Magalang, U. J., Rajesh, S. K., Watwe, V., & Grant, B. J. (2005). Prevalence of positional sleep apnea in patients undergoing polysomnography. *Chest, 128*(4), 2130-2137. doi:10.1378/chest.128.4.2130

Mallampalli, M. P., & Carter, C. L. (2014). Exploring sex and gender differences in sleep health: a Society for Women's Health Research Report. *Journal of Women's Health, 23*(7), 553–562.

Manber, R., Kuo Tf Fau - Cataldo, N., Cataldo N Fau - Colrain, I. M., & Colrain, I. M. (2003). The effects of hormone replacement therapy on sleep-disordered breathing in postmenopausal women: a pilot study. *Sleep, 26*(2), 163-168.

Marklund, M., Persson, M., & Franklin, K. A. (1998). Treatment success with a mandibular advancement device is related to supine-dependent sleep apnea. *Chest, 114*(6), 1630-1635. doi:10.1378/chest.114.6.1630

Marques, M., Genta, P. R., Sands, S. A., Azarbazin, A., de Melo, C., Taranto-Montemurro, L., . . . Wellman, A. (2017). Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse. *Sleep, 40*(3). doi:10.1093/sleep/zsx005

McGee, M. A., Johnson, A. L., & Kay, D. W. (1998). The description of activities of daily living in five centres in England and Wales. Medical Research Council Cognitive Function and Ageing Study. *Age Ageing, 27*(5), 605-613. doi:10.1093/ageing/27.5.605

Mehra, R., Heinzer, R., & Castillo, P. (2021). Current Management of Residual Excessive Daytime Sleepiness Due to Obstructive Sleep Apnea: Insights for Optimizing Patient Outcomes. *Neurology and Therapy, 10*(2), 651-672. doi:10.1007/s40120-021-00289-6

Mirer, A. G., Young T Fau - Palta, M., Palta M Fau - Benca, R. M., Benca Rm Fau - Rasmuson, A., Rasmuson A Fau - Peppard, P. E., & Peppard, P. E. (2017). Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study. *Menopause, 24*(2), 157-162.

Mo, J. H., Lee, C. H., Rhee, C. S., Yoon, I. Y., & Kim, J. W. (2011). Positional dependency in Asian patients with obstructive sleep apnea and its implication for hypertension. *Arch Otolaryngol Head Neck Surg, 137*(8), 786-790. doi:10.1001/archoto.2011.122

Mok, Y., Tan, A., Hsu, P. P., Seow, A., Chan, Y. H., Wong, H. S., . . . Wong, K. K. H. (2020). Comparing treatment effects of a convenient vibratory positional device to CPAP in positional OSA: a crossover randomised controlled trial. *Thorax, 75*(4), 331-337. doi:https://dx.doi.org/10.1136/thoraxjnl-2019-213547

Moyer, C. A., Sonnad, S. S., Garetz, S. L., Helman, J. I., & Chervin, R. D. (2001). Quality of life in obstructive sleep apnea: a systematic review of the literature. *Sleep Med, 2*(6), 477-491.

NICE guidelines. (2021). NICE Evidence Reviews Collection. In *Positional modifiers: Obstructive sleep apnoea/hypopnoea syndrome and obesity hypoventilation syndrome in over 16s: Evidence review H*. London: National Institute for Health and Care Excellence (NICE).

O'Connor, C., Thornley Ks Fau - Hanly, P. J., & Hanly, P. J. (2000). Gender differences in the polysomnographic features of obstructive sleep apnea. *Am J Respir Crit Care Med, 161*(5), 1465.

Oksenberg, A., Arons, E., Greenberg-Dotan, S., Nasser, K., & Radwan, H. (2009). [The significance of body posture on breathing abnormalities during sleep: data analysis of 2077 obstructive sleep apnea patients]. *Harefuah, 148*(5), 304-309, 351, 350.

Oksenberg, A., Silverberg, D., Offenbach, D., & Arons, E. (2006). Positional therapy for obstructive sleep apnea patients: A 6-month follow-up study. *Laryngoscope, 116*(11), 1995-2000. doi:10.1097/01.mlg.0000237674.66716.a7

Olaithe, M., Bucks, R. S., Hillman, D. R., & Eastwood, P. R. (2018). Cognitive deficits in obstructive sleep apnea: Insights from a meta-review and comparison with deficits observed in COPD, insomnia, and sleep deprivation. *Sleep Med Rev, 38*, 39-49. doi:10.1016/j.smrv.2017.03.005

Osman, A. M., Carter, S. G., Carberry, J. C., & Eckert, D. J. (2018). Obstructive sleep apnea: current perspectives. *Nat Sci Sleep*(1179-1608 (Print)). doi:10.2147/NSS.S124657

Oulhaj, A., Al Dhaheri, S., Su, B. B., & Al-Houqani, M. (2017). Discriminating between positional and non-positional obstructive sleep apnea using some clinical characteristics. *Sleep Breath, 21*(4), 877-884. doi:10.1007/s11325-017-1499-0

Patel, S., Kon, S. S., Nolan, C. M., Simonds, A. K., Morrell, M. J., Man, W. D.-C., & Barker, R. E. (2017). Minimum clinically important difference of the Epworth Sleepiness Scale. *European Respiratory Journal, 50*.

Patil, S. P., Ayappa, I. A., Caples, S. M., Kimoff, R. J., Patel, S. R., & Harrod, C. G. (2019). Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. *J Clin Sleep Med, 15*(2), 301-334.

Pengo, M. F., Xiao, S., Ratneswaran, C., Reed, K., Shah, N., Chen, T., . . . Steier, J. (2016). Randomised sham-controlled trial of transcutaneous electrical stimulation in obstructive sleep apnoea. *Thorax, 71*(10), 923-931.

Pépin, J. L., Georgiev, O., Tiholov, R., Attali, V., Verbraecken, J., Buyse, B., . . . Dauvilliers, Y. (2021). Pitolisant for Residual Excessive Daytime Sleepiness in OSA Patients Adhering to CPAP: A Randomized Trial. *Chest, 159*(4), 1598-1609.

Phillips, C. L., Grunstein Rr Fau - Darendeliler, M. A., Darendeliler Ma Fau - Mihailidou, A. S., Mihailidou As Fau - Srinivasan, V. K., Srinivasan Vk Fau - Yee, B. J., Yee Bj Fau - Marks, G. B., . . . Cistulli, P. A. (2013). Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. *Am J Respir Crit Care Med, 187*(8), 879-887.

Pickett, C. K., Regensteiner Jg Fau - Woodard, W. D., Woodard Wd Fau - Hagerman, D. D., Hagerman Dd Fau - Weil, J. V., Weil Jv Fau - Moore, L. G., & Moore, L. G. (1985). Progestin and estrogen reduce sleep-disordered breathing in postmenopausal women. *J Appl Physiol, 66*(4), 1656-1661.

Portier, F., Portmann, A., Czernichow, P., Vascaut, L., Devin, E., Benhamou, D., . . . Muir, J. F. (2000). Evaluation of home versus laboratory polysomnography in the diagnosis of sleep apnea syndrome. *Am J Respir Crit Care Med, 162*(3 Pt 1), 814-818. doi:10.1164/ajrccm.162.3.9908002

Purcell, S. M., Manoach, D. S., Demanuele, C., Cade, B. E., Mariani, S., Cox, R., . . . Stickgold, R. (2017). Characterizing sleep spindles in 11,630 individuals from the National Sleep Research Resource. *Nat Commun, 8*, 15930. doi:10.1038/ncomms15930

Rabin, R., & de Charro, F. (2001). EQ-5D: a measure of health status from the EuroQol Group. *Ann Med, 33*(5), 337-343.

Randerath, W., Verbraecken, J., de Raaff, C. A. L., Hedner, J., Herkenrath, S., Hohenhorst, W., . . . Wijkstra, P. (2021). European Respiratory Society guideline on non-CPAP therapies for obstructive sleep apnoea. *European Respiratory Review, 30*(162), 210200. doi:10.1183/16000617.0200-2021

Ratnavadivel, R., Stadler, D., Windler, S., Bradley, J., Paul, D., McEvoy, R. D., & Catcheside, P. G. (2009). Upper airway function and arousability to ventilatory challenge in slow wave versus stage 2 sleep in obstructive sleep apnoea. *Thorax, 65*(2), 107-112. doi:10.1136/thx.2008.112953

Ravesloot, M. J., Frank, M. H., van Maanen, J. P., Verhagen, E. A., de Lange, J., & de Vries, N. (2016). Positional OSA part 2: retrospective cohort analysis with a new classification system (APOC). *Sleep Breath, 20*(2), 881-888. doi:10.1007/s11325-015-1206-y

Ravesloot, M. J., van Maanen, J. P., Dun, L., & de Vries, N. (2013). The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. *Sleep Breath, 17*(1), 39-49. doi:10.1007/s11325-012-0683-5

Ravesloot, M. J. L., White, D., Heinzer, R., Oksenberg, A., & Pépin, J.-L. (2017). Efficacy of the New Generation of Devices for Positional Therapy for Patients With Positional Obstructive Sleep

Apnea: A Systematic Review of the Literature and Meta-Analysis. *Journal of Clinical Sleep Medicine, 13*(6), 813-824. doi:10.5664/jcsm.6622

Redline, S., Kirchner Hl Fau - Quan, S. F., Quan Sf Fau - Gottlieb, D. J., Gottlieb Dj Fau - Kapur, V., Kapur V Fau - Newman, A., & Newman, A. (2004). The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med, 164*(4), 406-418.

Redline, S., Kirchner, H. L., Quan, S. F., Gottlieb, D. J., Kapur, V., & Newman, A. (2004). The effects of age, sex, ethnicity, and sleep-disordered breathing on sleep architecture. *Arch Intern Med, 164*(4), 406-418. doi:10.1001/archinte.164.4.406

Rosenberg, R., Schweitzer, P. K., Steier, J., & Pepin, J. L. (2021). Residual excessive daytime sleepiness in patients treated for obstructive sleep apnea: guidance for assessment, diagnosis, and management. *Postgrad Med, 133*(7), 772-783.

Roth, T., Walsh Jk Fau - Krystal, A., Krystal A Fau - Wessel, T., Wessel T Fau - Roehrs, T. A., & Roehrs, T. A. (2005). An evaluation of the efficacy and safety of eszopiclone over 12 months in patients with chronic primary insomnia. *Sleep Med, 6*(6), 487-495.

Saigusa, H., Suzuki, M., Higurashi, N., & Kodera, K. (2009). Three-dimensional morphological analyses of positional dependence in patients with obstructive sleep apnea syndrome. *Anesthesiology, 110*(4), 885-890. doi:10.1097/ALN.0b013e31819b5d57

Sands, S. A., Terrill, P. I., Edwards, B. A., Taranto Montemurro, L., Azarbarzin, A., Marques, M., . . . Wellman, A. (2018). Quantifying the Arousal Threshold Using Polysomnography in Obstructive Sleep Apnea. LID - 10.1093/sleep/zsx183 [doi] LID - zsx183. *Sleep, 41*(1). doi:10.1093/sleep/zsx183.

Scarlata, S., Rossi Bartoli, I., Santangelo, S., Giannunzio, G., Pedone, C., & Antonelli Incalzi, R. (2016). Short-term effects of a vibrotactile neck-based treatment device for positional obstructive sleep apnea: preliminary data on tolerability and efficacy. *J Thorac Dis, 8*(7), 1820-1824. doi:10.21037/jtd.2016.04.69

Schumm, W. R., Higgins, M., Lockett, L., Huang, S., Abdullah, N., Asiri, A., . . . Review, F. (2017). Does dividing the range by four provide an accurate estimate of a standard deviation in family science research? A teaching editorial. In (Vol. 53, pp. 1-23): Taylor & Francis.

Schwab, R. J., Pasirstein, M., Pierson, R., Mackley, A., Hachadoorian, R., Arens, R., . . . Pack, A. I. (2003). Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. *Am J Respir Crit Care Med, 168*(5), 522-530. doi:10.1164/rccm.200208-866OC

Schweitzer, P. K., Rosenberg, R., Zammit, G. K., Gotfried, M., Chen, D., Carter, L. P., . . . Strohl, K. P. (2019). Solriamfetol for Excessive Sleepiness in Obstructive Sleep Apnea (TONES 3). A Randomized Controlled Trial. *Am J Respir Crit Care Med, 199*(11), 1421-1431.

Sforza, E., Bacon, W., Weiss, T., Thibault, A., Petiau, C., & Krieger, J. (2000). Upper Airway Collapsibility and Cephalometric Variables in Patients with Obstructive Sleep Apnea. *American journal of respiratory and critical care medicine, 161*(2), 347-352. doi:10.1164/ajrccm.161.2.9810091

Sforza, E., Petiau, C., Weiss, T., Thibault, A., & Krieger, J. (1999). Pharyngeal critical pressure in patients with obstructive sleep apnea syndrome. Clinical implications. *Am J Respir Crit Care Med, 159*(1), 149-157.

Shepertycky, M. R., Banno, K., & Kryger, M. H. (2009). Differences between men and women in the clinical presentation of patients diagnosed with obstructive sleep apnea syndrome. *Sleep, 28*(3), 309-314.

Shin, W., Jen, R., Li, Y., & Malhotra, A. (2016). Tailored treatment strategies for obstructive sleep apnea. *Respiratory Investigation, 54*(1), 2-7. doi:10.1016/j.resinv.2015.09.007

Silva, G. E., Goodwin, J. L., Vana, K. D., & Quan, S. F. (2016). Obstructive Sleep Apnea and Quality of Life: Comparison of the SAQLI, FOSQ, and SF-36 Questionnaires. *Southwest J Pulm Crit Care, 13*(3), 137-149. doi:10.13175/swjpcc082-16

Sohmer, H. (2017). Soft Tissue Conduction: Review, Mechanisms, and Implications. *Trends Hear, 21*, 2331216517734087. doi:10.1177/2331216517734087

Steier, J., Seymour, J., Rafferty, G. F., Jolley, C. J., Solomon, E., Luo, Y., . . . Moxham, J. (2011). Continuous transcutaneous submental electrical stimulation in obstructive sleep apnea: a feasibility study. *Chest, 140*(4), 998-1007.

Stradling, J., Smith, D., Radulovacki, M., & Carley, D. (2003). Effect of ondansetron on moderate obstructive sleep apnoea, a single night, placebo-controlled trial. *J Sleep Res, 12*(2), 169-170.

Strollo Jr, P. J., Soose, R. J., Maurer, J. T., de Vries, N., Cornelius, J., Froymovich, O., . . . Gillespie, M. B. (2014). Upper-airway stimulation for obstructive sleep apnea. *New England Journal of Medicine, 370*(2), 139-149.

Sullivan, C., Berthon-Jones, M., Issa, F., & Eves, L. (1981). Reversal of obstructive sleep apnoea by continuous positive airway pressure applied through the nares. *The Lancet, 317*(8225), 862-865.

Sutherland, K., Takaya, H., Qian, J., Petocz, P., Ng, A. T., & Cistulli, P. A. (2015). Oral Appliance Treatment Response and Polysomnographic Phenotypes of Obstructive Sleep Apnea. *J Clin Sleep Med, 11*(8), 861-868.

Suzuki, M., Funayama, Y., Homma, M., Shibasaki, K., Furukawa, T., & Yosizawa, T. (2021). Effect of position therapy and oral devices on sleep parameters in patients with obstructive sleep apnea. *European archives of oto-rhino-laryngology, 278*(11), 4545-4550. doi:https://dx.doi.org/10.1007/s00405-021-06817-2

Thomas, R. J. (2003). Arousals in sleep-disordered breathing: patterns and implications. *Sleep, 26*(8), 1042-1047.

Trinder, J., Allen, N., Kleiman, J., Kralevski, V., Kleverlaan, D., Anson, K., & Kim, Y. (2003). On the nature of cardiovascular activation at an arousal from sleep. *Sleep, 26*(5), 543-551.

Vagiakis, E., Kapsimalis F Fau - Lagogianni, I., Lagogianni I Fau - Perraki, H., Perraki H Fau - Minaritzoglou, A., Minaritzoglou A Fau - Alexandropoulou, K., Alexandropoulou K Fau - Roussos, C., . . . Kryger, M. (2006). Gender differences on polysomnographic findings in Greek subjects with obstructive sleep apnea syndrome. *Sleep Med, 7*(5), 424-430.

van Kesteren, E. R., & Hilgevoord, A. A. J. (2015). The Contribution of Head Position to the Apnea/Hypopnea Index in Patients with Position-Dependent Obstructive Sleep Apnea. In N. de Vries, M. Ravesloot, & J. P. van Maanen (Eds.), *Positional Therapy in Obstructive Sleep Apnea* (pp. 65-79). Cham: Springer International Publishing.

