Intervention to enhance adherence to mandibular advancement appliance in patients with obstructive sleep apnoea: a randomised clinical trial

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Abstract

Aims:

To systematically review the factors influencing adherence to mandibular advancement appliances (MAA) in adults with obstructive sleep apnoea (OSA) and the potential effectiveness of interventions to promote improved adherence.

To assess the effectiveness of a stage-matched intervention on adherence to MAA in participants with OSA.

To qualitatively explore and understand adherent and non-adherent patients' experiences.

Methods:

A systematic review and meta-analysis were performed.

A randomised parallel-arm, Hospital-based, clinical trial was undertaken at the Royal London Dental Hospital, UK. Fifty-six participants (Adults 18 years or over) with newly diagnosed OSA were enrolled in the study and randomised to intervention care (IC) and standardized care (SC) groups. Participants in the SC group received routine care whilst participants in the IC group received the stage-matched intervention, developed using the behaviour change model, the Health action process approach (HAPA). Data indicating MAA adherence was collected both objectively and subjectively, from micro-sensors embedded in the MAA design and sleep diaries, respectively at 3- and 6-months. In addition, a range of questionnaires designed to assess risk perception, outcome expectancy, and self-efficacy (SEMSA) and quality of sleep and life, socio-economic and social support scales were used.

One-to-one interviews were conducted to identify patients' perceptions concerning adherence and non-adherence. The Behaviour change taxonomy by Crane et al. was applied as a coding framework to identify behaviour change techniques influencing adherence.

Results:

The review observed a weak relationship between objective adherence and patient and disease characteristics such as age, sex, obesity, AHI, and daytime sleepiness. Non-adherent patients reported more side effects than users and tended to discontinue treatment within the first 3 months. Increased patient adherence was identified with custom-made MAA in comparison to ready-made MAA. The review identified limited evidence concerning the influence of psychological and social factors on MAA adherence. Given that majority of the studies relied upon patient-reported adherence, the review observed a considerable lack of objective adherence monitoring.

The mean objective adherence for 30 participants at 3-month (IC = 15, SC = 15) was 2.02 (SD = 2.68) vs 2.63 (SD = 2.57) hours/night in the IC and SC group respectively. Whilst the mean objective adherence for 25 participants at 6-month (IC = 10, SC = 15) was 2.42 (SD = 2.59) vs 3.21 (SD = 3.37) hours/night for IC and SC groups respectively. No correlation was seen between ESS ($p = 0.24$), PSQI ($p = 0.96$), social support ($p = 0.52$), socio-economic position ($p = 0.96$) and mean adherence. However, linear regression for adherence presented a positive coefficient for risk perception ($p = 0.035$) ($r^2 = 0.16$) and outcome expectancy ($p = 0.003$) ($r^2 = 0.28$).

The behaviour change techniques that were observed to have a positive influence on adherence were reward and threat, repetition and substitution, antecedents, associations, natural consequences, feedback and monitoring, social support and comparison of outcomes. Whilst a negative influence on adherence was observed with antecedents.

Conclusion:

Further research would be beneficial to describe the determinants of adherence, such as risk perception, self-efficacy, and outcome expectancy and to facilitate patient education and development of tailor-made interventions to enhance adherence to MAA. Similarly, the lack of objective adherence monitoring necessitates the need for future studies that assess adherence objectively.

The analysis to-date demonstrates the stage-matched intervention does not enhance adherence to MAA. Notwithstanding this, adherence might be dependent on predictors such as risk perception and outcome expectancy.

A varied range of behaviour change techniques was observed in the current study that aided participants in the initiation, enactment and maintenance of the behaviour. Further research is needed to better understand the application of these techniques in a clinical setting to enhance MAA adherence.

Limitation: The clinical trial was severely impacted due to the COVID-19 Pandemic as eight months of recruitment and data collection time was lost. Hence, a limited data quantity of data was available for analysis.

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List of Abbreviations

AHI	Apnoea/Hypopnoea index
BCTs	Behaviour change techniques
BMI	Body mass index
CI	Confidence interval
CPAP	Continuous positive airway pressure
ESS	Epworth sleepiness scale
EDS	Excessive daytime sleepiness
EQ-5D	EuroQol-5 Dimension
HAPA	Health action process approach
IC	Intervention care
MAA	Mandibular advancement appliance
NC	Neck circumference
NREM	Non-rapid eye movement
NS-SEC	National Statistics Socio-economic Classification
OSA	Obstructive sleep apnoea
PSQI	Pittsburgh sleep quality index
QUIPS	Quality in prognosis studies
REM	Rapid-eye movement
SEMSA	Self-efficacy measure for sleep apnoea
SDB	Sleep disordered breathing
SSQ	Social support questionnaire
SC	Standardized care
S.E.	Standard error
SD	Standard deviation
T0	Baseline
T1	Fit appointment
T2	3-month follow-up observation
T3	6-month follow-up observation
TMD	Temporomandibular disorder

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Some realize the Self within them through the practice of meditation, some by the path of wisdom, and others by selfless service. Others may not know these paths but hearing and following the instructions of an illumined teacher, they too go beyond death.

- Bhagavad Gita

Impact of COVID-19

The present study was significantly adversely affected due to the COVID-19 pandemic. The global scale lockdown set the recruitment and data collection eight months behind, and recruitment was stopped once fifty-six participants were enrolled into the study. In-turn, this had an impact on the data that was available for analysis as only 30 and 25 participants completed the 3- and 6-month treatment follow-up period.

Furthermore, participants withdrew, discontinued and were lost to follow-up, as they felt no longer safe to commute to the hospital environment, even after the restrictions were made more lenient.

Therefore, it would be much appreciated if the above were considered whilst interpreting the results of the current study.

Chapter 1. Introduction

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder characterised by the repeated episodic collapse of the upper airway during sleep, with accompanying apnoeas and hypopnoeas, resulting in sleep deprivation amongst the many associated co-morbidities (Banno and Kryger, 2007).

Based on the severity of OSA, there are two primary treatment modalities: continuous positive airway pressure (CPAP) and mandibular advancement appliance (MAA) therapy (Network, 2003, McDaid et al., 2009). CPAP is prescribed to those suffering from moderate to severe OSA. According to the recent NICE guideline, MAA therapy is prescribed as a non-surgical treatment for mild to moderate OSA and is the second line treatment of choice for patients who remain intolerant or refuse CPAP therapy (NICE, 2021).

MAA act to enlarge the cross-sectional upper airway dimension by anterior displacement of the mandible and the attached tongue, resulting in improved upper airway patency (Tsuiki et al., 2004, Ng et al., 2005, Clark et al., 1993).