Van Kesteren, E. R., van Maanen, J. P., Hilgevoord, A. A., Laman, D. M., & de Vries, N. (2011). Quantitative effects of trunk and head position on the apnea hypopnea index in obstructive sleep apnea. *Sleep, 34*(8), 1075-1081.

van Maanen, J. P., & de Vries, N. (2014). Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. *Sleep, 37*(7), 1209-1215. doi:10.5665/sleep.3840

van Maanen, J. P., Meester, K. A., Dun, L. N., Koutsourelakis, I., Witte, B. I., Laman, D. M., . . . de Vries, N. (2013). The sleep position trainer: a new treatment for positional obstructive sleep apnoea. *Sleep Breath, 17*(2), 771-779. doi:10.1007/s11325-012-0764-5

van Maanen, J. P., Richard, W., Van Kesteren, E. R., Ravesloot, M. J., Laman, D. M., Hilgevoord, A. A., & de Vries, N. (2012). Evaluation of a new simple treatment for positional sleep apnoea patients. *J Sleep Res, 21*(3), 322-329. doi:10.1111/j.1365-2869.2011.00974.x

Vgontzas, A. N., Zoumakis, E., Bixler, E. O., Lin, H. M., Follett, H., Kales, A., & Chrousos, G. P. (2004). Adverse effects of modest sleep restriction on sleepiness, performance, and inflammatory cytokines. *J Clin Endocrinol Metab, 89*(5), 2119-2126. doi:10.1210/jc.2003-031562

Victores, A. J., Hamblin, J., Gilbert, J., Switzer, C., & Takashima, M. (2014). Usefulness of sleep endoscopy in predicting positional obstructive sleep apnea. *Otolaryngol Head Neck Surg, 150*(3), 487-493. doi:10.1177/0194599813517984

Walsh, J. H., Leigh, M. S., Paduch, A., Maddison, K. J., Armstrong, J. J., Sampson, D. D., . . . Eastwood, P. R. (2008). Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea. *Sleep, 31*(11), 1543-1549. doi:10.1093/sleep/31.11.1543

Walsleben, J. A., Kapur, V. K., Newman, A. B., Shahar, E., Bootzin, R. R., Rosenberg, C. E., . . . Nieto, F. J. (2004). Sleep and reported daytime sleepiness in normal subjects: the Sleep Heart Health Study. *Sleep, 27*(2), 293-298. doi:10.1093/sleep/27.2.293

Wan, X., Wang, W., Liu, J., & Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol, 14*, 135. doi:10.1186/1471-2288-14-135

Ware, J. E., Jr., & Sherbourne, C. D. (1992). The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care, 30*(6), 473-483.

Weaver, T. E., Laizner, A. M., Evans, L. K., Maislin, G., Chugh, D. K., Lyon, K., . . . Dinges, D. F. (1997). An instrument to measure functional status outcomes for disorders of excessive sleepiness. *Sleep, 20*(10), 835-843.

Weaver, T. E., Menno, D. M., Bron, M., Crosby, R. D., Morris, S., & Mathias, S. D. (2021). Determination of thresholds for minimally important difference and clinically important response on the functional outcomes of sleep questionnaire short version in adults with narcolepsy or obstructive sleep apnea. *Sleep Breath, 25*(3), 1707-1715. doi:10.1007/s11325-020-02270-3

Wellman, A., Eckert, D. J., Jordan, A. S., Edwards, B. A., Passaglia, C. L., Jackson, A. C., . . . White, D. P. (2011). A method for measuring and modeling the physiological traits causing obstructive sleep apnea. *Journal of Applied Physiology, 110*(6), 1627-1637. doi:10.1152/japplphysiol.00972.2010

Wellman, A., Edwards, B. A., Sands, S. A., Owens, R. L., Nemati, S., Butler, J., . . . White, D. P. (2013). A simplified method for determining phenotypic traits in patients with obstructive sleep apnea. *Journal of Applied Physiology, 114*(7), 911-922. doi:10.1152/japplphysiol.00747.2012

Wellman, A., Malhotra, A., Jordan, A. S., Stevenson, K. E., Gautam, S., & White, D. P. (2008). Effect of oxygen in obstructive sleep apnea: Role of loop gain. *Respiratory Physiology & Neurobiology, 162*(2), 144-151. doi:10.1016/j.resp.2008.05.019

Wheaton, A. G., Perry, G. F., Chapman, D., & Croft, J. B. (2012). Sleep disordered breathing and depression among U.S. adults: National Health and Nutrition Examination Survey, 2005-2008. *Sleep, 35*(4), 461-467.

White, D. P. (2016). Pharmacologic Approaches to the Treatment of Obstructive Sleep Apnea. *Sleep Med Clin, 11*(2), 203-212.

White, D. P., & Younes, M. K. (2012). Obstructive sleep apnea. *Compr Physiol, 2*(4), 2541-2594. doi:10.1002/cphy.c110064

Wimms, A. J., Kelly, J. L., Turnbull, C. D., McMillan, A., Craig, S. E., O'Reilly, J. F., . . . Morrell, M. J. (2020). Continuous positive airway pressure versus standard care for the treatment of people with mild obstructive sleep apnoea (MERGE): a multicentre, randomised controlled trial. *Lancet Respir Med, 8*(4), 349-358. doi:10.1016/s2213-2600(19)30402-3

Wozniak, D. R., Lasserson, T. J., & Smith, I. (2014). Educational, supportive and behavioural interventions to improve usage of continuous positive airway pressure machines in adults with obstructive sleep apnoea. *Cochrane Database of Systematic Reviews, 1*, Cd007736. doi:10.1002/14651858.CD007736.pub2

Yingjuan, M., Siang, W. H., Leong Alvin, T. K., & Poh, H. P. (2019). Positional Therapy for Positional Obstructive Sleep Apnea. *Sleep Medicine Clinics, 14*(1), 119-133. doi:10.1016/j.jsmc.2018.10.003

Younes, M. (2004). Role of arousals in the pathogenesis of obstructive sleep apnea. *Am J Respir Crit Care Med, 169*(5), 623-633. doi:10.1164/rccm.200307-1023OC

Young, T., Finn L Fau - Austin, D., Austin D Fau - Peterson, A., & Peterson, A. (2003). Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med, 167*(9), 1181-1185.

Zaghi, S., Holty, J. E., Certal, V., Abdullatif, J., Guilleminault, C., Powell, N. B., . . . Camacho, M. (2016). Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. *JAMA Otolaryngol Head Neck Surg, 142*(1), 58-66.

Zhou, X., Zhou, B., Li, Z., Lu, Q., Li, S., Pu, Z., & Luo, F. (2021). Gender differences of clinical and polysomnographic findings with obstructive sleep apnea syndrome. (2045-2322 (Electronic)).

Zhu, K., Bradley, T. D., Patel, M., & Alshaer, H. (2017). Influence of head position on obstructive sleep apnea severity. *Sleep Breath, 21*(4), 821-828. doi:10.1007/s11325-017-1525-2

Zinchuk, A., & Yaggi, H. K. (2020). Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. *Chest, 157*(2), 403-420.

Zinchuk, A. V., Gentry, M. J., Concato, J., & Yaggi, H. K. (2017). Phenotypes in obstructive sleep apnea: A definition, examples and evolution of approaches. *Sleep Med Rev, 35*(1532-2955 (Electronic)), 35:113. doi:0.1016/j.smrv.2016.10.002.

Appendix 1: Permission for Figure 1.1 and 1.2

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	05-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1174284-1		
ISSN	1931-3543	Publisher	AMERICAN COLLEGE OF CHEST PHYSICIANS
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Chest	Publication Type	e-Journal
Article Title	Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. : A Challenge and Opportunity for Precision Medicine	Start Page	403
		End Page	420
		Issue	2
		Volume	157
Author/Editor	American College of Chest Physicians.	URL	http://search.ebscohost.com/direct.asp?db=hch&jid=%221G4%22&scope=site
Date	01/01/1965		
Language	English		
Country	United States of America		
Rightsholder	Elsevier Science & Technology Journals		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	2	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof. Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A

The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	figure 1 and 2	Title of the article/chapter the portion is from	Phenotypic Subtypes of OSA: A Challenge and Opportunity for Precision Medicine. : A Challenge and Opportunity for Precision Medicine
Editor of portion(s)	Yaggi, Henry K.; Zinchuk, Andrey	Author of portion(s)	Yaggi, Henry K.; Zinchuk, Andrey
Volume of serial or monograph	157	Issue, if republishing an article from a serial	2
Page or page range of portion	403-420	Publication date of portion	2020-02-01

RIGHTSHOLDER TERMS AND CONDITIONS

Elsevier publishes Open Access articles in both its Open Access journals and via its Open Access articles option in subscription journals, for which an author selects a user license permitting certain types of reuse without permission. Before proceeding please check if the article is Open Access on http://www.sciencedirect.com and refer to the user license for the individual article. Any reuse not included in the user license terms will require permission. You must always fully and appropriately credit the author and source. If any part of the material to be used (for example, figures) has appeared in the Elsevier publication for which you are seeking permission, with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder. Please contact permissions@elsevier.com with any queries.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set

Appendix 2: Permission for Figure 1.3

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1156829-2	Publisher	Springer International Publishing
ISBN-13	978-3-319-09625-4	Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Positional Therapy in Obstructive Sleep Apnea	Rightsholder	Springer
		Publication Type	Book
Article Title	The Contribution of Head Position to the Apnea/Hypopnea Index in Patients with Position-Dependent Obstructive Sleep Apnea	Start Page	65
		End Page	79
		URL	http://link.springer.com/10.1007/978-3-319-09626-1
Date	01/01/2015		
Language	English		
Country	Switzerland		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 1 A	Title of the article/chapter the portion is from	The Contribution of Head Position to the Apnea/Hypopnea Index in Patients with Position-Dependent Obstructive Sleep Apnea
Editor of portion(s)	van Kesteren, Ellen R.; Hilgevoord, Anthony A. J.	Author of portion(s)	van Kesteren, Ellen R.; Hilgevoord, Anthony A. J.
Volume of serial or monograph	N/A	Issue, if republishing an article from a serial	N/A
Page or page range of portion	65-79	Publication date of portion	2015-01-01

RIGHTSHOLDER TERMS AND CONDITIONS

A maximum of 10% of the content may be licensed for republication. The user is responsible for identifying and seeking separate licenses for any third party materials that are identified anywhere in the work. Without a separate license, such third party materials may not be reused.
If you are placing a request on behalf of/for a corporate organization, please use RightsLink. For further information visit http://www.nature.com/reprints/permission-requests.html and https://www.springer.com/gp/rights-permissions/obtaining-permissions/882. If the content you are requesting to reuse is under a CC-BY 4.0 licence (or previous version), you do not need to seek permission from Springer Nature for this reuse as long as you provide appropriate credit to the original publication. https://creativecommons.org/licenses/by/4.0/

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3.

Appendix 3: Permission for Figure 1.4

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173904-1		
ISSN	0161-8105	Publisher	Oxford University Press
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Sleep	Rightsholder	Oxford University Press - Journals
Article Title	Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea.	Publication Type	Journal
		Start Page	1543
		End Page	1549
Author/Editor	Sleep Research Society	Issue	11
Date	01/01/1978	Volume	31
Language	English, English		
Country	United States of America		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	Yes
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figrure 5	Title of the article/chapter the portion is from	Effect of body posture on pharyngeal shape and size in adults with and without obstructive sleep apnea.
Editor of portion(s)	Walsh, Jennifer H; Leigh, Matthew S; Paduch, Alexandre; Maddison, Kathleen J; Armstrong, Julian J; Sampson, David D; Hillman, David R; Eastwood, Peter R	Author of portion(s)	Walsh, Jennifer H; Leigh, Matthew S; Paduch, Alexandre; Maddison, Kathleen J; Armstrong, Julian J; Sampson, David D; Hillman, David R; Eastwood, Peter R
Volume of serial or monograph	31	Issue, if republishing an article from a serial	11
Page or page range of portion	1543-1549	Publication date of portion	2008-11-01

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

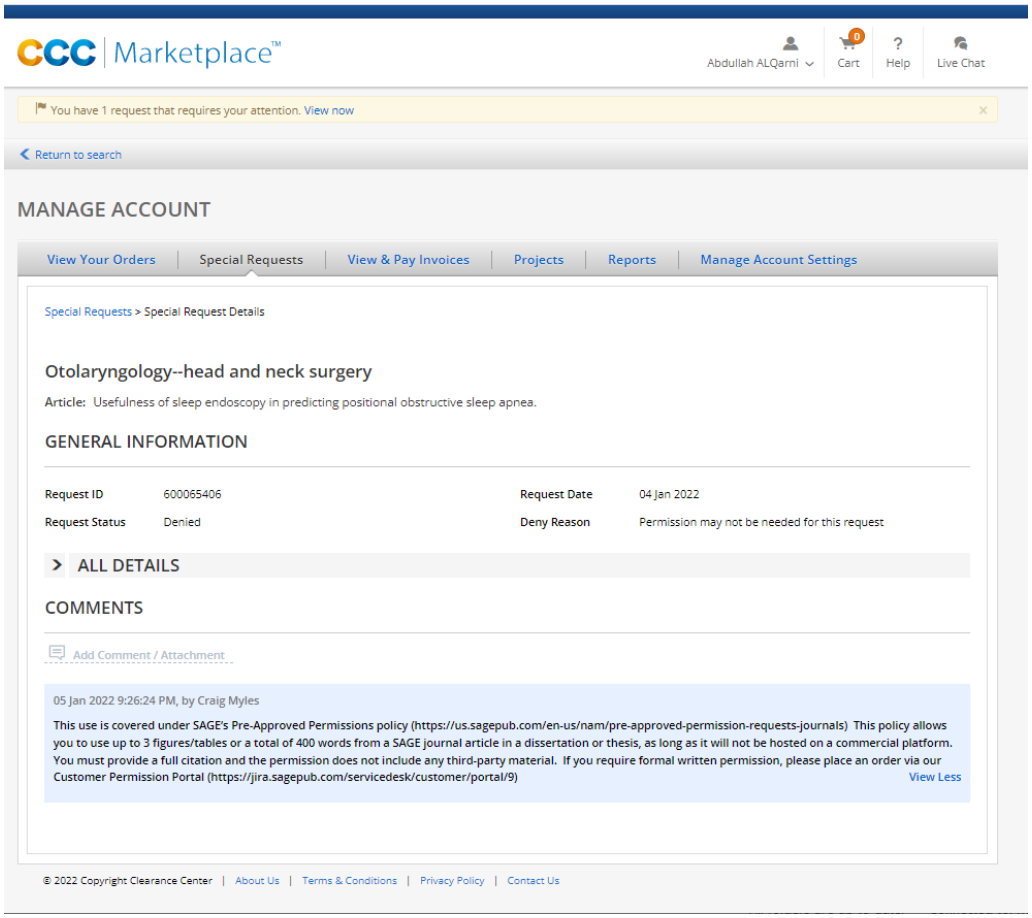
3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3. Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii) is subject to any and all limitations and restrictions (such as, but not limited to, limitations on duration of use or circulation) included in the Order Confirmation or invoice and/or in these terms and conditions. Upon completion of the licensed use, User shall either secure a new permission for further use of the Work(s) or immediately cease any new use of the Work(s) and shall render inaccessible (such as by deleting or by removing or severing links or other locators) any further copies of the Work (except for copies printed on paper in accordance with this license and still in User's stock at the end of such period).

Appendix 4: Permission for Figure 1.5



Appendix 5: Permission for Figure 1.6

CCC Marketplace™

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173909-1		
ISSN	1550-9109	Publisher	Oxford University Press
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Sleep	Rightsholder	Oxford University Press - Journals
Article Title	Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse.	Publication Type	e-Journal
		Issue	3
		Volume	40
		URL	http://bibpurl.oclc.org/web/21399
Author/Editor	American Academy of Sleep Medicine., Sleep Research Society., Associated Professional Sleep Societies.		
Date	01/01/1978		
Language	English		
Country	United States of America		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	2	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College Lonodn
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A

The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 2 and 4	Title of the article/chapter the portion is from	Effect of Sleeping Position on Upper Airway Patency in Obstructive Sleep Apnea Is Determined by the Pharyngeal Structure Causing Collapse.
Editor of portion(s)	Marques, Melania; Genta, Pedro R; Sands, Scott A; Azarbazin, Ali; de Melo, Camila; Taranto-Montemurro, Luigi; White, David P; Wellman, Andrew	Author of portion(s)	Marques, Melania; Genta, Pedro R; Sands, Scott A; Azarbazin, Ali; de Melo, Camila; Taranto-Montemurro, Luigi; White, David P; Wellman, Andrew
Volume of serial or monograph	40		
Page or page range of portion	1550-9109	Issue, if republishing an article from a serial	3
		Publication date of portion	2017-03-01

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3.

Appendix 6: Permission for Figure 1.7

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173920-1		
ISSN	1522-1709	Publisher	SPRINGER-VERLAG
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Sleep & breathing : international journal of the science and practice of sleep medicine	Publication Type	e-Journal
		Start Page	637
		End Page	644
Article Title	A promising concept of combination therapy for positional obstructive sleep apnea.	Issue	2
		Volume	19
		URL	http://www.thieme-connect.com/ejournals/toc/sbr
Author/Editor	American Sleep Apnea Association., Sleep Disorders Dental Society (U.S.), American Academy of Dental Sleep Medicine.		
Date	01/01/1997		
Language	English		
Country	Germany		
Rightsholder	Springer Nature BV		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 2	Title of the article/chapter the portion is from	A promising concept of combination therapy for positional obstructive sleep apnea.
Editor of portion(s)	De Backer, Wilfried A.; Vroegop, Anneclaire V.; Willemen, Marc; Verbraecken, Johan A.; de Vries, Nico; Van de Heyning, Paul H.; Braem, Marc J.; Vanderveken, Olivier M.; Dieltjens, Marijke; Wouters, Kristien; Verbruggen, Annelies E.	Author of portion(s)	De Backer, Wilfried A.; Vroegop, Anneclaire V.; Willemen, Marc; Verbraecken, Johan A.; de Vries, Nico; Van de Heyning, Paul H.; Braem, Marc J.; Vanderveken, Olivier M.; Dieltjens, Marijke; Wouters, Kristien; Verbruggen, Annelies E.
Volume of serial or monograph	19	Publication date of portion	2015-05-01
Page or page range of portion	637-644		

RIGHTSHOLDER TERMS AND CONDITIONS

If you are placing a request on behalf of/for a corporate organization, please use RightsLink. For further information visit http://www.nature.com/reprints/permission-requests.html and https://www.springer.com/gp/rights-permissions/obtaining-permissions/882. If the content you are requesting to reuse is under a CC-BY 4.0 licence (or previous version), you do not need to seek permission from Springer Nature for this reuse as long as you provide appropriate credit to the original publication. https://creativecommons.org/licenses/by/4.0/

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are

CCC Marketplace™

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173918-1		
ISSN	1532-3064	Publisher	W.B. SAUNDERS CO. LTD.
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Respiratory medicine	Rightsholder	Elsevier Science & Technology Journals
Article Title	A new postural device for the treatment of positional obstructive sleep apnea. A pilot study.	Publication Type	e-Journal
		Start Page	111
		End Page	117
Author/Editor	British Thoracic Society.	Volume	151
Date	01/01/1989	URL	http://www.harcourt-international.com/journals
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	Yes
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 1 a, b, c	Title of the article/chapter the portion is from	A new postural device for the treatment of positional obstructive sleep apnea. A pilot study.
Editor of portion(s)	Armas, Laura Hidalgo; Barbé, Ferrán; Carrillo, Juan; Cordero-Guevara, José; Durán-Cantolla, Joaquín; Durán-Carro, Joaquín; Egea, Carlos; Inglés, Sandra; Manjón, Jose Luis; Sanchez-de-la-Torre, Manuel; Turino, Cecilia; Ullate, Jorge; Vaca, Rafaela	Author of portion(s)	Armas, Laura Hidalgo; Barbé, Ferrán; Carrillo, Juan; Cordero-Guevara, José; Durán-Cantolla, Joaquín; Durán-Carro, Joaquín; Egea, Carlos; Inglés, Sandra; Manjón, Jose Luis; Sanchez-de-la-Torre, Manuel; Turino, Cecilia; Ullate, Jorge; Vaca, Rafaela
Volume of serial or monograph	151	Issue, if republishing an article from a serial	N/A
Page or page range of portion	111-117	Publication date of portion	2019-05-01

RIGHTSHOLDER TERMS AND CONDITIONS

Elsevier publishes Open Access articles in both its Open Access journals and via its Open Access articles option in subscription journals, for which an author selects a user license permitting certain types of reuse without permission. Before proceeding please check if the article is Open Access on http://www.sciencedirect.com and refer to the user license for the individual article. Any reuse not included in the user license terms will require permission. You must always fully and appropriately credit the author and source. If any part of the material to be used (for example, figures) has appeared in the Elsevier publication for which you are seeking permission, with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder. Please contact permissions@elsevier.com with any queries.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of

CCC Marketplace™

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173928-1		
ISSN	1556-4088	Publisher	Elsevier
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Sleep medicine clinics	Publication Type	e-Journal
Article Title	Positional Therapy for Positional Obstructive Sleep Apnea.	Start Page	119
		End Page	133
Date	01/01/2006	Issue	1
Language	English	Volume	14
Country	United States of America	URL	http://www.mdconsult.com/public/search?search_type=journal&j_sort=pub_date&j_issn=1556-407X
Rightsholder	Elsevier Science & Technology Journals		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary MOrrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	figure 3	**Title of the article/chapter the portion is from**	Positional Therapy for Positional Obstructive Sleep Apnea.
Editor of portion(s)	Yingjuan, Mok; Siang, Wong Hang; Poh, Hsu Pon; Leong Alvin, Tan Kah	**Author of portion(s)**	Yingjuan, Mok; Siang, Wong Hang; Poh, Hsu Pon; Leong Alvin, Tan Kah
Volume of serial or monograph	14	**Issue, if republishing an article from a serial**	1
Page or page range of portion	119-133	**Publication date of portion**	2019-03-01

RIGHTSHOLDER TERMS AND CONDITIONS

Elsevier publishes Open Access articles in both its Open Access journals and via its Open Access articles option in subscription journals, for which an author selects a user license permitting certain types of reuse without permission. Before proceeding please check if the article is Open Access on http://www.sciencedirect.com and refer to the user license for the individual article. Any reuse not included in the user license terms will require permission. You must always fully and appropriately credit the author and source. If any part of the material to be used (for example, figures) has appeared in the Elsevier publication for which you are seeking permission, with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder. Please contact permissions@elsevier.com with any queries.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3. Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii)

CCC Marketplace™

Order Date	05-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1174285-2	Publisher	AMERICAN ACADEMY OF SLEEP MEDICINE
ISSN	15509397	Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	JOURNAL OF CLINICAL SLEEP MEDICINE. ONLINE	Rightsholder	American Academy of Sleep Medicine
Article Title	Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device.	Publication Type	Other
		Start Page	376
		End Page	383
		Issue	4
		Volume	7
Author/Editor	American Academy of Sleep Medicine.		
Date	01/01/2005		
Language	English		
Country	United States of America		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A

The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 1	Title of the article/chapter the portion is from	Accurate position monitoring and improved supine-dependent obstructive sleep apnea with a new position recording and supine avoidance device.
Editor of portion(s)	Bignold, James J; Mercer, Jeremy D; Antic, Nick A; McEvoy, R Doug; Catcheside, Peter G	Author of portion(s)	Bignold, James J; Mercer, Jeremy D; Antic, Nick A; McEvoy, R Doug; Catcheside, Peter G
Volume of serial or monograph	7	Issue, if republishing an article from a serial	4
Page or page range of portion	376-383	Publication date of portion	2011-08-15

RIGHTSHOLDER TERMS AND CONDITIONS

Figures/tables/diagrams cannot be modified.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	05-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1174285-4		
ISSN	15509397	Publisher	AMERICAN ACADEMY OF SLEEP MEDICINE
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	JOURNAL OF CLINICAL SLEEP MEDICINE. ONLINE	Rightsholder	American Academy of Sleep Medicine
Article Title	Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea.	Publication Type	Other
		Start Page	863
		End Page	871
		Issue	8
Author/Editor	American Academy of Sleep Medicine.	Volume	10
Date	01/01/2005		
Language	English		
Country	United States of America		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	United States and Canada
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
		Copies for the disabled?	No
Format (select all that apply)	Electronic	Minor editing privileges?	Yes
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	figure 1	**Title of the article/chapter the portion is from**	Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea
Editor of portion(s)	Levendowski, Daniel J; Seagraves, Sean; Popovic, Djordje; Westbrook, Philip R	**Author of portion(s)**	Levendowski, Daniel J; Seagraves, Sean; Popovic, Djordje; Westbrook, Philip R
Volume of serial or monograph	10		
Page or page range of portion	863-871	**Issue, if republishing an article from a serial**	8
		Publication date of portion	2014-08-15

RIGHTSHOLDER TERMS AND CONDITIONS

Figures/tables/diagrams cannot be modified.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3. Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including the editions and product family specified in the license), (ii) is non-exclusive and non-transferable and (iii) is subject to any and all limitations and restrictions (such as, but not limited to, limitations on duration of use or circulation) included in the Order Confirmation or invoice and/or in these terms and conditions.

Appendix 7: Permission for Figure 1.8 and Table 1.1

CCC Marketplace™

This is a License Agreement between Abdullah Saad S ALQarni ("User") and Copyright Clearance Center, Inc. ("CCC") on behalf of the Rightsholder identified in the order details below. The license consists of the order details, the CCC Terms and Conditions below, and any Rightsholder Terms and Conditions which are included below.

All payments must be made in full to CCC in accordance with the CCC Terms and Conditions below.

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173926-1		
ISSN	2213-2600	Publisher	Elsevier
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	The lancet respiratory medicine	Publication Type	Journal
		Start Page	533
Article Title	Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis.	End Page	543
		Issue	6
		Volume	7
Date	01/01/2013		
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		
Rightsholder	Elsevier Science & Technology Journals		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	2	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	Yes
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	table 3 and figure 3	**Title of the article/chapter the portion is from**	Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis.
Editor of portion(s)	Murray, Brian J; Mekhael, Anastasia; Kendzerska, Tetyana; Jairam, Trevor; Im, James; Boulos, Mark I	**Author of portion(s)**	Murray, Brian J; Mekhael, Anastasia; Kendzerska, Tetyana; Jairam, Trevor; Im, James; Boulos, Mark I
Volume of serial or monograph	7	**Issue, if republishing an article from a serial**	6
Page or page range of portion	533-543	**Publication date of portion**	2019-06-01

RIGHTSHOLDER TERMS AND CONDITIONS

Elsevier publishes Open Access articles in both its Open Access journals and via its Open Access articles option in subscription journals, for which an author selects a user license permitting certain types of reuse without permission. Before proceeding please check if the article is Open Access on http://www.sciencedirect.com and refer to the user license for the individual article. Any reuse not included in the user license terms will require permission. You must always fully and appropriately credit the author and source. If any part of the material to be used (for example, figures) has appeared in the Elsevier publication for which you are seeking permission, with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder. Please contact permissions@elsevier.com with any queries.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been

Appendix 8: Permission for Figure 1.9

CCC Marketplace™

Order Date	04-Jan-2022	Type of Use	Republish in a thesis/dissertation
Order License ID	1173927-1		
ISSN	1087-0792	Publisher	W.B./SAUNDERS CO. LTD.
		Portion	Chart/graph/table/figure

LICENSED CONTENT

Publication Title	Sleep medicine reviews	Publication Type	Journal
Article Title	Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy	Start Page	45
		End Page	59
		Volume	37
Date	01/01/1997	URL	http://www.idealibrary.com/links/toc/smrv/
Language	English		
Country	United Kingdom of Great Britain and Northern Ireland		
Rightsholder	Elsevier Science & Technology Journals		

REQUEST DETAILS

Portion Type	Chart/graph/table/figure	Distribution	U.K. and Commonwealth (excluding Canada)
Number of charts / graphs / tables / figures requested	1	Translation	Original language of publication
Format (select all that apply)	Electronic	Copies for the disabled?	No
		Minor editing privileges?	No
Who will republish the content?	Academic institution	Incidental promotional use?	No
Duration of Use	Life of current edition	Currency	GBP
Lifetime Unit Quantity	Up to 499		
Rights Requested	Main product		

NEW WORK DETAILS

Title	The Effect of Therapy on Arousal from Sleep in Patients with Respiratory Sleep Disorders	Institution name	Imperial College London
		Expected presentation date	2022-01-05
Instructor name	Prof Mary Morrell		

ADDITIONAL DETAILS

Order reference number	N/A	The requesting person / organization to appear on the license	Abdullah Saad S ALQarni

REUSE CONTENT DETAILS

Title, description or numeric reference of the portion(s)	Figure 8	**Title of the article/chapter the portion is from**	Phenotypic approaches to obstructive sleep apnoea – New pathways for targeted therapy
Editor of portion(s)	Eckert, Danny J.	**Author of portion(s)**	Eckert, Danny J.
Volume of serial or monograph	37	**Issue, if republishing an article from a serial**	N/A
Page or page range of portion	45-59	**Publication date of portion**	2018-02-01

RIGHTSHOLDER TERMS AND CONDITIONS

Elsevier publishes Open Access articles in both its Open Access journals and via its Open Access articles option in subscription journals, for which an author selects a user license permitting certain types of reuse without permission. Before proceeding please check if the article is Open Access on http://www.sciencedirect.com and refer to the user license for the individual article. Any reuse not included in the user license terms will require permission. You must always fully and appropriately credit the author and source. If any part of the material to be used (for example, figures) has appeared in the Elsevier publication for which you are seeking permission, with credit or acknowledgement to another source it is the responsibility of the user to ensure their reuse complies with the terms and conditions determined by the rights holder. Please contact permissions@elsevier.com with any queries.

CCC Terms and Conditions

1. Description of Service; Defined Terms. This Republication License enables the User to obtain licenses for republication of one or more copyrighted works as described in detail on the relevant Order Confirmation (the "Work(s)"). Copyright Clearance Center, Inc. ("CCC") grants licenses through the Service on behalf of the rightsholder identified on the Order Confirmation (the "Rightsholder"). "Republication", as used herein, generally means the inclusion of a Work, in whole or in part, in a new work or works, also as described on the Order Confirmation. "User", as used herein, means the person or entity making such republication.

2. The terms set forth in the relevant Order Confirmation, and any terms set by the Rightsholder with respect to a particular Work, govern the terms of use of Works in connection with the Service. By using the Service, the person transacting for a republication license on behalf of the User represents and warrants that he/she/it (a) has been duly authorized by the User to accept, and hereby does accept, all such terms and conditions on behalf of User, and (b) shall inform User of all such terms and conditions. In the event such person is a "freelancer" or other third party independent of User and CCC, such party shall be deemed jointly a "User" for purposes of these terms and conditions. In any event, User shall be deemed to have accepted and agreed to all such terms and conditions if User republishes the Work in any fashion.

3. Scope of License; Limitations and Obligations.

   3.1. All Works and all rights therein, including copyright rights, remain the sole and exclusive property of the Rightsholder. The license created by the exchange of an Order Confirmation (and/or any invoice) and payment by User of the full amount set forth on that document includes only those rights expressly set forth in the Order Confirmation and in these terms and conditions, and conveys no other rights in the Work(s) to User. All rights not expressly granted are hereby reserved.

   3.2. General Payment Terms: You may pay by credit card or through an account with us payable at the end of the month. If you and we agree that you may establish a standing account with CCC, then the following terms apply: Remit Payment to: Copyright Clearance Center, 29118 Network Place, Chicago, IL 60673-1291. Payments Due: Invoices are payable upon their delivery to you (or upon our notice to you that they are available to you for downloading). After 30 days, outstanding amounts will be subject to a service charge of 1-1/2% per month or, if less, the maximum rate allowed by applicable law. Unless otherwise specifically set forth in the Order Confirmation or in a separate written agreement signed by CCC, invoices are due and payable on "net 30" terms. While User may exercise the rights licensed immediately upon issuance of the Order Confirmation, the license is automatically revoked and is null and void, as if it had never been issued, if complete payment for the license is not received on a timely basis either from User directly or through a payment agent, such as a credit card company.