Studies evaluating MAA adherence have observed variable adherence in relation to MAA use and a gradual decline over time (Hui et al., 2000, Saglam-Aydinatay and Taner, 2018). The removable nature of MAA renders it highly patient dependant and adherence to treatment is crucial for its effectiveness (Dieltjens and Vanderveken, 2019). However, there is a lack of evidence concerning the factors influencing adherence remains (Pahkala and Suominen, 2021) and minimal research has been undertaken in relation to methods to enhance adherence to MAA therapy (Liu et al., 2022). The current NICE (2021) guidelines have identified this shortfall and emphasises the need for further research in relation to optimising adherence to MAA therapy. In addition, no qualitative evaluation has been conducted to-date, in relation to the factors associated with MAA adherence.

Thus, the current research aims to bridge the above gaps in the literature in the following ways:

I. Identify the factors influencing adherence to MAA therapy

II. Evaluate the effectiveness of stage-matched intervention in enhancing adherence to MAA treatment

III. Conduct a qualitative assessment of the factors influencing adherence to mandibular advancement appliance.

Chapter 2. A review of obstructive sleep apnoea causes, consequences and treatment

2.1. Definitions

Sleep-disordered breathing (SDB) comprises a pathophysiologic spectrum of sleep-related breathing abnormalities, ranging from snoring to the more severe obstructive sleep apnoea-hypopnoea.

Obstructive sleep apnoea (OSA) is characterized by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation.

Habitual snoring (non-apnoeic snoring) is a condition of regular snoring during sleep that does not cause the consequence of excessive daytime sleepiness (EDS). It results from an insufficient increase in upper airway resistance during sleep, with excessive vibration of upper airway tissues resulting in a loud audible snoring (Lévy et al., 1996).

Sleep Apnoea is defined as a reduction in airflow greater than ≥ 90 per cent of baseline for ≥ 10 seconds. There are three different types of sleep apnoea: central, characterised by the absence of respiratory effort; obstructive, presented as continued respiratory effort against an obstructed upper airway and mixed, which initiates with a central apnoea and accompanied with one or more obstructed breaths (Berry et al., 2012).

Hypopnoea in adults has been defined as a reduction in airflow below 50 per cent for 10 seconds or longer associated with a reduction in oxygen saturation ≥ 3 per cent from baseline prior to the event or appearance of an arousal. Alternatively, it can be defined as a respiratory event that characterised by a reduction in airflow ≥ 30 per cent from baseline for ≥ 10 seconds and reduction in saturation at least ≥ 4 per cent from baseline SpO2 per cent prior to the event (Iber, 2007).

Apnoea-hypopnoea index (AHI) is defined as the number of apnoeas and hypopnoeas occurring per hour of sleep and thus gives an indication of the severity of OSA. The AHI has

been classified into the following severity grades (FORCE, 1999) mild (AHI of 5-15 events per hour), moderate (AHI of 16-30 events per hour) and severe (AHI greater than 30 events per hour).

2.2. Prevalence

OSA is emerging as a major health problem, particularly in high-income countries. Its high disease burden is related to both, the health care costs attributable to OSA and to its contribution as an independent risk factor for cardiovascular, metabolic, and psychiatric disorders such as hypertension, stroke, diabetes, and depression (Park et al., 2011) which are global health priorities.

One early study on the prevalence of snoring and OSA estimated that 40% and 3.8% of the UK population reported snoring and breathing pauses during sleep, respectively (Ohayon et al., 1997). The study also went on to report that 1.9% of the population suffered from OSA syndrome according to the International Classification of Sleep Disorders (1990). However, the last 20 years has observed a significant increase in the rates of sleep apnoea and obesity (Lechner et al., 2019), with the association between OSA and obesity theorised to be directly proportional (Ryan et al., 2014). Similarly, a recent systematic review confirms that with advancing age, males and a high body-mass index, increase OSA prevalence (Senaratna et al., 2017).

Recent, global estimates demonstrate that the number of people with moderate to severe OSA, for which treatment is recommended, is 425 million (Benjafield et al., 2019). Moreover, the prevalence at ≥5 events/h AHI, in the elderly population is strikingly high; and reported 88 per cent in men aged 65-69 years (Lee et al., 2014) and 90 per cent in men aged 60-85 years (Heinzer et al., 2015). The corresponding figures in women being 66 per cent (Lee et al., 2014) and 78 per cent (Heinzer et al., 2015). Even at the clinically important level (≥ l5 AHI), the prevalence in the overall adult population ranged from 6 (Reddy et al., 2009) to 17 per cent (Tufik et al., 2010), whereas in the advanced age groups this was as high as 49 per cent (Heinzer et al., 2015). Although these studies have different designs, ethnic groups and defined cut-off values for OSA, the overall prevalence rate reported remains approximately similar (Senaratna et al., 2017).

Nevertheless, methodological heterogeneity in sampling methods, diagnostic criteria and methods used to measure airflow can preclude epidemiological studies in estimating a global prevalence of OSA (Senaratna et al., 2017, Benjafield et al., 2019). Heizner et al demonstrated that AHIs is analysed differently between AASM 1999 and AASM 2007 or AASM 2012, even within the same age- and sex- specific subgroups (Heinzer et al., 2015). Furthermore, risk factors of OSA such as obesity and population ageing can pose as confounders in studies reporting prevalence from different timeframes. Hence, it is important to consider OSA as having a continuum in the general population and to generate a consensus on methodology and diagnostic threshold to define OSA so that the prevalence can be validly compared across regions and countries and within age-/sex-specific subgroups (Senaratna et al., 2017).

2.3. Pathogenesis

During wakefulness, the airway is patent and held open by the high activity of the numerous upper airway dilator muscles, but after the onset of sleep, when the muscle loses its tone, the airways of vulnerable patients collapses (Mezzanotte et al., 1992, Malhotra and Loscalzo, 2009). Although this is characteristic of obstructive sleep apnoea, several factors are attributed to the narrowing of the upper airway.

2.3.1. Anatomical Factors

2.3.1.1. Narrowing of the upper airway

Anatomically, the upper airway is composed of the nasal cavity and the pharynx. The pharynx is a potentially collapsible tube lined by mucosa and supported by connective tissue, the constrictor muscles and the cervical spine posteriorly. Airflow within the pharynx is directly proportional to the pressure difference across the pharynx and its radius (to the power of four) and, it is inversely proportional to the length of the pharynx (Dempsey et al., 2010). Imaging of the pharyngeal airway has consistently showed that individuals with OSA have a narrower pharyngeal airway in comparison to their non-OSA counterparts (Whyte and Boeddinghaus, 2020).