   3.3. Unless otherwise provided in the Order Confirmation, any grant of rights to User (i) is "one-time" (including

Appendix 9: Search strategy - chapter 3

Database: Embase (1947 to September 10, 2021)

1 exp *sleep disordered breathing/

2 sleep apn?ea*.mp.

3 (position* adj5 apn?ea*).mp.

4 (supine* adj5 apn?ea*).mp.

5 1 or 2 or 3 or 4

6 ((supine* or position* or postur* or lateral* or dorsal*) adj4 (therap* or treatment* or device* or train*)).mp.

7 5 and 6

8 limit 7 to english language

Database: Ovid MEDLINE (1946 to September 10, 2021)

1 sleep apnea syndromes/ or sleep apnea, obstructive/

2 sleep apn?ea*.mp.

3 (position* adj5 apn?ea*).mp.

4 (supine* adj5 apn?ea*).mp.

5 1 or 2 or 3 or 4

6 ((supine* or position* or postur* or lateral* or dorsal*) adj4 (therap* or treatment* or device* or train*)).mp.

7 5 and 6

8 limit 7 to english language

Cochrane database for Systematic Reviews (upto September 10, 2021)

ID	Search
#1	MeSH descriptor: [Sleep Apnea, Obstructive] explode all trees
#2	MeSH descriptor: [Sleep Apnea, Syndromes] explode all trees
#3	sleep apn?ea*
#4	position* near apn?ea
#5	supine* near apn?ea
#6	#1 OR #2 OR #3 OR #4 OR #5
#7	(supine* OR position* OR postur* OR lateral OR dorsal)near(therap* OR treatment* OR device* OR trainer*)
#8	#6 AND #7

Appendix 10: Ongoing registered clinical trials – chapter 3

The systematic search of the literature revealed four ongoing registered clinical trials. The POSA Trial is a three-month, multicentre, randomised, parallel, double-blind trial. The POSA Trial (ISRCTN51740863) includes seven nationwide participating UK sites. The planned sample size is 138 participants. The aim of this trial is to compare positional therapy to sham-positional therapy using a neck-worn device in patients with POSA. The primary outcome measure is the change in OSA severity defined by the AHI. The secondary outcome measures include:

- changes in subjective sleepiness-measured by the ESS
- changes in quality of life - measured by FOSQ
- changes in anxiety and depression using the Hospital Anxiety and Depression Scale (HADS)
- changes in Independent Functioning using the Townsend Disability Scale
- changes in quality of life measured by the SF-36
- changes in subjective sleep quality and bed partner's perspective using the Pittsburgh Sleep Quality Index (PSQI)
- changes in healthcare utilisation measured by a Healthcare Utilisation Questionnaire
- comfort and tolerance of the positional therapy device; visual analogue scale (VAS) of comfort and tolerance of device.
- adherence to positional therapy measured by the Night Shift device
- change in percentage supine sleep compared to total sleep time

The second ongoing trial is The SLEEP ON Your SIDE (SOS) trial. It is a three-month, multicentre, prospective, crossover, randomised trial. The SOS trial (NCT04211350) includes sites from three countries; UK, Germany and France. The aim of this trial is to compare the chest-worn sleep position trainer against positive airway pressure (PAP) in patients with POSA. The planned sample size is 150 participants. The primary outcome of this trial is the change in the AHI. Secondary outcome measures include:

- daytime sleepiness using ESS
- impact of sleepiness on activities of daily living using FOSQ

- health related quality of life measured using EQ-5D
- fatigue measured using Pichot Fatigue Scale
- quality of life utilising SF-36
- health economics and resource utilisation are assessed using a healthcare utilisation diary which is completed by patients.
- adherence

A third trial (NCT04425408) is a randomized cross over trial taking place in Belgium. In this trial the investigators are assessing the efficacy of two different positional therapies (Positional pillow and vibrating belt), each is worn for 3 nights by patients with POSA. The planned sample size is 52 participants. The primary outcome measures is the change in the percentage of supine sleep on treatment. The investigators will also assess the subjective quality of sleep "Quality of sleep questionnaire"

A fourth trial is a two-month prospective, crossover, randomised trial (the PaCT study) (ACTRN12619000475145) taking place in Australia. The planned sample size is 30 participants. The aim of this study is to compare positional therapy (NightShift device) and continuous positive airway pressure in patients with POSA. The primary outcome is sleepiness as assessed by the Epworth Sleepiness Scale. Secondary outcomes include:

- Adherence
- Quality of Life as assessed by the Functional Outcomes of Sleep Questionnaire
- Depression, Anxiety, Stress Scale (DASS-21)
- Composite outcome of the following Neurocognitive tests: (PVT, Tower of London, Go/No-Go, Match to Sample, Corsi test, Wisconsin Card-sorting test)
- Quality of Life as assessed by the Short Form 36 item Quality of Life questionnaire.

Appendix 11: Secondary outcomes

Figure 1: Forest plot of clinical trials and cohort studies comparing FOSQ global scores with and without vibrotactile PT (baseline). This forest plot shows the effect of PT on the FOSQ global score in which PT minimally improved the FOSQ global score compared to baseline.

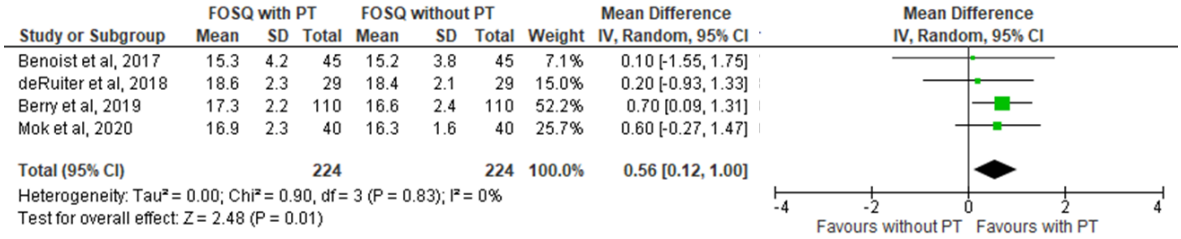


Figure 1: Forest plot of clinical trials and cohort studies comparing FOSQ global scores with and without vibrotactile PT (baseline). FOSQ, Functional Outcome of Sleep Questionnaire; PT, positional therapy. One study(van Maanen & de Vries, 2014) was excluded as they used different FOSQ scale.

Figure 2: Forest plot of clinical trials and cohort studies comparing SF-36 vitality score with and without vibrotactile PT (baseline). This forest plot shows the effect of PT on the SF-36 vitality score in which PT significantly improved the vitality score by 6.72 points compared to baseline.

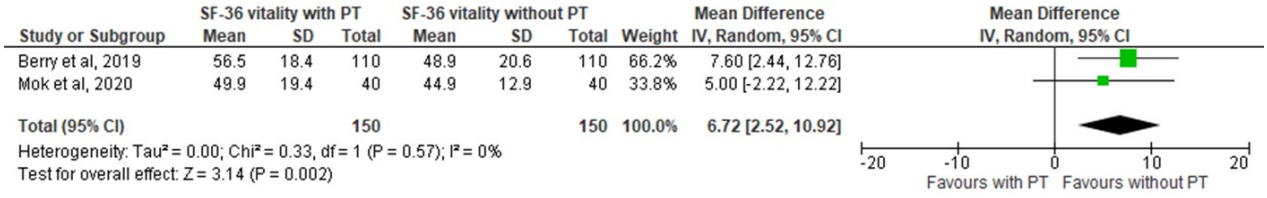


Figure 2: Forest plot of clinical trials and cohort studies comparing SF-36 vitality score with and without vibrotactile PT (baseline). SF-36, Short Form 36 questionnaire; PT, positional therapy

Figure 3: Forest plot of clinical trials and cohort studies comparing sleep efficiency with and without vibrotactile PT (baseline). This forest plot shows the effect of PT on the SE in which PT minimally improved the SE compared to baseline.

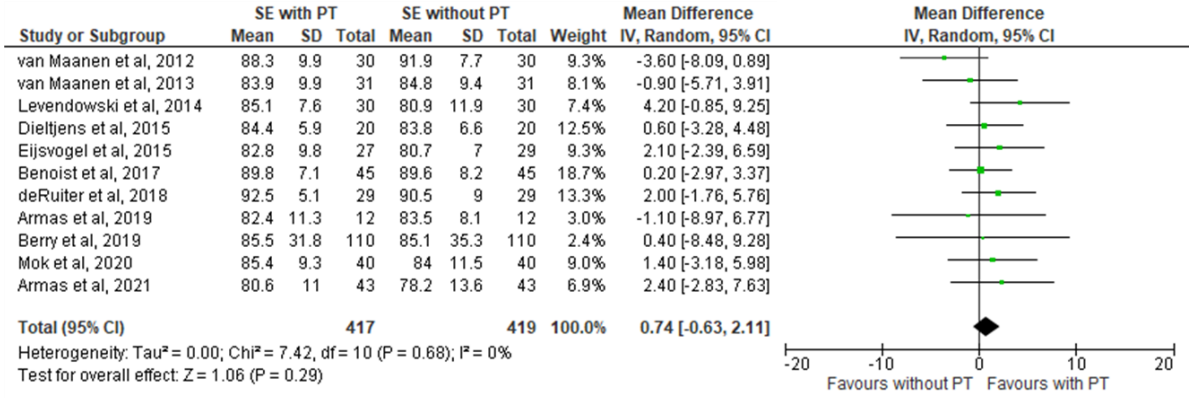


Figure 3: Forest plot of clinical trials and cohort studies comparing sleep efficiency with and without vibrotactile PT (baseline). SE, sleep efficiency; PT, positional therapy.

Figure 4: Forest plot of clinical trials and cohort studies comparing arousal index with and without vibrotactile PT (baseline). This forest plot shows the effect of PT on the AI in which PT minimally improved the AI compared to baseline.

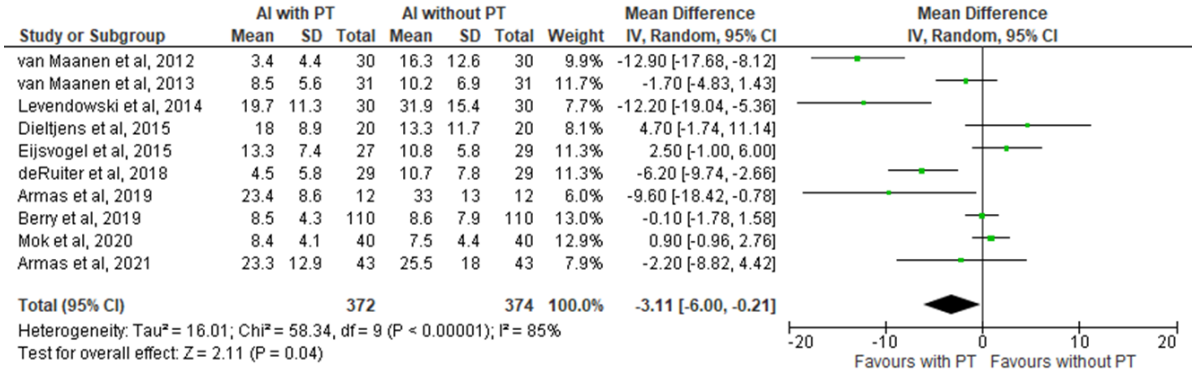


Figure 4: Forest plot of clinical trials and cohort studies comparing arousal index with and without vibrotactile PT (baseline). AI, arousal index; PT, positional therapy.

Appendix 12: Sensitivity analyses

Figure 5: Forest plot of clinical trials and cohort studies comparing total AHI with and without vibrotactile PT (baseline) in mild OSA. This forest plot shows the effect of PT on AHI in patients with mild OSA in which PT reduced the AHI by 4.4 events/hrs compared to baseline.

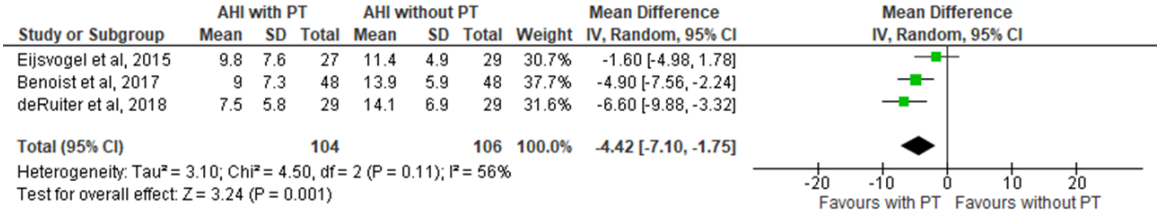


Figure 5: Forest plot of clinical trials and cohort studies comparing total AHI with and without vibrotactile PT (baseline) in mild OSA. AHI, apnoea hypopnea index; PT, positional therapy; OSA, obstructive sleep apnoea

Figure 6: Forest plot of clinical trials and cohort studies comparing total AHI with and without vibrotactile PT (baseline) in moderate and severe OSA. This forest plot shows the effect of PT on AHI in patients with moderate and severe OSA in which PT reduced the AHI by 10.50 events/hrs compared to baseline.

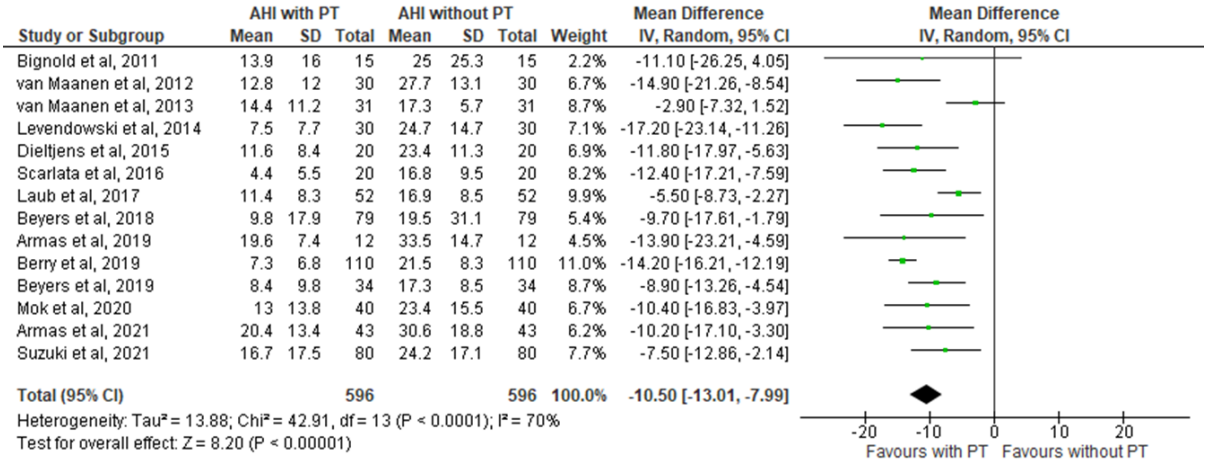


Figure 6: Forest plot of clinical trials and cohort studies comparing total AHI with and without vibrotactile PT (baseline) in moderate and severe OSA. AHI, apnoea hypopnea index; PT, positional therapy; OSA, obstructive sleep apnoea

Figure 7: Forest plot of clinical trials and cohort studies comparing percentage of time spent in supine position with and without vibrotactile PT (baseline) in mild OSA patients. This forest plot shows the effect of PT on percentage of time spent in supine position in patients with mild OSA in which PT reduced it by 25.6% compared to baseline.

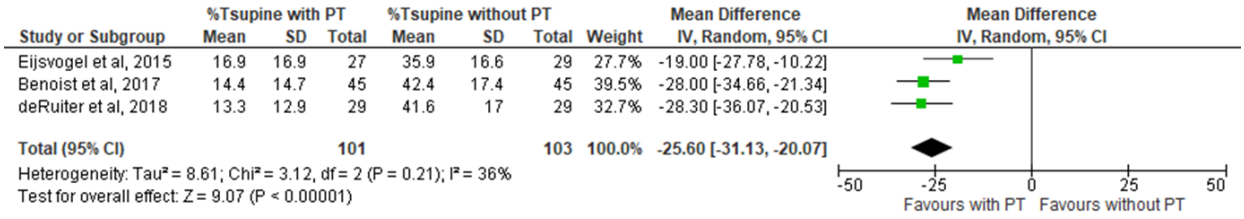


Figure 7: Forest plot of clinical trials and cohort studies comparing percentage of time spent in supine position with and without vibrotactile PT (baseline) in mild OSA patients. %Tsupine, percentage of time spent in supine position; PT, positional therapy; OSA, obstructive sleep apnoea

Figure 8: Forest plot of clinical trials and cohort studies comparing percentage of time spent in supine position with and without vibrotactile PT (baseline) in moderate and severe OSA patients. This forest plot shows the effect of PT on percentage of time spent in supine position in patients with moderate and severe OSA in which PT reduced it by 34.6% compared to baseline.

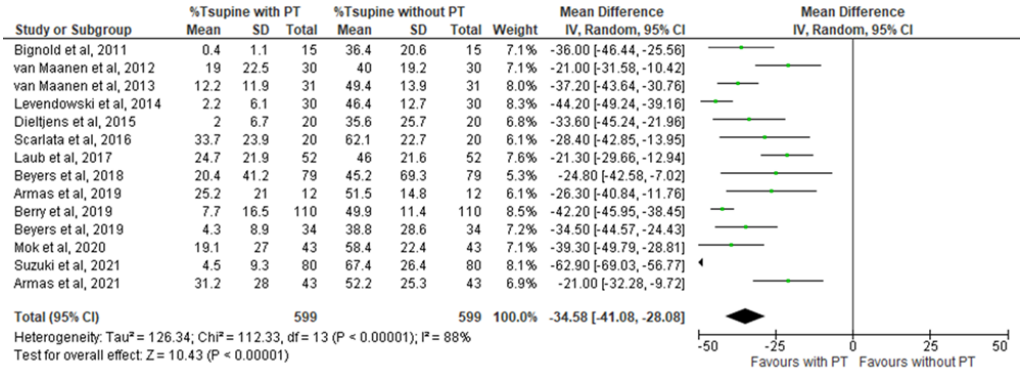


Figure 8: Forest plot of clinical trials and cohort studies comparing percentage of time spent in supine position with and without vibrotactile PT (baseline) in moderate and severe OSA patients. %Tsupine, percentage of time spent in supine position; PT, positional therapy; OSA, obstructive sleep apnoea

Appendix 13: Ethical approval for chapter 4 – before COVID-19

NHS
Health Research Authority

Yorkshire & The Humber - South Yorkshire Research Ethics Committee
NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Telephone: 0207 1048091

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

04 July 2019

Dr Julia Kelly
Clinical Research Fellow in Sleep and Ventilation
Royal Brompton and Harefield NHS Foundation Trust
Clinical and Academic Department of Sleep and Breathing
National Heart and Lung Institute, Imperial College London
Royal Brompton Hospital
SW3 6NP

Dear Dr Kelly

Study title:	**Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trialto assess the effect on Health and Wellbeing in Older and Younger People.**
REC reference:	**19/YH/0222**
IRAS project ID:	**252494**

The Research Ethics Committee reviewed the above application at the meeting held on 27 June 2019. Thank you for attending to discuss the application.

Ethical opinion

The members of the Committee present gave a **favourable ethical opinion** of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

A Research Ethics Committee established by the Health Research Authority

Number	Recommendation
1	Consideration be given to keeping fully anonymised data for future ethically approved research purposes rather than it being destroyed.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA and HCRW Approval (England and Wales)/ NHS permission for research is available in the Integrated Research Application System.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

It is a condition of the REC favourable opinion that all clinical trials are registered on a publicly accessible database. For this purpose, clinical trials are defined as the first four project categories in IRAS project filter question 2. For clinical trials of investigational medicinal products (CTIMPs), other than adult phase I trials, registration is a legal requirement.

Registration should take place as early as possible and within six weeks of recruiting the first research participant at the latest. Failure to register is a breach of these approval conditions, unless a deferral has been agreed by or on behalf of the Research Ethics Committee (see here for more information on requesting a deferral: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/research-registration-research-project-identifiers/

As set out in the UK Policy Framework, research sponsors are responsible for making information about research publicly available before it starts e.g. by registering the research project on a publicly accessible register. Further guidance on registration is available at: https://www.hra.nhs.uk/planning-and-improving-research/research-planning/transparency-responsibilities/

You should notify the REC of the registration details. We routinely audit applications for compliance with these conditions.

Publication of Your Research Summary

We will publish your research summary for the above study on the research summaries section of our website, together with your contact details, no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, make a request to defer, or require further information, please visit:

https://www.hra.nhs.uk/planning-and-improving-research/application-summaries/research-summaries/

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

After ethical review: Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study, including early termination of the study
- Final report

The latest guidance on these topics can be found at https://www.hra.nhs.uk/approvals-amendments/managing-your-approval/.

Ethical review of research sites

NHS/HSC Sites

The favourable opinion applies to all NHS/HSC sites taking part in the study taking part in the study, subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or NHS management permission (in Scotland) being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS/HSC sites

I am pleased to confirm that the favourable opinion applies to any non-NHS/HSC sites listed in the application, subject to site management permission being obtained prior to the start of the study at the site.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [POSA_GPLetter]	1.0	05 June 2019
Instructions for use of medical device [POSA_PatientInstructions]	1.0	05 June 2019
Instructions for use of medical device [POSA_NightShiftCE]	1.0	28 November 2017
Instructions for use of medical device [POSA_NightShiftAgreement]	1.0	07 September 2018
IRAS Application Form [IRAS_Form_11062019]		11 June 2019
IRAS Checklist XML [Checklist_11062019]		11 June 2019
Letter from funder [POSA_NIHRContract]	1.0	14 December 2018
Non-validated questionnaire [POSA_HealthUtilisation]	1.0	23 May 2019
Non-validated questionnaire [POSA_PositionalTherapy&VAS]	1	07 June 2019
Participant consent form [POSA_ICF]	1.0	05 June 2019

Participant information sheet (PIS) [POSA_PIS]	1.0	05 June 2019
Research protocol or project proposal [POSA_Protocol]	1.0	05 June 2019
Summary CV for Chief Investigator (CI) [CV_Julia Kelly]	1.0	05 June 2019
Validated questionnaire [POSA_EQ5D]	1.0	23 May 2019
Validated questionnaire [POSA_ESS]	1.0	23 May 2019
Validated questionnaire [POSA_FOSQ]	1.0	23 May 2019
Validated questionnaire [POSA_HADS]	1.0	23 May 2019
Validated questionnaire [POSA_PSQI]	1.0	23 May 2019
Validated questionnaire [POSA_SF36]	1.0	05 June 2019
Validated questionnaire [POSA_TownsendDisability]	1.0	23 May 2019

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

19/YH/0222	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely

PP

Dr Ian Woollands
Chair

E-mail: nrescommittee.yorkandhumber-southyorks@nhs.net

Enclosures: List of names and professions of members who were present at the meeting and those who submitted written comments

A Research Ethics Committee established by the Health Research Authority

Appendix 14: Ethical approval for chapter 4 – during COVID-19

NHS
Health Research Authority

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

NHSBT Newcastle Blood Donor Centre
Holland Drive
Newcastle upon Tyne
NE2 4NQ

Tel: 0207 104 8079

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

25 August 2020

Dr Julia Kelly
Clinical Research Fellow in Sleep and Ventilation
Royal Brompton and Harefield NHS Foundation Trust
Clinical and Academic Department of Sleep and Breathing
National Heart and Lung Institute
Imperial College London
Royal Brompton Hospital
SW3 6NP

Dear Dr Kelly

Study title:	**Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to assess the effect on Health and Wellbeing in Older and Younger People.**
REC reference:	**19/YH/0222**
Amendment number:	**Substantial Amendment 2**
Amendment date:	**22 July 2020**
IRAS project ID:	**252494**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [POSA_SA02_Amendment_Tool]	0	26 July 2020
Other [POSA_Patient_Instructions_V3.0_23Jun2020_Clean]	V3.0	23 June 2020

A Research Ethics Committee established by the Health Research Authority

Other [POSA_Patient_Instructions_V3.0_23Jun2020_Tracked_Changes]	V3.0	23 June 2020
Participant information sheet (PIS) [POSA_PIS_V3.0_23Jun2020_Clean]	V3.0	23 June 2020
Participant information sheet (PIS) [POSA_PIS_V3.0_23Jun2020_Tracked_Changes]	V3.0	23 June 2020
Research protocol or project proposal [POSA_Protocol_V4.0_26Jun2020_Clean]	V4.0	26 June 2020
Research protocol or project proposal [POSA_Protocol_V4.0_26Jun2020_Tracked_Changes]	V4.0	26 June 2020

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Amendments related to COVID-19

We will update your research summary for the above study on the research summaries section of our website. During this public health emergency, it is vital that everyone can promptly identify all relevant research related to COVID-19 that is taking place globally. If you have not already done so, please register your study on a public registry as soon as possible and provide the HRA with the registration detail, which will be posted alongside other information relating to your project.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

HRA Learning

We are pleased to welcome researchers and research staff to our HRA Learning Events and online learning opportunities– see details at: https://www.hra.nhs.uk/planning-and-improving-research/learning/

IRAS Project ID - 252494:	**Please quote this number on all correspondence**

Yours sincerely
Pp

Dr Max Huxham
Chair

E-mail: southyorks.rec@hra.nhs.uk

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Dr Julia Kelly, Royal Brompton and Harefield NHS Foundation Trust*

Yorkshire & The Humber - South Yorkshire Research Ethics Committee

Attendance at Sub-Committee of the REC meeting via correspondence

Committee Members:

Name	*Profession*	*Present*
Dr Max Huxham (Chair)	Retired Scientist	Yes
Mrs Carole Taylor	Deputy Chief Pharmacist	Yes

Also in attendance:

Name	*Position (or reason for attending)*
Miss Donna Bennett	Approvals Administrator

Appendix 15: Validated questionnaires

The Epworth Sleepiness Scale (ESS)

POSA Trial Number: P O - | | | | | | | Date of visit: DD MMM YYYY NHS National Institute for Health Research

Epworth Sleepiness Scale

How likely are you to doze off or fall asleep in the following situations, in contrast to feeling just tired?

This refers to your usual way of life in recent times.

Even if you haven't done some of these things recently try to work out how they would have affected you.

Use the following scale to choose the **most appropriate number** for each situation:

0 = would **never** doze
1 = **slight chance** of dozing
2 = **moderate chance** of dozing
3 = **high chance** of dozing

It is important that you answer each question as best you can.

Situation	**Chance of Dozing (0-3)**
Sitting and reading	
Watching TV	
Sitting, inactive in a public place (e.g. a theatre or a meeting)	
As a passenger in a car for an hour without a break	
Lying down to rest in the afternoon when circumstances permit	
Sitting and talking to someone	
Sitting quietly after a lunch without alcohol	
In a car, while stopped for a few minutes in the traffic	

THANK YOU FOR YOUR COOPERATION

Functional Outcomes of Sleep Questionnaire (FOSQ)

POSA

Trial Number: P O -

Date of visit: DD MMM YYYY

NHS National Institute for Health Research

FUNCTIONAL OUTCOMES OF SLEEP QUESTIONNAIRE (FOSQ)

Some people have difficulty performing everyday activities when they feel tired or sleepy. The purpose of this questionnaire is to find out if you generally have difficulty carrying out certain activities because you are too sleepy or tired. In this questionnaire, when the words "sleepy" or "tired" are used, it means the feeling that you can't keep your eyes open, your head is droopy, that you want to "nod off", or that you feel the urge to take a nap. These words do not refer to the tired or fatigued feeling you may have after you have exercised.

DIRECTIONS: Please put a (_) in the box for your answer to each question. Select only **one** answer for each question. Please try to be as accurate as possible. All information will be kept confidential.

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
1.Do you have difficulty concentrating on the things you do because you are sleepy or tired?		❒	❒	❒	❒
2.Do you generally have difficulty remembering things, because you are sleepy or tired?		❒	❒	❒	❒
3.Do you have difficulty finishing a meal because you become sleepy or tired?		❒	❒	❒	❒
4.Do you have difficulty working on a hobby (for example, sewing, collecting, gardening) because you are sleepy or tired?	❒	❒	❒	❒	❒

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
5.Do you have difficulty doing work around the house (for example, cleaning house, doing laundry, taking out the trash, repair work) because you are sleepy or tired?	❒	❒	❒	❒	❒
6.Do you have difficulty operating a motor vehicle for short distances (less than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒
7.Do you have difficulty operating a motor vehicle for long distances (greater than 100 miles) because you become sleepy or tired?	❒	❒	❒	❒	❒
8.Do you have difficulty getting things done because you are too sleepy or tired to drive or take public transportation?	❒	❒	❒	❒	❒
9.Do you have difficulty taking care of financial affairs and doing paperwork (for example, writing checks, paying bills, keeping financial records, filling out tax forms, etc.) because you are sleepy or tired?	❒	❒	❒	❒	❒

Functional Outcomes of Sleep Questionnaire (FOSQ)

fosq.97 updated 11/98
Page 2

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
10.Do you have difficulty performing employed or volunteer work because you are sleepy or tired?	❒	❒	❒	❒	❒
11. Do you have difficulty maintaining a telephone conversation, because you become sleepy or tired?	❒	❒	❒	❒	❒
12. Do you have difficulty visiting with your family or friends in <u>your</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒
13. Do you have difficulty visiting with your family or friends in <u>their</u> home because you become sleepy or tired?	❒	❒	❒	❒	❒
14. Do you have difficulty doing things for your family or friends because you are too sleepy or tired?	❒	❒	❒	❒	❒

	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely	
15. Has your relationship with family, friends or work colleagues been affected because you are sleepy or tired?	❒	❒	❒	❒	

In what way has your relationship been affected? _____

_____

_____

Functional Outcomes of Sleep Questionnaire (FOSQ)

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
16. Do you have difficulty exercising or participating in a sporting activity because you are too sleepy or tired?	❒	❒	❒	❒	❒
17. Do you have difficulty watching a movie or videotape because you become sleepy or tired?	❒	❒	❒	❒	❒
18. Do you have difficulty enjoying the theater or a lecture because you become sleepy or tired?	❒	❒	❒	❒	❒
19. Do you have difficulty enjoying a concert because you become sleepy or tired?	❒	❒	❒	❒	❒
20. Do you have difficulty watching TV because you are sleepy or tired?	❒	❒	❒	❒	❒
21. Do you have difficulty participating in religious services, meetings or a group or club, because you are sleepy or tired?	❒	❒	❒	❒	❒

	(0) I don't do this activity for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
22. Do you have difficulty being as active as you want to be in the evening because you are sleepy or tired?		❒	❒	❒	❒
23. Do you have difficulty being as active as you want to be in the morning because you are sleepy or tired?		❒	❒	❒	❒

	(0) I don't do this for other reasons	(4) No difficulty	(3) Yes, a little difficulty	(2) Yes, moderate difficulty	(1) Yes, extreme difficulty
24. Do you have difficulty being as active as you want to be in the afternoon because you are sleepy or tired?		❒	❒	❒	❒
25. Do you have difficulty keeping pace with others your own age because you are sleepy or tired?		❒	❒	❒	❒

	(1) Very Low	(2) Low	(3) Medium	(4) High
26. How would you rate your general level of activity?	❒	❒	❒	❒

	(0) I don't engage in sexual activity for other reasons	(4) No	(3) Yes, a little	(2) Yes, moderately	(1) Yes, extremely
27. Has your intimate or sexual relationship been affected because you are sleepy or tired?	❒	❒	❒	❒	❒
28. Has your desire for intimacy or sex been affected because you are sleepy or tired?	❒	❒	❒	❒	❒
29. Has your ability to become sexually aroused been affected because you are sleepy or tired?	❒	❒	❒	❒	❒
30. Has your ability to "come" (have an orgasm) been affected because you are sleepy or tired?	❒	❒	❒	❒	❒

Thank you for completing this questionnaire.

Functional Outcomes of Sleep Questionnaire (FOSQ)

RAND HEALTH

Trial Number: P O -

Date of visit: DD MMM YYYY

RAND > RAND Health > Surveys > RAND Medical Outcomes Study > 36-Item Short Form Survey (SF-36) >

36-Item Short Form Survey Instrument (SF-36)

RAND 36-Item Health Survey 1.0 Questionnaire Items

Choose one option for each questionnaire item.