Obesity leads to excess fat deposition and increased volume of the soft tissues surrounding the upper airway and is therefore, a major cause of the upper airway narrowing. Accumulation of adipose tissue surrounding the neck and the pharyngeal muscles directly reduces the pharyngeal airspace (Hamilton and Joosten, 2017). Studies have also observed that central adiposity is also attributed to OSA, as fat around the abdomen leads to a reduction in lung volume. Given, that men are more likely to accumulate fat around the neck muscles, OSA is more prevalent in men as compared to women (Vos et al., 2010, Whyte and Gibson, 2018).

The pharyngeal dilator muscles insert into soft tissues forming the margin of the pharynx and attach to other soft-tissue structures, cartilage (the Eustachian tube), the skull base and several bones of the surrounding maxillofacial skeleton, including the palate, mandible, hyoid bone and styloid process. Consequently, these craniofacial structures encompassing the

upper airway also influence the cross-sectional area of the pharyngeal airway (Susarla et al., 2010). A deficient maxillofacial system contributes to oropharyngeal crowding as observed in the Asian population. Whilst obesity is seen as major cause of OSA in the Caucasian population (Lam et al., 2007). Furthermore, recent investigations have also indicated that the stiffness of the tongue is lower in individuals diagnosed with OSA (Eckert, 2018).

2.3.1.2. Elongation of the upper airway

An anatomically elongated upper airway is common in individuals diagnosed with OSA (Whyte and Gibson, 2018). The airflow within the pharynx is inversely proportional to the length of the pharynx. Studies have observed that the inferior displacement of the hyoid results in elongation and narrowing of the pharynx. This is mainly associated with the posterior and inferior prolapse of an enlarged and flaccid tongue. Consequently, this is yet another factor accounting for higher incidence of OSA in men, as men have longer upper airways compared to women (Eggensperger et al., 2005, Eckert and Malhotra, 2008, Whyte and Gibson, 2020).

2.3.1.3. Upper airway collapsibility during sleep

The collapsibility of the upper airway is quantified using the pharyngeal critical closing pressure technique (Pcrit) (Carberry et al., 2016). Pharyngeal Pcrit is the pressure at which the airway can no longer remain patent and collapses. The collapsibility behaviour of the pharyngeal air way can be explained using the Starling resistor model. Knowlton and Starling devised a model for collapsible tube behaviour of most of the biologic systems, such as the vascular system, respiratory system, as well as the pharyngeal airway. The modalities of the starling resistor model can be summarised in the following statements:

- When the inflow pressure is greater than the outflow pressure, and the outflow pressure is greater than the surrounding pressure, the flow is proportional to the difference between the inflow and the outflow pressure, independent of the surrounding pressure.

- When the inflow pressure is greater than the surrounding pressure, and the surrounding pressure is greater than the outflow pressure, the flow is proportional to the difference between the inflow pressure and the surrounding pressure, independent of the changes in the outflow pressure.
- When the surrounding pressure is greater than the inflow pressure, there will be no flow throughout the tube.

Furthermore, in a Starling resistor the pressure gradient that drives the flow and the maximum flow is fixed. Any increase in the surrounding pressure higher than the internal pressure within the tube, results in the collapse of the pharynx. At the moment of collapse, right before the surrounding pressure rises to a level above the pressure inside the tube and causes its collapse, the pressure within the tube is equal to the surrounding pressure. The pressure at this specific moment is known as the Pcrit of that segment. During wakefulness, the upper airway is patent by increased drive to the dilator muscles, especially genioglossus. However, during sleep, specifically during the rapid eye movement phase, there is maximum reduction in the tone of genioglossus. In patients with OSA, this leads to severe circumferential narrowing of the oropharynx and contributes to increased collapsibility (Kazemeini et al., 2022). The more negative the pressure is, compared to the atmospheric pressure, less effort is needed to open the airway. Therefore, the lower the Pcrit is, the less collapsible the upper airway is. Therefore, normal or “good” upper airway anatomy prevents collapse such that suction pressures below -5cmH_2O are required to close the airway. These individuals are anatomically protected from OSA. On average, people with OSA have a higher Pcrit than people without OSA (−5 to > +5 cmH2O). Furthermore, OSA severity, measured by the AHI, is directly proportional to the Pcrit; however, there is considerable variance in the AHI for a given level of anatomical predisposition. Thus, upper airway patency during sleep is also dependant on several non- anatomical factors for many individuals (Eckert and Malhotra, 2008).

2.3.2. Non-anatomical factors

2.3.2.1. Impaired function of the pharyngeal dilator muscles

The pharyngeal dilator muscles, such as the genioglossus and tensor palatini, receive complex patterns of neural drive. The neural drives in turn are received from pattern generator neurons in the brainstem, reflex input from pressure sensitive mechanoreceptors in the upper airway and chemical drive via increases in CO_2 and hypoxia. This summation of various drives results in the constant level of activation i.e. tonic activity during quite breathing (Edwards and White, 2011). Both, genioglossus and tensor palatini have a similar short-latency reflex excitation to oppose the collapsing forces when larger brief suction pressures are applied to the upper airway during wakefulness. Consequently, neural drive to genioglossus and tensor palatini is strongly influenced by the sleep-wake system (Eckert et al., 2007). However, the mechanisms responsible are not as simple as a loss of reflex excitation during sleep as initially suspected. Lack of upper airway resistance progressively decreases genioglossus muscle activity from slow wave sleep, to N2 and REM (Rapid eye movement) sleep. In contrast to this, tensor palatini activity markedly decreases during sleep onset, however, remains consistent across the different sleep stages. However, these sleep-dependant changes in the upper airway reflex and neural control only partly attribute to OSA (Cori et al., 2018).

Muscle effectiveness is the ability of the muscle to translate the neural drive received by the upper airway muscles into airway dilation to increase airflow (Eckert and Malhotra, 2008). The pharyngeal muscles are capable of increasing their activity when challenged with respiratory stimuli during sleep. This concept is known as muscle responsiveness (Loewen et al., 2011). In individuals with OSA, there is failure of the pharyngeal muscles to respond appropriately from neural drive perspective. A lack of muscle responsiveness alone, in the absence of impaired upper airway anatomy, does not lead to OSA (Dempsey et al., 2010). This poor muscle responsiveness during sleep, in combination with impaired upper airway anatomy is likely to be a cause of OSA in these individuals (Edwards and White, 2011). Nevertheless, normal or good muscle can compensate for impaired upper anatomy during sleep. Despite this, respiratory events can occur during the REM phase due to decreased muscle activity and

lower chemosensitivity than NREM (Non-rapid eye movement) sleep. Some individuals generate adequate pharyngeal muscle activity when the airway is narrowed during sleep. However, this does not lead to adequate pharyngeal dilation and increased airflow due to poor muscle effectiveness (Eckert and Malhotra, 2008). Evidence concerning poor muscle effectiveness is limited; however, factors such as poor coordination of the neural drive to the various upper airway muscles during sleep, excess fat or muscle hypertrophy or changes in muscle fibre type can contribute to it.