1. In general, would you say your health is:

- 1 - Excellent
- 2 - Very good
- 3 - Good
- 4 - Fair
- 5 - Poor

2. **Compared to one year ago**, how would you rate your health in general **now**?

- 1 - Much better now than one year ago
- 2 - Somewhat better now than one year ago
- 3 - About the same
- 4 - Somewhat worse now than one year ago
- 5 - Much worse now than one year ago

Trial Number: P O - | | | | | | |

Date of visit: DD | MMM | YYYY

The following items are about activities you might do during a typical day. Does **your health now limit you** in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
3. **Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	○ 1	○ 2	○ 3
4. **Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	○ 1	○ 2	○ 3
5. Lifting or carrying groceries	○ 1	○ 2	○ 3
6. Climbing **several** flights of stairs	○ 1	○ 2	○ 3
7. Climbing **one** flight of stairs	○ 1	○ 2	○ 3
8. Bending, kneeling, or stooping	○ 1	○ 2	○ 3
9. Walking **more than a mile**	○ 1	○ 2	○ 3
10. Walking **several blocks**	○ 1	○ 2	○ 3
11. Walking **one block**	○ 1	○ 2	○ 3
12. Bathing or dressing yourself	○ 1	○ 2	○ 3

Trial Number: P O - | Date of visit: DD MMM YYYY

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of your physical health**?

	Yes	No
13. Cut down the **amount of time** you spent on work or other activities	1	2
14. **Accomplished less** than you would like	1	2
15. Were limited in the **kind** of work or other activities	1	2
16. Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

During the **past 4 weeks**, have you had any of the following problems with your work or other regular daily activities **as a result of any emotional problems** (such as feeling depressed or anxious)?

	Yes	No
17. Cut down the **amount of time** you spent on work or other activities	1	2
18. **Accomplished less** than you would like	1	2
19. Didn't do work or other activities as **carefully** as usual	1	2

20. During the **past 4 weeks**, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?

- 1 - Not at all
- 2 - Slightly
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

Trial Number:	P	O	-					Date of visit:	DD	MMM	YYYY

21. How much **bodily** pain have you had during the **past 4 weeks**?

- 1 - None
- 2 - Very mild
- 3 - Mild
- 4 - Moderate
- 5 - Severe
- 6 - Very severe

22. During the **past 4 weeks**, how much did **pain** interfere with your normal work (including both work outside the home and housework)?

- 1 - Not at all
- 2 - A little bit
- 3 - Moderately
- 4 - Quite a bit
- 5 - Extremely

Trial Number: P O - | | | | | | | Date of visit: DD MMM YYYY

These questions are about how you feel and how things have been with you **during the past 4 weeks**. For each question, please give the one answer that comes closest to the way you have been feeling.

How much of the time during the **past 4 weeks**...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little of the time	None of the time
23. Did you feel full of pep?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
24. Have you been a very nervous person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
25. Have you felt so down in the dumps that nothing could cheer you up?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
26. Have you felt calm and peaceful?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
27. Did you have a lot of energy?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
28. Have you felt downhearted and blue?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
29. Did you feel worn out?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
30. Have you been a happy person?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6
31. Did you feel tired?	○ 1	○ 2	○ 3	○ 4	○ 5	○ 6

32. During the **past 4 weeks**, how much of the time has **your physical health or emotional problems** interfered with your social activities (like visiting with friends, relatives, etc.)?

○ 1 - All of the time

○ 2 - Most of the time

○ 3 - Some of the time

○ 4 - A little of the time

○ 5 - None of the time

Trial Number:	P	O	-					Date of visit:	DD	MMM	YYYY

How TRUE or FALSE is **each** of the following statements for you.

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
33. I seem to get sick a little easier than other people	1	2	3	4	5
34. I am as healthy as anybody I know	1	2	3	4	5
35. I expect my health to get worse	1	2	3	4	5
36. My health is excellent	1	2	3	4	5

ABOUT

The RAND Corporation is a research organization that develops solutions to public policy challenges to help make communities throughout the world safer and more secure, healthier and more prosperous. RAND is nonprofit, nonpartisan, and committed to the public interest.

1776 Main Street
Santa Monica, California 90401-3208

Pittsburgh Sleep Quality Index (PSQI)

POSA

Trial Number: P O - | | | | | |

Date of visit: DD MM YYYY

NHS National Institute for Health Research

PITTSBURGH SLEEP QUALITY INDEX

INSTRUCTIONS:
The following questions relate to your usual sleep habits during the past month only. Your answers should indicate the most accurate reply for the majority of days and nights in the past month. Please answer all questions.

1. During the past month, what time have you usually gone to bed at night?

   BED TIME _____

2. During the past month, how long (in minutes) has it usually taken you to fall asleep each night?

   NUMBER OF MINUTES _____

3. During the past month, what time have you usually gotten up in the morning?

   GETTING UP TIME _____

4. During the past month, how many hours of actual sleep did you get at night? (This may be different than the number of hours you spent in bed.)

   HOURS OF SLEEP PER NIGHT _____

For each of the remaining questions, check the one best response. Please answer all questions.

5. During the past month, how often have you had trouble sleeping because you . . .

a) Cannot get to sleep within 30 minutes

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Wake up in the middle of the night or early morning

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Have to get up to use the bathroom

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Cannot breathe comfortably

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Cough or snore loudly

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

f) Feel too cold

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

g) Feel too hot

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

h) Had bad dreams

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

i) Have pain

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

j) Other reason(s), please describe_____

_____

How often during the past month have you had trouble sleeping because of this?

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

6. During the past month, how would you rate your sleep quality overall?

Very good _____

Fairly good _____

Fairly bad _____

Very bad _____

7. During the past month, how often have you taken medicine to help you sleep (prescribed or "over the counter")?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in social activity?

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

9. During the past month, how much of a problem has it been for you to keep up enough enthusiasm to get things done?

No problem at all _____

Only a very slight problem _____

Somewhat of a problem _____

A very big problem _____

10. Do you have a bed partner or room mate?

No bed partner or room mate _____

Partner/room mate in other room _____

Partner in same room, but not same bed _____

Partner in same bed _____

If you have a room mate or bed partner, ask him/her how often in the past month you have had . . .

a) Loud snoring

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

b) Long pauses between breaths while asleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

c) Legs twitching or jerking while you sleep

Not during the past month_____	Less than once a week_____	Once or twice a week_____	Three or more times a week_____

d) Episodes of disorientation or confusion during sleep

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

e) Other restlessness while you sleep; please describe_____

_____

Not during the past month_____ Less than once a week_____ Once or twice a week_____ Three or more times a week_____

Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ: Psychiatry Research, 28:193-213, 1989.

Euroqol 5 Dimension Questionnaire (EQ-5D):

POSA

Trial Number: P O -

Date of visit: DD MMM YYYY

NHS National Institute for Health Research

Health Questionnaire

English version for the UK

POSA

Trial Number: P O -

Date of visit: DD MMM YYYY

NHS National Institute for Health Research

Under each heading, please tick the ONE box that best describes your health TODAY.

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

POSA

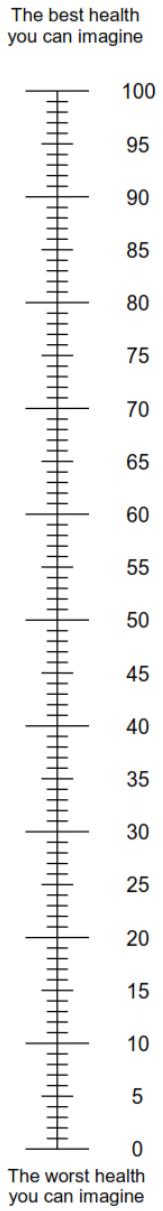
Trial Number: P O - | | | | | |

Date of visit: DD | MMM | YYYY

NHS National Institute for Health Research

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Townsend Disability Scale

POSA

Trial Number: P O -

Date of visit: DD MMM YYYY

NHS National Institute for Health Research

Townsend Disability Index

Please tell us if you are able to:
(Even if you haven't done some of these things recently try to work out how they would affect you)
Please tick one box on each line

	Yes, with no difficulty	Yes, with some difficulty	No, need help
Cut your own toenails?			
Wash all over or bathe?			
Get on a bus?			
Go up and down stairs?			
Do the heavy housework?			
Shop and carry heavy bags?			
Prepare and cook a hot meal?			
Reach an overhead shelf?			
Tie a good knot in a piece of string?			

Appendix 16: Participant information sheet for chapter 4

POSA

NHS
National Institute for Health Research

POSA TRIAL – **Positional Therapy: Patient Instructions**

Positional Therapy For Obstructive Sleep Apnoea: a Randomised Controlled Trial To Assess The Effect on Health and Wellbeing in Older and Younger People (POSA Trial)

Aims: We want to find out whether Positional Therapy, using a small vibrating device fitted to the neck, can help to stop people from sleeping on their backs and whether this helps to reduce the severity of their sleep apnoea. We also want to know whether patients feel better and how easy the treatment is to use.

How will we do this: The new **Positional Therapy** device will be compared to **Sham-Positional Therapy.** This is the best way of assessing a treatment because the 'sham' is a placebo, where the patients think that they are getting the treatment, but they are not.

We will measure breathing at night to determine the response to treatment and to see if this is different in older people. We will ask questions before and after 3 months of treatment to see if patients feel less sleepy and generally better.

The Night Shift™ Device

The Night Shift™ device, worn on the back of your neck, provides gentle vibration feedback when you try to sleep on your back - this is to try to stop you from sleeping on your back. It has a quick-release magnetic clasp and a soft silicone neck strap for a comfortable, safe and secure fit.

What will happen to me?

All patients who take part in this trial will be given a Night Shift device to wear every night for 3 months.

At your first study visit, you will be given the opportunity to try the device to make sure that you are happy to use it at home. You will be shown how to fit the device comfortably, and also practice fitting it yourself. You will experience the vibration sensation.

We will then use a computer programme to randomise you – this is just like 'tossing a coin' to determine if you will receive **Positional Therapy** or **Sham-Positional Therapy** (which are both provided by the same device). You will not be told which you will be receiving. The person who is treating you will also not know which setting you have been randomized to. This is called 'blinding' to make sure that your results are not influenced by which group you are in.0

At home:

For all patients, on the first night, the device will be **monitoring only** with no feedback, which will allow you to get used to sleeping with the device without the disruption of the vibration therapy. On all other nights, **NO** devices provide any vibration feedback for the **first 30 minutes** of wearing it. This is so that you can get to sleep in your usual comfortable position. We do not wish to make your sleeping problem worse by keeping you awake at the start of the night. When you are asleep, if you have been randomized to therapy, the device will deliver the gentle vibration feedback to the back of your neck if you try to sleep on your back. The strength and the duration of the vibration varies from person to person. Up to one third of our patients never even notice the vibration because it is designed to be gentle so that it does not wake you up or make your sleep worse.

Normal Sleep

During normal sleep, we go through periods of light sleep and deep sleep. During light sleep, we are more likely to be woken up by noises, lights, touch or other sensations like vibrations. During deep sleep we are much less likely to wake up to the same stimuli. This might explain why some of our patients never notice the vibration on their neck. Please do NOT worry if you do not feel the vibration. The Sleep Therapist will contact you on Day 4 and you can discuss your experience with them when and troubleshoot any difficulties. If you have any concerns in the meantime, you can contact Julia Kelly on juliakelly2@nhs.net or on 0207 3528121 extension 4183.

Using the Night Shift™ device:

You will receive the product information sheet for the full information.

- Once you get your device, please **DO NOT** turn the device on until bedtime on your first night wearing the device. This is because we want to record your sleep on the first night when the device is set in the MONITOR-only mode.
- **Prior to first use**, completely charge the device. It is important to charge the device **DAILY** even the device seems to be charged. If you forgot, the device will be able to work for 2-3 nights.
- When ready for bed, fit the strap so it is adjusted evenly on both sides. If worn too tight, the magnetic clasp will detach during the night. If worn too loose, incorrect positional feedback will occur when the device is not centered on the back of your neck.
- The blue label must be facing away from your neck and On/Off button facing down.

Starting the Night:

- Hold the On-Button down for 1-second.
- The LED indicator and vibration feedback patterns will confirm if there is sufficient battery power to record and provide feedback for the entire night (for at least 8 hours):

Battery charge sufficient for	LED indicator pattern	Vibration feedback
3 nights	Green - 3 blinks	3 times
2 nights	Green - 2 blinks	2 times
1 night	Green - 1 blink	1 time
Needs charging	Yellow - 1 blink per second	1 time every 5 seconds

- When the device is powered on for the night, the LED indicator will blink green for 5 min. After 5 min. the LED will become solid green (and this will stay lit for the whole night). DO NOT switch back off/on on the first night. If unsure check the light indicator is on.
  Place the device on the neck and go to sleep.
- Vibration feedback will not begin for the first 30 minutes to allow adequate time to fall asleep.
- When the Night Shift recognizes you are sleeping on your back, it will vibrate until you change position.
- Night Shift records your position, sleep quality, and snoring so we can monitor your response to positional feedback.

In the morning:

- To turn the Device OFF, quick-press the On-Button and the Green LED will turn OFF.
  - Remember to recharge the battery **at least** once every three days; do not wear the device while charging.

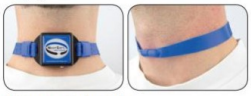
POSA

NHS
National Institute for Health Research *POSA TRIAL* – **Positional**

Therapy: Patient Instructions

Intelligent, Interactive Monitoring

Night Shift is worn around the neck; it uses and measures the effectiveness of vibration feedback to discourage back-sleeping.



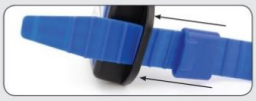
Using the Night Shift:

- Prior to first use, completely charge the device.
- Fit the strap so it is adjusted evenly on both sides. If worn too tight, the magnetic clasp will detach during the night. If worn too loose, incorrect positional feedback will occur when not centered on the back of your neck.
- Just after you turn the device on, it will provide feedback to confirm sufficient battery capacity to record and provide feedback for at least eight hours. Remember to recharge the battery at least once every three days.
- When the Night Shift recognizes you are sleeping on your back, it will vibrate with increasing intensity until you change position.
- Night Shift records your position, sleep quality, and snoring so you can print reports to monitor your response to positional feedback.

Fitting the Night Shift: Step-by-step

The Strap

1 Begin by feeding one end of the strap through one of the slots on the side of the enclosure. The strap should be fed through from the back to the front of the device, and with the ridged side facing out.

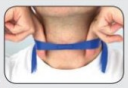


2 Loop the strap back and slide it through the retention band. Pull the strap through the band just enough to hold it in place. Repeat the process with the other side.

3 With the blue label right-side up, center the Night Shift on the back of your neck. **The blue label must be facing away from the neck and the On/Off button facing down.**

4 Re-fasten the magnetic clasp and tighten both sides of the strap evenly, keeping the enclosure centered on the back of your neck and the magnetic clasp centered on the front.

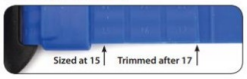
5 The Night Shift strap should be just tight enough to prevent it from sliding around the neck. Two fingers on each side should fit between the strap and the neck without causing the magnets to release.



6 Use the numbers provided on the strap as a guide to help even out each side.

7 With the straps evened out, try the Night Shift on again and verify the fit is still comfortable and snug.

8 Once a good fit is determined, excess length can be trimmed off the ends of the strap. Leave at least 2 extra sizes in case you need to loosen the strap later. The Night Shift is now properly fit.



9 Unclasp the strap by bending at a 90° angle, like snapping a stick. To avoid damage, do not pull apart.

⚠ **Caution:** Replace the strap immediately if the clasps become demagnetized and do not retain during the night.

Appendix 17: Written informed consent for chapter 4

POSA

Royal Brompton & Harefield NHS
NHS Foundation Trust

POSA TRIAL - INFORMED CONSENT FORM
IRAS project ID: 252494

Patient Identification Number for this trial: _____

Title: Positional Therapy for Obstructive Sleep Apnoea: a Randomised Controlled Trial to assess the effect on Health and Wellbeing in Older and Younger People. **The POSA Trial**

Name of Researcher:
Dr Julia Kelly, PhD
Clinical and Academic Unit of Sleep and Breathing
Royal Brompton Hospital, London, SW3 6NP

Please initial box

1. I confirm that I have read and understand the information sheet dated ..... (Version .....) for the above study and have had the opportunity to consider the information, ask questions and have these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of any of my medical notes and data collected during the study may be looked at by responsible individuals from the research trial team, from the sponsors Royal Brompton and Harefield NHS Foundation Trust, from regulatory authorities or from Oxford Respiratory Trials Unit (ORTU) as trial management site, and from the NHS Trust where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ☐

4. I agree to my contact details (Name, Telephone Number, email address) being passed on to the Trial Sleep Therapist in order to contact me regarding my treatment during the study. ☐

5. I agree to take part in the above study. ☐

6. I agree to my GP being informed of my participation in the above study. ☐

7. I understand that the positional therapy device (Night Shift™; Advanced Brain Monitoring, USA) is CE marked but not currently offered as a therapy by the NHS. At the end of the trial, I acknowledge that I may keep the device, but that continued use will be at my own risk. ☐

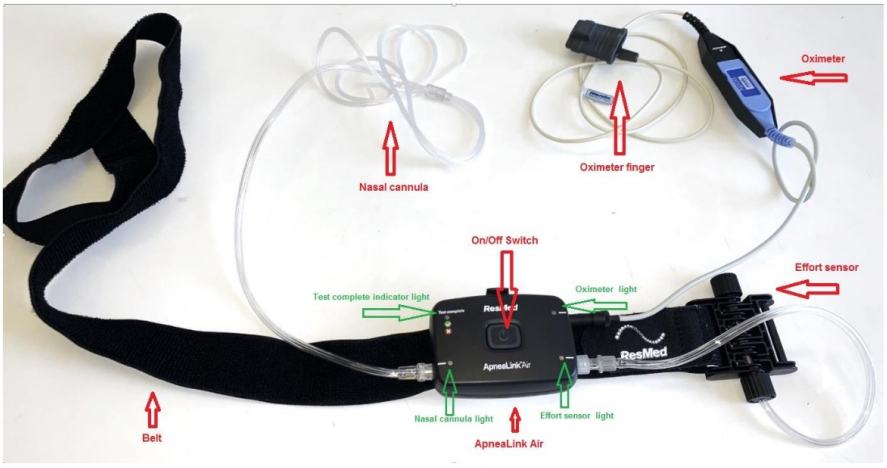
_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of person taking consent	Date	Signature

When completed 1 for patient; 1 for researcher; 1 (original) to be kept with hospital notes

Appendix 18: ApneaLink Air Sleep Test instruction for patient for chapter 4

POSA

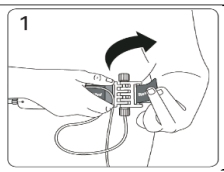
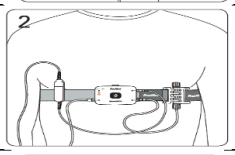
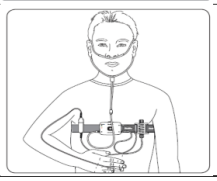
ApneaLink Air Sleep Test Instructions for Patients



1

POSA

Thank you for completing this sleep test for the POSA Trial; Please don't forget to also wear the NightShift device around your neck if this is your 3-month sleep study

Fitting the kit	
• The sleep test has been setup for you to use • Pull the belt around your body. • Thread the end of the belt through the slot on the effort sensor and fasten the tab to the belt.	
• Check that the belt is secure and comfortable, firm but not tight and that the device is positioned over the centre of your chest	
• Put the oximeter on any finger with the lead on the top of your finger • Place the nasal cannula into your nostrils, then loop over your ears and under your chin. • Pull the toggle under your chin to keep the cannula in place • When complete, setup should look like this	

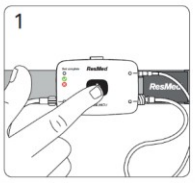
2

POSA

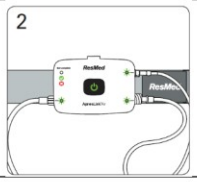
Starting the test

If this your end of trial sleep test, please ensure that you are also wearing the Night Shift device around your neck

- **Press and hold the power button in the centre of the device for about three seconds or until the light turns on.**



- **Check that the 3 small lights (left lower, right upper and lower) are GREEN.**
- **If any of these lights are red and blinking, the accessories are not attached correctly.**
- **After a few minutes, all the lights might turn off so that they do not disturb your sleep**



- **In the morning, please press and hold the power button in the centre of the device for about 3 seconds until the lights turn off.**

If the sleep test has worked, the light in the top left corner will be green. If it is red this means that something went wrong, please call your local team; you may be able to repeat the test the next night (the batteries should last for 2 nights).

3

Appendix 19: Ethical approval for chapter 5 from Imperial College London

Imperial College London

Imperial College Research Ethics Committee
Imperial College London
Room 221
Medical School Building
St Marys Campus
London
W2 1PG
Tel: +44 (0)207 594 1872

researchethicscommittee@imperial.ac.uk

06/07/2020

Dear Dr Julia Kelly

Study Title: The Impact of Chest-worn, Forehead-worn and Neck-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals

ICREC reference: 20IC5874

The above study was approved by your Head of Department on 30/06/20 and by the Joint Research Compliance Office on 06/07/20.

Under the Imperial College Research Ethics Committee process, a study that has been reviewed by the Joint Research Compliance Office and Head of Division, where no significant ethical issues have been identified in the protocol or ethics application, can be approved without requiring it to go to full committee.

Documents
The documents reviewed were:

- ICREC-SETREC Application form (v1.0 13/06/20)
- Protocol (v1.0 13/06/2020)
- Participant Information Sheet (v1.0 13/06/2020)
- Consent Form (v1.0 13/06/2020)
- Sleep Quality Questionnaire (v1.0 13/06/2020)

Yours sincerely,

Ruth Nicholson Digitally signed by Ruth Nicholson Date: 2020.07.06 14:12:01 +01'00'

Ruth Nicholson,
Head of Research Governance and Integrity,
Imperial College London

Appendix 20: Ethical approval for chapter 5 from Imam Abdulrahman Bin Faisal University

Kingdom of Saudi Arabia
Ministry of Education
Imam Abdulrahman Bin Faisal University
Office of the Vice President for Research & Higher Studies

جامعة الإمام عبد الرحمن بن فيصل
IMAM ABDULRAHMAN BIN FAISAL UNIVERSITY

المملكة العربية السعودية
وزارة التعليم
جامعة الإمام عبد الرحمن بن فيصل
وكالة الجامعة للدراسات العليا والبحث العلمي

اللجنة الدائمة لأخلاقيات البحث على المخلوقات الحية
Institutional Review Board

IRB Number	IRB -2020-04-275		أيرب -٢٧٥-٠٤-٢٠٢٠
Project Title	The Impact of Forehead-worn and Neck-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals		
Study Type	Quasi-experimental study		
Principal Investigator	Dr. Yousef Dhifullah Alqurashi		
College / Center	Applied Medical Sciences	**Department**	RC
Approval Date	30/09/2020		

The application was reviewed and approved at Imam Abdulrahman Bin Faisal University IRB meeting on Wednesday, September 30, 2020.

Approval is given for one year from the date of approval. Projects, which have not commenced within six months of the original approval, must be re-submitted to the University Institutional Review Board (IRB) Committee. If you are unable to complete your research within the validation period, you will be required to request an extension from the IRB Committee.

On completion of the research, the Principal Investigator is required to advise the Institutional Review Board if any changes are made to the protocol, a revised protocol must be submitted to the Institutional Review Board for reconsideration.

Approval is given on the understanding that the "Guidelines for Ethical Research Practice" are adhered to. Where required, a signed written consent form must be obtained from each participant in the study group.

Chairman of the Institutional Review Board

Professor Badr Abdulrahman Aljandan Stamp

CC. - Dean
Deanship of Scientific Research
- Director General
King Fahd Hospital of the University
- Director
Center for Research and Medical Consultations
- Supervisor General for Quality and Safety
King Fahd Hospital of the University
- Director
Monitoring Office for Research and Research Ethics
- Director
Pharmacy @ KFHU

Appendix 21: Patient information sheets for chapter 5

Imperial College London

Participant Information Sheet:

The Impact of Chest, Neck and Forehead-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals

PI: Dr. Julia Kelly
Co-investigators: Abdullah ALQarni (AA), Dr Christopher James Harvey, Prof Mary Morrell

Invitation

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

Newly developed Positional Therapy techniques use small, non-invasive, watch-like devices that use vibration to urge people to stay off their back when sleeping. The Positional Therapy devices can be worn around the chest, the neck or the forehead (see Figure 1).

Figure 1: *New positional therapy devices on different bodily sites; the neck, the chest and the forehead.*

These devices have position sensors and a vibrating motor that is like the motors used in smartphones. When an individual attempts to sleep on their back, the position is detected which activates the motor to produce gentle vibrations to urge the person to move onto their side. By reducing the time spent on the back, snoring and breathing events might be reduced, which in turn may improve sleep quality and daytime function.

There may be variation between individuals in their sensitivity to the vibrations and therefore the level of sleep disturbance. Additionally, the site of vibration (neck, chest or forehead) might affect their sensitivity. The only way to measure the level of disturbance that the vibration causes is by measuring overnight sleep objectively by a sleep study and to ask you to report your subjective sleep quality and daytime function.

The aim of this project is to compare the effect of Positional Therapy devices, worn on 2 different sites (neck and forehead) on sleep quality, daytime sleepiness and functioning. We will collect subjective and objective sleep data while using the different Positional Therapy devices. Anonymised data from this study will be used in a PhD thesis by the collaborator (AA).

Imperial College London

Why have I been invited?

You have been asked to participate because you are a student from Imperial College School of Medicine (ICSM). We would like to invite you to consider having two overnight home sleep studies which give detailed information about your quality sleep while wearing the Positional Therapy devices. You will also provide subjective feedback on what it is like to sleep with the devices.

Do I have to take part?

Taking part in this research project is completely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep. You will be asked to sign a consent form. You are free to withdraw from the study at any time without a reason. If you wish to withdraw you may do so at any time by contacting Dr. Julia Kelly at J.Kelly@rbht.nhs.uk. If you decide to withdraw, the data that has been collected will be used in the analysis as appropriate, unless you specifically communicate your withdrawal of consent to do so.

What will happen to me if I take part?

If you agree to take part, you will be shown a pre-recorded video that explains how to do your own sleep study (polysomnography).This will be shared with you via a link sent to your email. The collaborator (AA) will be also available remotely for further assistance via phone or video call.

You will do two overnight home sleep studies which give us detailed information about your sleep. We would like that you perform two studies so that you can use a different Positional Therapy device on each night. You will use two of the Positional Therapy devices, each one for one night. The order of the Positional Therapy devices will be randomly allocated.

If you give informed consent to these sleep studies, they will be performed in your home by yourself and with remote help from the collaborator (AA), or designated researcher. These studies will be performed according to the American Academy of Sleep Medicine standards for performing polysomnography. Polysomnography is considered a routine clinical sleep test. There are multiple non-invasive sensors placed on various sites of the body to collect physiological signals which can recorded and analysed. At first, you might be surprised by the number of sensors electrodes and think that you may not be able to sleep, but from our experience most people are able to sleep. No invasive tests will be done.

Night 1:
You will be asked to maintain a regular wake up and sleep time for the two nights preceding the study. On the day of the sleep studies, you will be asked to refrain from drinking caffeine (after 12 noon) and alcohol.

On the night of the sleep study, a member of the research team will deliver the sleep study equipment to the participant's home approximately 2 – 3 hours before bedtime. The drop off and pick up of sleep equipment to participants' homes, and the cleaning of equipment will be in line with COVID-19 precautions, including the use of PPE, as outlined in a risk assessment to minimise risk to participant and researchers. In addition, the

Imperial College London

collaborator AA will send you a copy of the questionnaires via email. This questionnaire includes three sections, a section that you need to complete before the first sleep study, another one that you need to complete in the morning following the first sleep study and a section that you need to complete the morning following the second sleep study. We ask you to complete these sections and send it to the collaborator (AA) via email.

The 2-3 hours is needed to complete the baseline questionnaire, set up the sleep equipment, and check the quality of the physiological signals. You will complete baseline questionnaires that ask about sleep habits for the past week. Then you will fit yourself with one of the positional therapy devices. Following that, you will fit yourself with equipment to measure sleep and breathing. This includes two bands across the chest and abdomen to measure breathing, and a finger clip to measure oxygen level. You will fit yourself with sensors on the head to monitor brain activity, sensors near the eyes to record the movement of the eyes, and sensors on the chin and legs to monitor muscle activity during sleep. This set up is necessary to measure sleep accurately. (See Figure 2)

Once the equipment is attached, you will do some simple activities (such as blinking eyes, moving legs, and taking deep breaths) to make sure that all electrodes are working properly. After that, will be able to go to sleep. You will be able to move around, go to the bathroom or perform other activities that are needed prior to bedtime.

On the next morning, following the sleep study, you will fill in a short questionnaire that asks about sleep quality of the previous night and remove the sleep equipment.

Imperial College London

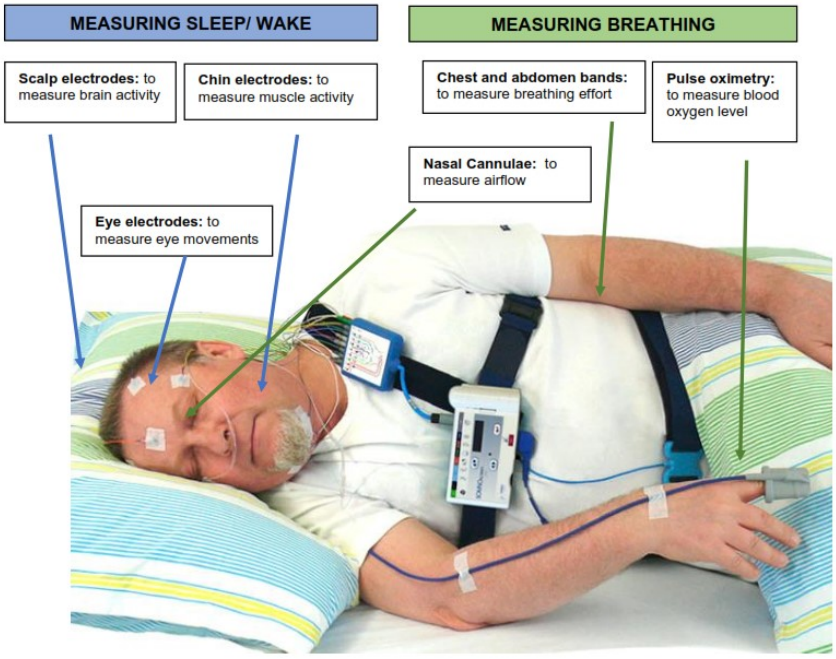


Figure 2: A patient wearing the detailed sleep study – polysomnography- kit (picture adapted from SOMNOmedics GmbH website)

Night 2:
On the second night, you will repeat the procedures described above in Night 1, but for the second night's sleep study you will be wearing an alternative Positional Therapy device.

On the next morning, following the sleep study, you will fill in a short questionnaire that asks about sleep quality of the previous night and remove the sleep equipment.

After this second home sleep study, participation in this study is complete. The collaborator (AA), or designated researcher, will come back to collect the equipment and this will occur according to COVID-19 risk assessment plans including wearing PPE.

What are the possible disadvantages and risks of taking part?

Imperial College London

This project involves two overnight sleep studies. These overnight sleep studies, called polysomnography, are routinely performed in clinical settings to evaluate sleep. At first, participants can be overwhelmed by the number of electrodes and think that may not be able to sleep, but most people are able to sleep. The sleep studies will be performed in your own home.

What are the possible benefits of taking part?

Your participation in this research project will help you learn how to carry out a sleep study.

It is possible that you may experience improvements in your sleep and subsequently in your quality of life when using the vibration device. You might also have an improvement in snoring.

What if something goes wrong?

If something goes wrong during the course of this study then you should immediately inform the principle investigator, Dr. Julia Kelly at J.Kelly@rbht.nhs.uk

If you are unhappy with any procedure during or after the study, you can contact the one of the research team. Imperial College London holds insurance policies which apply to this study. If you experience harm or injury as a result of taking part in this study, you will be eligible to claim compensation without having to prove that Imperial College is at fault. This does not affect your legal rights to seek compensation.