2.3.2.2. Low respiratory arousal threshold

Premature awakening in response to mild airway narrowing, rather than collapse, contributes to OSA by disrupting sleep continuity and limiting the opportunity for adequate upper airway muscle recruitment to restore airflow during sleep (Eckert et al., 2014).

2.3.2.3. Loop gain

Loop gain describes the stability of the respiratory feedback control system; a high loop gain indicates an unstable ventilator chemoreflex control system. The overall loop gain is governed by the ratio of the ventilator response to the disturbance that elicited the response (Khoo 2000). The theory suggests there is a controller and a plant component, with a delay between the two. The controller senses the stimulus and dictates the action of the plant, which responds to decrease the stimulus. In ventilatory control, chemoreceptor sensitivity to blood gases reflects controller gain, and the effectiveness of the lungs to alter blood gases reflects plant gain. The product of controller and plant gain provides the overall loop gain of the system (Khoo 2018). Furthermore, there is a circulation delay between when ventilation begins to alter blood gases and when the chemoreceptors sense the change. Therefore, if the gain of either the controller or the plant is too high, there is the potential for ventilatory overshoot producing instability in the system (Khoo 2000). People with high loop gain have an exaggerated ventilator response to minimal increases in carbon dioxide levels, usually during a hypopnoea, as detected by chemoreceptors in the carotid body (Li et al., 2019). In OSA, the delay in the closed loop system is not just a function of lung to chemoreceptor circulatory delay. When the

airway is obstructed, the delay is the duration of the event, as chemical drive continues to build and the ventilatory response cannot be expressed until the airway re-opens (Younes 2014). Loop gain is also not a static value, rather it changes constantly. During an apnoeic event, as there is no ventilatory response, loop gain is actually zero (Dempsey, Smith et al. 2004). However, as chemical drive accumulates, because hypoxia sensitizes the carotid body hypercapnic response, progressive hypoxia and hypercapnia increases controller gain. As PaO_2, the partial pressure of oxygen in the arterial blood, is depleted and CO_2 accumulates in the lungs, plant gain progressively increases such that when the airway opens, every unit increase in minute ventilation would produce greater fluctuations in alveolar gas tensions (Khoo 2000, Dempsey, Smith et al. 2004). Thus, in OSA, the loop gain that is most relevant to apnea propagation is the loop gain at airway opening, when both controller and plant gains are at their peak. However, if the airway does not fully open the ventilatory response will be restricted, such that the net loop gain, being the loop gain that is actually expressed, will be lower than the chemical loop gain, being the actual drive to breathe (Younes 2014).

2.4. Clinical Symptoms

2.4.1. Symptoms during sleep

2.4.1.2. Snoring

Snoring is the vibration, especially of the soft palate and uvula, within a narrow but patent upper airway that occurs during sleep and creates noise as the air passes in and out while breathing. Habitual snoring affects 95% of OSA subjects, however, it is highly prevalent in the general population affecting around 35–45 per cent of men and 15–28 per cent of women (Campos et al., 2020). The negative consequences of snoring include both a social and medical impact such as embarrassment and decreased quality of sleep for the bed partner and, is the hallmark symptom of OSA and therefore, most often the primary reason to seek medical help. A reduction in snoring is perceived by patients as therapeutic efficacy and therefore favours treatment adherence (Dieltjens et al., 2015).

2.4.1.3. Choking and grasping

Complete closure of the airway, usually at the retropalatal level, results in cessation of snoring and apnoea. This can result in the sudden awakening of patients with the feeling of choking or gasping (Liu et al., 2016).

2.4.1.4. Nocturia

Nocturia is an often-described symptom of sleep-disordered breathing (SDB).The frequency of nocturnal urination in OSA patients increases by between 52 and 72 per cent depending on OSA severity (Kaynak et al., 2004). A recent meta-analysis suggested that men with OSA have a high incidence of Nocturia in comparison to women (Zhou et al., 2020). The pathophysiological link between OSA and Nocturia involves a complete or partially obstructed upper airway and increased intra-abdominal pressure. A corresponding decrease in the atrial natriuretic peptide and increase in the vasopressin secretion, consequently leads to an increase in urine production (Roux et al., 2000).

2.4.1.5. Abnormal Motor activity

Subjects with OSA experiencing asphyxiation during sleep due to upper airway obstruction may complain of restlessness, which may be manifested by increased tossing and involuntary movements during sleep (Zhou et al., 2021b).

2.4.2. Daytime symptoms

2.4.2.1. Daytime sleepiness

Increased daytime sleepiness is an important symptom of OSA resulting from sleep fragmentation (Verstraeten et al., 2004) which significantly affects neurocognitive performance. There is a clear relationship between excessive daytime sleepiness and limitation in work performance, which in turn can have serious implications on the quality of life (Turner et al., 2019). Furthermore, hypertensive patients with OSA have been associated with increased daytime sleepiness, as measured by the Epworth sleepiness scale (ESS). However, studies have reported conflicting observations concerning this interaction. Kapur et al. (2008) observed that the association of OSA with hypertension is stronger in individuals who report daytime sleepiness, than in those who do not. Notwithstanding this, recent studies have found that ESS scores are higher in normotensive OSA patients as compared to hypertensive counterparts (Martynowicz et al., 2017, Tam et al., 2019). Hence, more studies with standardised methodologies are needed to evaluate this association.

2.4.2.2. Depression & Psychological dysfunction

Depressive symptoms are common in OSA and related to its severity. Using the patient health questionnaire (PHQ-9), with score ≥ 10 as an indication for clinically significant depressive symptoms, Edwards et al (2015) found significant positive association at baseline between PHQ-9 score and AHI ($p < 0.0001$), particularly in men and women with severe OSA ($p < 0.001$). After effective treatment of 228 OSA patients with CPAP, symptoms of depression were improved, changing PHQ-9 from 11.27 ± 6.09 to 3.71 ± 2.86 ($p < 0.001$). This highlighted that the effective treatment of OSA with CPAP seems to improve depression symptoms (Edwards et al., 2015). Moreover, research has observed an association between OSA and

reduction in grey matter and argues in the favour of early treatment (Morrell et al., 2010). Similarly, a recent review has reported that cognitive functions (e.g. attention) deficit caused by untreated OSA can be irreversible and shows only partial recovery after a period of treatment with CPAP. Consequently, the review highlighted the need of more research to analyse the relationship between OSA and cognitive disorders, in terms of treatment (Vanek et al., 2020).

2.4.2.3. Sexual problems

Several studies have shown a high incidence of sexual dysfunction among OSA patients, ranging from 47.1 per cent to 80.0 per cent (Budweiser et al., 2009, Li et al., 2016, Kellesarian et al., 2018). The underlying mechanism of interaction between OSA and sexual dysfunction remains unknown, although several theories have been proposed, including peripheral neuropathy due to hypoxemia, or vascular endothelial dysfunction (Shin et al., 2008). Interestingly, severity of OSA is considered to be an important factor in the development of impotence in men (Margel et al., 2004, Zhang et al., 2016). In contrary to this, Jeon et al (2015) demonstrated that no significant association was observed between erectile dysfunction and OSA severity (Jeon et al., 2015). The role of OSA severity is still unclear concerning sexual dysfunction and therefore, further research is emphasised in this context (Steinke et al., 2016). Furthermore, Jeon et al (2015) also demonstrated that sexual dysfunction was independently associated with sleep apnoea quality of life index (SAQII) and depressive symptoms. This is consistent with recent findings that has observed the same association between depression and sexual dysfunction in women with mild OSA (Coelho et al., 2021). Nevertheless, the above findings lack generalisability, as they cannot be applied to men or to those women with moderate or severe OSA.

2.4.2.4. Headaches

Morning Headaches or headaches in general are frequent in patients with OSA due to fragmented or non-restful sleep. It has been hypothesised that OSA does play a role in triggering Hypnic headaches (Ferini-Strambi et al., 2019), a very rare primary

headachecharacterized by recurring attacks developing only during sleep (Raskin, 1988). Nevertheless, a lack of a temporal correlation of headache attacks with the drop of oxygen saturation has been observed in OSA patients (Ferini-Strambi et al., 2019). Furthermore, Studies have reported an increased prevalence of tension-type headaches (TTH) in individuals with sleep disturbances. However, the association between TTH and OSA is contentious, since headaches associated with OSA are categorised separately in the International Classification of Headache Disorders (ICHD-3) and reported to be distinct from TTH. Hence, there is no definitive evidence concerning the association between TTH and OSA (Engstrøm et al., 2014, Russell et al., 2014, Wang et al., 2015).

2.5. Medical complications

2.5.1. Hypertension

OSA is one of the major modifiable risk factors of hypertension and is significantly associated with short sleep duration and poor sleep quality scores. Cross-sectional studies have observed that the odds of hypertension increased by 1% for every episode of apnoea per hour of sleep and increased by 13% for every 10% decrease in oxygen saturation (Lavie et al., 2000). The prevalence of hypertension was found to be 59%, 62%, and 67% in a cohort of 6132 mild, moderate and severe sleep apnoea patients, respectively (Nieto et al., 2000). Hedner et al. (1988) demonstrated that patients with OSA have progressively increased sympathetic activity during apnoeic events. Furthermore, patients with OSA have also demonstrated elevated sympathetic activity during wakefulness (Somers et al., 1995). Consequently, a persistent increase in sympathetic drive ultimately leads to an increase in vascular resistance and vascular remodelling, contributing to increased blood pressure (Phillips and O'Driscoll, 2013). Similarly, a recent systematic review and meta-analysis has demonstrated a significant correlation between OSA and hypertension (Odds Ratio [OR] = 6.44, Confidence interval [CI] = 95%, $P < 0.00001$) (Hou, Zhao et al. 2018). Nonetheless, the findings should be interpreted with caution, as the quality of most of the studies included in the analysis was low.

2.5.2. Coronary Heart Disease

OSA has reported to be a potential trigger for coronary heart disease (CHD) (Peker et al., 2006, Somers et al., 2008). Studies have attributed this association to intermittent hypoxia, formation of free radicals that enhance lipid peroxidation, downregulation of antioxidant activity, increased expression of markers of systematic inflammation and immune cells, increased sympathetic activation and impairment of vasomotor activity (Bradley and Floras, 2009, Ali et al., 2014). Given, that patients with OSA generally present with comorbidities, the association between OSA and CHD could be ascribed to the clustering of comorbidities, especially type 2 diabetes or due to a true causal role (Somers et al., 2008, Lurie, 2011,

Sánchez-de-la-Torre et al., 2013). Similarly, genetic investigations have also revealed high genetic correlations between OSA and CHD, and including other comorbidities such as hypertension, type 2 diabetes, stroke, depression, hypothyroidism, asthma and inflammatory rheumatic disease (Strausz et al., 2021).

2.5.3. Heart Failure

Epidemiological studies have demonstrated a significant correlation between OSA and heart failure (Kasai and Bradley, 2011), given, that patients with OSA present with severe coronary heart disease and increased cardiovascular risk and ventricular deterioration. Patients with OSA are at higher odds of having heart failure compared to their counterparts (Nakashima et al., 2006). Furthermore, observational studies in relation to heart failure have revealed that survival is generally reduced in patients with OSA, as compared to those without OSA (Wang et al., 2007, Yumino et al., 2007). Moreover, research has emphasised the cautious use of adaptive servo-ventilation therapy in patients with heart failure as no significant effect was observed in such patients (Cowie et al., 2015, Arnaud et al., 2020).

2.5.4. Stroke

OSA is a recognized risk factor for stroke occurrence. Epidemiological studies of 4- and 8- year follow-up data have demonstrated a 2-3-fold increased risk for incident stroke in those with moderate to severe OSA (Redline, Yenokyan et al. 2010). Although, the mechanism by which OSA causes stroke is still being investigated. OSA causes intermittent and repetitive hypoxia during sleep, recurrent arousals and the generation of negative intrathoracic pressure. This cascade might entail sympathetic activation and catecholamine release leading to post apnoeic surges in blood pressure and heart rate, increased sleep fragmentation, and intermittent reductions in cerebral blood flow. The acute effects of this downstream cascade include arrhythmias; reactive oxidative stress, endothelial dysfunction and atherosclerosis; altered cerebral blood flow; hypertension; autonomic dysfunction and hypercoagulability might pre-dispose to stroke (Dempsey, Veasey et al. 2010). Furthermore, post-stroke period OSA leads to longer hospitalisation and rehabilitation, increased stroke recurrence, and increased

mortality. Stroke patients with moderate OSA, followed-up for a period of 10 years showed an increased mortality rate by 75% when adjusted for multiple confounders (Khot and Morgenstern 2019). However, CPAP therapy for OSA with a follow-up data of 5-7 years has exhibited a reduction in mortality and morbidity. Alternative treatment modalities for OSA (e.g. mandibular advancement appliances, weight reduction, and positional therapy) have undergone limited or no assessment in the stroke population and therefore their efficacy is uncertain (Ou, Chen et al. 2015). Nevertheless, a recent scientific statement by American Heart Association has summarised the evidence in relation to the efficacy of MAA in stroke patients. The authors highlighted the improvement in 24-hours ambulatory blood pressure measures and inflammation markers of cardiovascular disease with mandibular advancement therapy (Roger, Go et al. 2012).