If you are harmed due to someone's negligence, then you may have grounds for a legal action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study then you should immediately inform the Investigator (Dr. Julia Kelly at J.Kelly@rbht.nhs.uk). If you are still not satisfied with the response, you may contact the Imperial College, Joint Research Compliance Office.

- **What will happen to the results of the research study?**

Results of this study will be used by the collaborator (AA) as part of his PhD thesis. Some results may form part of published research papers in the future. No participants will be identified in the reports or publications.

- **Who is organising and funding the research?**

This study is sponsored by Imperial College London and funded by the Academic Unit of Sleep and Breathing, NHLI, Imperial College London.

- **Who has reviewed the study?**

This study was given ethical approval by (individuals name), Head of Department and Joint Research Compliance Office (JRCO).

Contact for Further Information

Imperial College London

For further information you may contact the PI: Dr. Julia Kelly at J.Kelly@rbht.nhs.uk or collaborator Abdullah ALQarni at asa19@ic.ac.uk

Thank you for taking part in this study!

A copy of the written information and signed Informed Consent form will be given to you to keep.

HOW WILL WE USE INFORMATION ABOUT YOU?
Research Study Title: The Impact of Chest, Neck and Forehead-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals
[20IC5874]

Imperial College London is the sponsor for this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. Imperial College London will keep your personal data for:

- 10 years after the study has finished in relation to data subject consent forms.
- 10 years after the study has completed in relation to primary research data.

We will need to use information from you for this research project. This information will include your name and email address. People will use this information to do the research or to check your records to make sure that the research is being done properly. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a study identification number instead. We will keep all information about you safe and secure. Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

LEGAL BASIS

As a university we use personally identifiable information to conduct research to improve health care and services. As a publicly funded organisation, we have to ensure that it is in the public interest when we use personally identifiable information from people who have agreed to take part in research. This means that when you agree to take part in a research study, we will use your data in the ways needed to conduct and analyse the research study.
Health and care research should serve the public interest, which means that we have to demonstrate that our research serves the interests of society as a whole. We do this by following the UK Policy Framework for Health and Social Care Research

INTERNATIONAL TRANSFERS

Imperial College London

There may be a requirement to transfer information to countries outside the European Economic Area (for example, to a research partner). Where this information contains your personal data, Imperial College London will ensure that it is transferred in accordance with data protection legislation. If the data is transferred to a country which is not subject to a European Commission (**EC**) adequacy decision in respect of its data protection standards, Imperial College London will enter into a data sharing agreement with the recipient organisation that incorporates EC approved standard contractual clauses that safeguard how your personal data is processed.

SHARING YOUR INFORMATION WITH OTHERS

For the purposes referred to in this privacy notice and relying on the bases for processing as set out above, we will share your personal data with certain third parties.

- Other College employees, agents, contractors and service providers (for example, suppliers of printing and mailing services, email communication services or web services, or suppliers who help us carry out any of the activities described above). Our third-party service providers are required to enter into data processing agreements with us. We only permit them to process your personal data for specified purposes and in accordance with our policies.

WHAT ARE YOUR CHOICES ABOUT HOW YOUR INFORMATION IS USED?

You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.

- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study.

WHERE CAN YOU FIND OUT MORE ABOUT HOW YOUR INFORMATION IS USED

You can find out more about how we use your information;

- by asking one of the research team
- by sending an email to PI: Dr. Julia Kelly at J.Kelly@rbht.nhs.uk or
- by ringing us on 0207 3528121 ext 84183.

COMPLAINTS

If you wish to raise a complaint on how we have handled your personal data, please contact Imperial College London's Data Protection Officer via email at dpo@imperial.ac.uk, via telephone on 020 7594 3502 and/or via post at Imperial College London, Data Protection Officer, Faculty Building Level 4, London SW7 2AZ.

Imperial College London

If you are not satisfied with our response or believe we are processing your personal data in a way that is not lawful you can complain to the Information Commissioner's Office (ICO). The ICO does recommend that you seek to resolve matters with the data controller (us) first before involving the regulator.

Appendix 22: Written informed consent for chapter 5

Imperial College London

Consent Form for Participants Able to Give Consent

Full Title of Project: The Impact of Chest, Neck and Forehead-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals

Name of Principal Investigator: Dr Julia Kelly

	Please initial box
1. I confirm that I have read and understand the participant information sheet (dated …13.06.2020……..version …1.0……) for the above study and have had the opportunity to ask questions which have been answered fully.	
2. I understand that my participation is voluntary, and I am free to withdraw at any time, without giving any reason and without my legal rights being affected.	
3. I understand that if my data is used in reports, presentations or publications the investigators will not attribute the data to me and that my data will remain anonymous.	
4. I give permission for Imperial College London to access my records that are relevant to this research.	
5. I give consent for information collected about me to be used to support other research in the future, including those outside of the EEA.	
6. I consent to take part in the above study.	
7. I agree to do the sleep study by myself at my home.	
8. I agree that the collaborator (AA), or a designated researcher, come to my home to deliver and collect the equipment	
9. I give consent to being contacted to potentially taking part in other research studies.	

_____	_____	_____
Name of Participant	Signature	Date
_____	_____	_____
Name of Person taking consent (if different from Principal Investigator)	Signature	Date
_____	_____	_____
Principal Investigator	Signature	Date

1 copy for participant; 1 copy for Principal Investigator

Appendix 23: Subjective, bespoke, visual analogue scale questionnaire

Imperial College London

Study ID Number: C R I - | | | | Date of Completion: DD MM YYYY

The Impact of Chest, Neck and Forehead-worn Positional Therapy Devices on Quality of Sleep Among Healthy Individuals: Positional therapy Questionnaire

This Section will be answered at night 1, before the detailed Sleep Study

In answering the followings questions, unless otherwise stated, please respond by making a single vertical mark on the horizontal line provided below.

Sleep Quality over the past week

1. Overall, how do you rate your sleep quality over the last week?

0 — 10
Worst Ever — *Best Ever*

2. Overall, during the day how fresh and well rested have you been over the last week?

0 — 10
Worst Ever — *Best Ever*

3. On average, how easy did you find falling asleep over the last week?

0 — 10
Very Easy — *Very difficult*

Imperial College London

Study ID Number: | C | R | I | - | | | | Date of Completion: | DD | MM | YYYY |

This Section will be answered in the *morning* following the Detailed Sleep Study for *Night 1*

Sleep Quality over the Last Night (Night 1)

1. Overall, how do you rate your sleep quality last night?

0 — 10
Worst Ever — *Best Ever*

2. Overall, how fresh and well rested you feel when you woke up today?

0 — 10
Worst Ever — *Best Ever*

Experience with the Positional Therapy Device over the last night

1. On average, how easy did you find falling asleep while wearing the Positional Therapy device over the last night?

0 — 10
Very Easy — *Very difficult*

2. Over the last night, did you feel the vibrations of the positional therapy device after falling asleep?

☐ No

☐ Yes

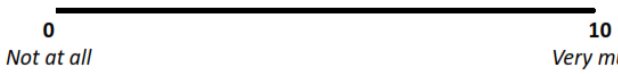
Please **Continue** If you answered **YES** to the previous question:

3. On average, how many times you felt the vibrations of the positional therapy device per night over the last night? *Please respond by a number in the box below*

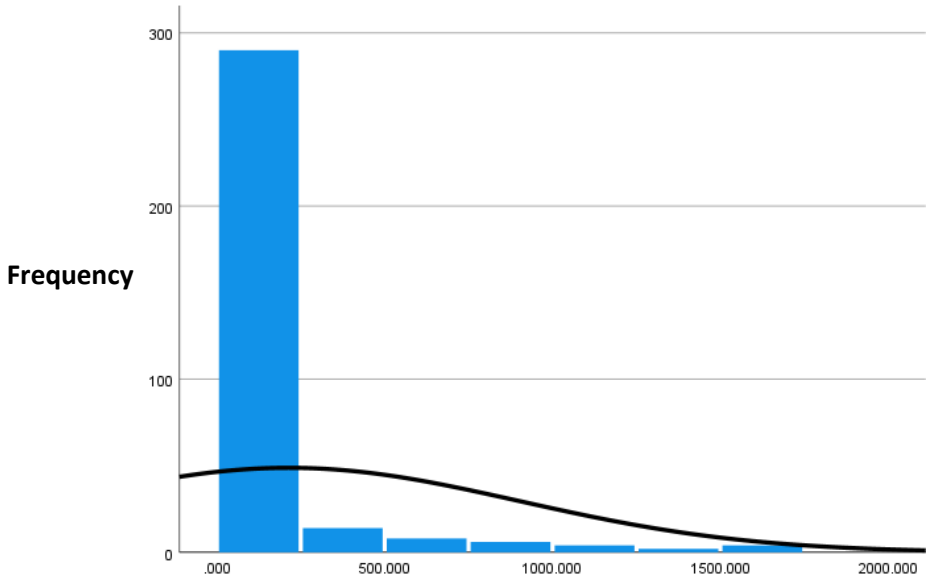
☐

4. If applicable, how much did the vibrations of the positional therapy device disturb your sleep over the last night?

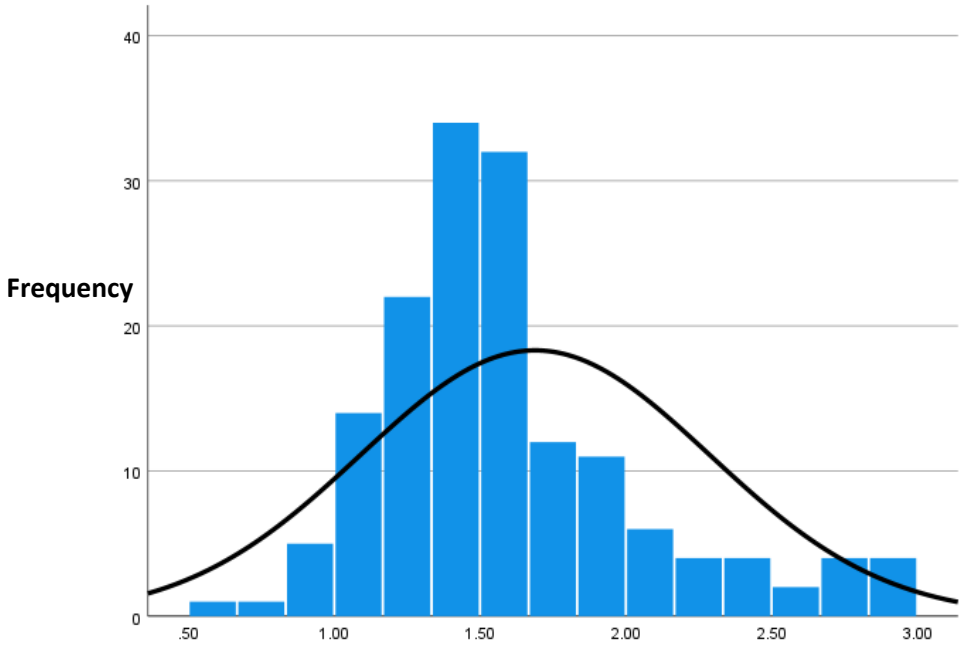
5. If applicable, how much did the vibrations of positional therapy device disturb your bed partner's sleep over the last night?



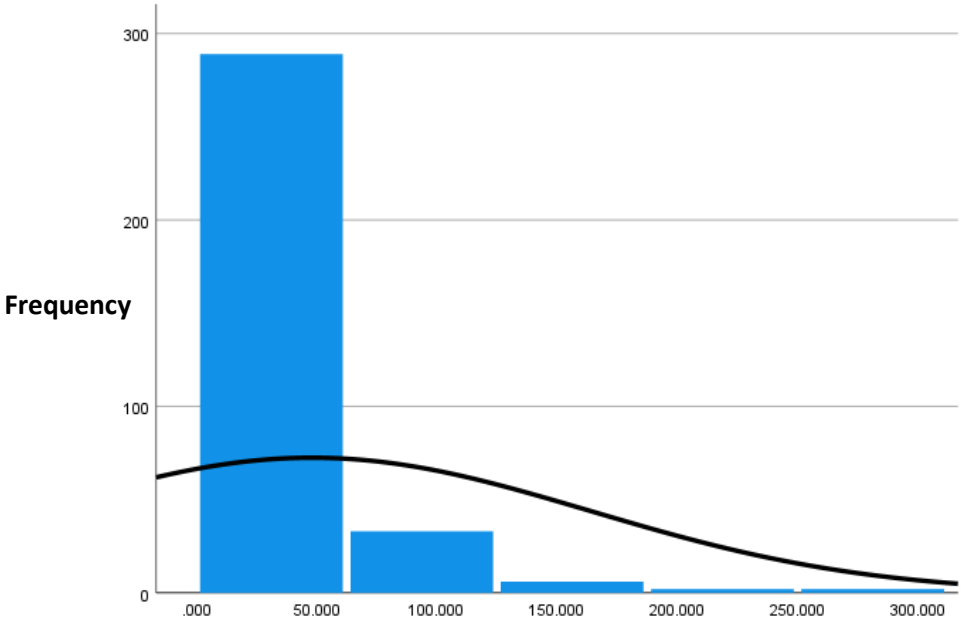
Appendix 24: Histogram of the original duration to change position



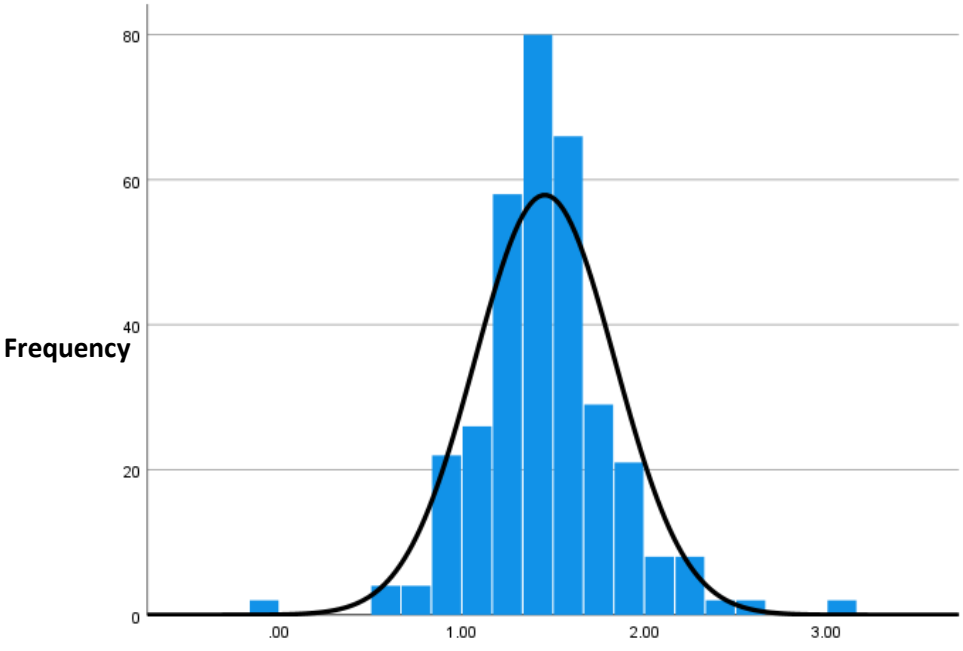
Appendix 25: Histogram of the Log transformed duration to change position



Appendix 26: Histogram of the original duration to return to sleep



Appendix 27: Histogram of the Log transformed duration to change position



Appendix 28:Number of paired data per participant per sleep stage

	Paired data per participant				
	N1	**N2**	**N3**	**REM**	**across all stages**
1	0	2	0	0	2
2	0	1	1	2	4
3	2	11	3	1	17
4	0	3	3	0	6
5	4	4	0	1	9
6	0	3	0	6	9
7	1	4	1	4	10
8	0	0	3	0	3
9	2	4	3	4	13
10	0	2	2	0	4
11	2	0	0	2	4
12	2	2	1	1	6
13	1	0	1	0	2
14	0	4	0	4	8
15	0	1	1	1	3
16	0	1	1	4	6
17	1	3	3	5	12
18	0	1	1	1	3
19	0	2	0	2	4
20	0	5	0	4	9
21	1	3	3	2	9
22	0	3	1	0	4
23	0	5	1	0	6
24	0	1	1	2	4
25	1	2	2	0	5
26	0	1	1	2	4
27	0	1	1	2	4
Number of participants	10	24	21	19	-
Total paired events	17	69	34	50	-