2.5.5. Sudden Death

Research has demonstrated a two-fold higher risk of deaths associated with OSA. However, this risk is mainly attributed to increased number of comorbidities associated with OSA (Pan et al., 2016). A recent systematic review and meta-analysis has demonstrated OSA to be a significant risk-factor for all-cause mortality and cardiac mortality (Heilbrunn et al., 2021). However, the authors combined adjusted and unadjusted risk ratios (RR) whilst calculating pooled estimates which could have introduced between-study heterogeneity. Therefore, the results should be interpreted with caution. Notwithstanding this, the review also emphasised on the urgency of strategies for the prevention and treatment to elevate the survival and quality of life in patients with OSA (Heilbrunn et al., 2021).

2.5. Diagnosis

2.6.1. History

A comprehensive sleep oriented history, physical examination, sleep evaluation, investigations and pharyngeal airway imaging are involved in the diagnosis of OSA. The clinical examination comprises the examination of the nose, soft palate, fauces and tongue, including awake nasendoscopy, in order to identify an obvious physical obstruction to breathing. Anthropometric measures such as neck circumference, height and weight are also recorded (Semelka et al., 2016).

The current NICE guidelines (NICE, 2021) states that an initial assessment for individuals suspected with OSA comprises of a sleep history and a clinical examination for the presence 2 or more of the following features:

- Snoring
- Witnessed apnoeas
- Unrefreshing sleep
- Waking headaches
- Unexplained excessive sleepiness, tiredness or fatigue
- Nocturia (waking from sleep to urinate)
- Choking during sleep
- Sleep fragmentation or insomnia
- Cognitive dysfunction or memory impairment

The guidelines have also highlighted the increased odds of having OSA in individuals with the following conditions/phenotypes:

- Obesity or overweight
- Obesity or overweight in pregnancy
- Treatment-resistant hypertension
- Type 2 diabetes
- Cardiac arrhythmia, particularly atrial fibrillation
- Stroke or transient ischaemic attack
- Chronic heart failure
- Moderate or severe asthma
- Polycystic ovary syndrome
- Down's syndrome
- Non-arteritic anterior ischaemic optic neuropathy (sudden loss of vision in 1 eye due to decreased blood flow to the optic nerve)
- Hypothyroidism
- Acromegaly

2.6.2. Investigations

2.6.2.1. Daytime sleepiness

The assessment of sleepiness is important in OSA and therefore, a number of tools are used to determine sleepiness. These include objective measures such as the multiple sleep latency test, maintenance of wakefulness test, and psychomotor vigilance testing as well as validated questionnaires. Likewise, the NICE guidelines (NICE, 2021) have recommended the use of Epworth sleepiness scale (Appendix 1).

2.6.2.2. Subjective assessment

The Epworth sleepiness scale is a validated questionnaire widely used in both research and clinical practice (Johns, 1991) . The self-administered questionnaire invites patients to rate on a scale of 0 (less likely) to 3 (more likely) how likely they would be to doze off or fall asleep in eight situations, based on their usual way of life in recent times. The scores for these eight situations, in the questionnaire, are added to give a final score for the patient, ranging between 0 to 24. Scores of 0 to 9 is considered normal while a score of 10 and above indicates excessive daytime sleepiness and that expert medical advice should be sought (Johns, 1991). However, the accuracy and test-retest reliability of ESS is a matter of debate. Studies with opposing views have emerged in the field of sleep medicine. Whilst studies have argued that ESS demonstrates a robust acceptable level of test-retest reliability (Walker et al., 2020, Rosenberg et al., 2022). Notwithstanding this, studies have suggested to interpret the ESS scores with caution because of its low test-retest reliability (Grewe et al., 2020, Lee et al., 2020, Rozgonyi et al., 2021). Hence, a wide-ranging assessment of a patient's daytime sleepiness beyond the ESS is necessary (Mazzotti et al., 2022).

2.6.2.3. Objective assessment

The multiple sleep latency test (MSLT), is designed to measure excessive daytime sleepiness, in a series of 4 to 6 half-hour naps taken 2 hours apart, during the day, in surroundings designed to encourage sleep (Carskadon, 1986). Conversely, the Maintenance of Wakefulness test (MWT) measures the patient's ability to stay awake, whilst sitting for 40

minutes, in a dimly lit room (Littner et al., 2005). These objective assessments provide an accurate measurement of sleepiness and overcome the limitation of subjective assessment scale. However, such tests are time-consuming and expensive and, accordingly, are rarely used in everyday clinical practice (Lévy et al., 2015).

2.6.2.4. Sleep studies

An overnight sleep study is required for the diagnosis of OSA. In accordance with the NICE guidelines (2021), the following should be considered while prioritising individuals within the sleep service:

- They have a vocational driving job
- They have a job for which vigilance is critical for safety
- They have unstable cardiovascular disease, for example, poorly controlled arrhythmia, nocturnal angina or treatment-resistant hypertension
- They are pregnant
- They are undergoing preoperative assessment for major surgery
- They have non-arteritic anterior ischaemic optic neuropathy

2.6.2.5. Polysomnography

Overnight polysomnography performed in a sleep laboratory in the presence of an attendant is considered the gold standard diagnostic study for OSA (Qaseem et al., 2014). A full night study is generally indicated for diagnosis and determines the severity of OSA, with a follow-up study used for positive airway pressure titration (Balachandran and Patel, 2014). However, a split-night study, in which diagnosis and positive airway pressure titration occur in the same night, can also be performed. Split-night studies are most useful in patients who have an apnoea-hypopnea index greater than 20 events per hour discovered within the first two hours of the study (Epstein et al., 2009) Although considered as a ‘‘gold-standard,’’ polysomnography is time consuming, labour intensive, and can be costly. It requires an overnight stay in a sleep laboratory staffed with qualified personnel that can collect and interpret complex physiologic data (Punjabi, 2008) . Given this, home sleep studies, which allow the patients to sleep in their own environment and potentially reflect normal ambient conditions, better than a sleep laboratory, appear more convenient and cost-effective. Moreover, home sleep tests can be an alternative to sleep laboratory studies in patients who are unable to present to a sleep laboratory (Collop et al., 2007, NICE, 2021). However, home sleep studies are limited to the estimation of AHI index and are unable to distinguish between sleep and wakefulness (El Shayeb et al., 2014). Additionally, home sleep tests are not recommended in patients with comorbidities such as congestive heart failure, chronic lung disease, or neurologic conditions because they have not been verified in these populations. These tests are more accurate in identifying patients with a higher probability of OSA and can rule out OSA in low-risk patients (Qaseem et al., 2014). Although, if home sleep studies are inaccessible, home oximetry can be prescribed for individuals with suspected OSA. Nonetheless, oximetry alone may be insufficient in distinguishing between OSA and other causes of hypoxemia in individuals with cardiovascular or respiratory conditions (NICE, 2021).

2.6.2.6. Imaging of the oropharyngeal airway

Studies in imaging have demonstrated a significant association between the dimensions and shape of the airway with the measure of airway collapsibility, as well as the severity of OSA (Susarla et al., 2010, Genta et al., 2014, Liu et al., 2016, Barrera et al., 2017, Whyte and Gibson, 2018). An inferiorly positioned hyoid bone has been reported to significantly correlate with the apnoea/hypopnoea index (Barkdull et al., 2008, Vos et al., 2010). Cross-sectional imaging the pharyngeal airway demonstrate a significantly narrowed, abnormally shaped and elongated airway in OSA but does not confirm the diagnosis (Ogawa et al., 2007).

The main limitation of traditional otorhinolaryngologic examinations is that they are performed during wakefulness. Drug-induced sleep endoscopy (DISE), introduced in the last decade by Pringle and Croft, entails endoscopic evaluation of the upper airway during pharmacologically induced sleep (Croft and Pringle, 1991). The advantage of observing upper airway collapse during sleep enables clinicians to target therapy according to the location and degree of the obstruction of the upper airway (De Corso et al., 2013, De Vito et al., 2014). Although, the similarity of DISE and natural sleep is debatable, Park et al., 2019 observed moderate to good agreement between DISE and natural sleep endoscopy (Park et al., 2019). Furthermore, DISE can be employed in OSA patients intolerant to CPAP therapy as can be used in identifying reasons for treatment withdrawal, especially in patients with a laryngeal collapse (Civelek et al., 2012). Moreover, mandibular thrust during sleep endoscopy can also aid in determining the prognosis of mandibular advancement therapy in OSA patients (Johal et al., 2007). However, despite the advantage of DISE in treatment selection, there still lacks a consensus concerning the scoring and classification (De Vito et al., 2014, Dijemeni et al., 2017, De Vito et al., 2018).

2.6. Treatment

Currently, treatment is recommended for all patients with an AHI of 15 or more events per hour, as well as for those with an AHI 5 to 14 events per hour with symptoms of sleepiness, impaired cognition, mood disturbance, or insomnia or with coexisting conditions such as

hypertension, ischemic heart disease, or a history of stroke (NICE, 2021). Therapies for obstructive sleep apnoea have been designed to reduce the frequency of sleep-disordered breathing events and normalisation of the AHI. These therapies can be broadly classified as non-surgical or surgical therapies. Additionally, treatments can also vary based on the severity of OSA (NICE, 2021).

2.7.1. Non-surgical treatments

2.7.1.1. Lifestyle changes & weight reduction

Obesity results in fatty deposits around the neck, which contribute to pharyngeal collapse (Shelton et al., 1993). Weight loss of more than 10 kg may resolve obstructive sleep apnoea in more than 50 per cent of persons with mild disease and improve cardio-metabolic health (Chirinos et al., 2014). However, there are inconsistent findings on the association between weight reduction and overall improvement in sleep and breathing patterns (Hargens et al., 2013). Notwithstanding this, lifestyle advice alone for mild OSA patients who have no symptoms or symptoms that do not affect usual daytime activities can aid to prevent OSA from deteriorating (NICE, 2021).

Several studies have examined the effect of weight reduction drugs in alleviating the signs and symptoms of OSA. A randomised, placebo-controlled trial of sibutramine, given to overweight males with OSAHS, found no change in AHI or weight over one month (Martinez and Basile 2005). However, the results of a cohort study, in which obese males with OSA were enrolled into a 6-month sibutramine-assisted weight loss program incorporating a dietary prescription and advice on exercise, have reported a significant improvement in ESS, AHI and RDI (Yee, Phillips et al. 2007, Phillips, Yee et al. 2009). In a further study, CPAP treatment vs sibutramine-assisted weight loss demonstrated no change in AHI or in ESS with sibutramine but an improvement in mean nocturnal oxygen saturations and also an improvement in sleep architecture. Whilst CPAP significantly improved both AHI and ESS, led to greater improvement in sleep architecture, and led to improvements in other sleep and respiratory variables (Ferland, Poirier et al. 2009). Moreover, sibutramine-assisted weight loss is concluded to be inferior to CPAP and sibutramine has been suspended by the Medicines and

Healthcare products Regulatory Agency due to concerns that cardiovascular risks outweigh the benefits (NICE 2006).

2.7.1.2. Change in sleeping posture

Studies have shown that sleeping in the supine position compared with the lateral position may double the apnoea-hypopnea index in patients with OSA. Strategies to avoid the supine position include placing tennis balls in a sock or pocket and pinning or sewing them onto the back of a shirt; wearing vests with posterior bumpers; and using positional alarms, verbal instruction, neck vibration devices and pillows (Randerath et al., 2011). Because of poor long-term compliance, positional therapy is not routinely recommended over standard positive airway pressure therapy (Bignold et al., 2009, de Vries et al., 2015). This is in accordance with the current NICE (2021) guidelines which does not advocate the positional modifiers as first-line of treatment over CPAP or MAD in patients with mild or moderate positional OSA. Furthermore, the guidelines also advise against their use in severe OSA patients.

2.7.1.3. Continuous positive airway pressure (CPAP)

Continuous positive airway pressure (CPAP) is regarded as the gold standard treatment for obstructive sleep apnoea (NICE, 2008). CPAP works via pneumatic splinting of the upper airway and provides a constant level of positive pressure across inspiration and expiration. Airway pressure may be applied through oro-nasal and nasal devices (Gay et al., 2006). Although CPAP is highly effective in reducing the AHI (to < 5 events per hour) in most patients, whilst reducing snoring and daytime sleepiness, when assessed in the sleep laboratory, it requires tremendous effort on the patient's part to position the mask properly and maintain the machine (Pépin et al., 2018). Hence, CPAP adherence rates ranges between 17 to 85 per cent, with adherence to treatment being defined as use for more than 4 hours per night for more than 70 per cent of nights (Sin et al., 2002, Weaver and Grunstein, 2008, Wolkove et al., 2008). However, interventions to improve adherence with CPAP have focused on patient education, clinical support, and behavioural interventions (Moran et al., 2010, Wozniak et al., 2014, Hoet et al., 2017). Baker et al. (2014) demonstrated increased CPAP adherence (n = 83) of 99min/hour for 6 months from a motivational enhancement intervention compared to

CPAP alone and the effect of the intervention lasted for 12 months in a subset of the participants. This was achieved by targeting the intervention on behaviour change rather than attempting to lengthen the sleep duration. Similarly, a number of studies in the field of sleep medicine have observed enhanced patient adherence to CPAP therapy due to behaviour change interventions (Stepnowsky et al., 2006, Richards et al., 2007, Aloia et al., 2013, Deng et al., 2013).

2.7.1.4. Mandibular advancement appliance (MAA)

The MAA is the most widely used intra-oral appliances for the treatment of OSA (Johal and Battagel, 2001). According to the current NICE guidelines, MAA therapy is recommended to individuals diagnosed with Mild OSA and symptoms that affect their usual daytime activities. The guidelines also prescribe MAA therapy to those with moderate or severe OSA intolerant to CPAP treatment as a second line of treatment. Patients recommended for MAA therapy are aged 18 and over and should present with optimal dental and periodontal health (NICE, 2021). MAA are categorised into the following types: custom titratable; custom non-titratable; non-custom titratable; and non-custom non-titratable. Seven studies evaluating the impact of ready-made (non-adjustable/ non-titratable) and custom-made MAA, observed an overwhelming patient-reported preference for custom-made MAA in comparison to ready-made devices (Vanderveken et al., 2008, Friedman et al., 2012, Quinnell et al., 2014, Wang and Liu, 2014, Al-Dharrab, 2017, Gagnadoux et al., 2017, Johal et al., 2017). Given the variation in the appliance fabrication and titration, all the appliances attempt to maintain an open airway by positioning the mandible forward. Although, CPAP has found to be more efficient than MAA in reducing AHI, arousal indices, and oxygen desaturation, particularly in patients with moderate to severe OSA, quality-of-life indices appear to be the same for both (Ramar et al., 2015). However, self-reported adherence with MAA is highly variable. Whilst, short-term adherence ranges from 76 to 95%, long-term adherence is reported to decline to 32% after 4 years of use (Marklund et al., 2012, Saglam-Aydinatay and Taner, 2018). Studies have observed that treatment withdrawal is more likely to occur in the first 2 years (Hoffstein, 2007, Doff et al., 2013a, Attali et al., 2016). Similarly, recent data concerning objective MAA

adherence detected that mean wearing time decreased by 4% after 1 year (Pahkala and Suominen, 2021). The study also observed that only half of the participants (Sample size = 24) were adherent to MAA therapy after 12 months (Pahkala and Suominen, 2021). Furthermore, adherence to MAA is highly patient dependant and influenced by numerous factors.

2.7.1.5. Surgical treatments

Surgical treatments proposed and attempted to correct anatomic obstruction in patients with OSA include: nasal procedures (e.g. septoplasty), oral procedures (e.g. uvulopalatopharyngoplasty [UPPP], uvulopalatopharyngoplasty with uvula preservation [HUPPP]), hypopharyngeal procedures (e.g. tongue reduction and stabilization), laryngeal procedures (e.g. epiglottoplasty), and global airway procedures (e.g. maxilla-mandibular advancement [MMA]) (Epstein et al., 2009). The current NICE guidelines recommend the referral of patients for surgical options who are unable to tolerate CPAP and a customised MAA despite medically supervised interventions. However, systematic reviews have observed insufficient evidence to support surgery in general or any type in particular for the management of OSA (Sundaram et al., 2005). Notwithstanding this, the results should be interpreted with caution as the review includes randomised controlled trials of mixed quality. More recently, a network meta-analysis evaluating the efficacy of surgical options in treatment of OSA observed MMA combined with HPPP demonstrated the highest efficacy. Nevertheless, the finding should be interpreted with caution due to increased level of heterogeneity among the included studies (Zhou et al., 2021a).

2.7. Adherence

2.8.1. Definitions of Adherence and Compliance

Adherence to treatment is a key link between process and outcome in health care (Urquhart, 1996). In contrast to previous literature, adherence to treatment extends beyond the idea of taking prescribed pharmaceuticals. A WHO Adherence meeting of June 2001, defined adherence as 'the extent to which the patient follows medical instructions' (Sabaté and Organization, 2001). Nevertheless, the term 'medical' is inadequate to encapsulate the variety of interventions implemented to manage chronic diseases. Additionally, the term 'instructions' infers that the patient is a merely passive, acquiescent receiver of expert medical guidance, rather than an involved participant in the treatment process. Consequently, the WHO Adherence project (2000) chose a definition of adherence, which was an amalgam of several previous definitions. It also extended the concept of adherence to include other elements of the patient's behaviour, such as following recommendations about diet or lifestyle. Accordingly, this project defined adherence as: "the extent to which a person's behaviour, taking medication, following a diet, and/ or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" (WHO, 2003).

The oldest term used to describe such behaviour is 'compliance'. The most common definition of compliance is ''the extent to which the patient's behaviour matches the prescriber's recommendations" (Chakrabarti, 2014). Compliance implies a one-sided interaction, where the clinician decides on the suitable treatment, which the patient has to consent to regardless of the suitability (Julius et al., 2009). Thus, compliance is synonymous with a paternalistic conceptualisation medication/treatment-taking behaviour, in which patient autonomy is disregarded. However, adherence focuses on the patient being an active collaborator in the decision-making process regarding the most suitable treatment and consequently yields the most appropriate treatment regimen to be followed, whilst emphasising the participation of both the clinician and the patient in a discussion. Thus, it has been suggested as an improvement over the term compliance, which has negative implications since it disapproves

of any patient-behaviour, which does not comply with the clinician's recommendations (Perkins, 1999).

2.8.2. Health beliefs and health behaviour change

Adherence to a new health behaviour change encapsulates a variation in of social, emotional and cognitive factors (Schwarzer, 2008). In health psychology, health behaviours are defined as any behaviour that is related to an individual's health status. Health behaviour aims to prevent disease, and was further defined by Matarazzo (1984) as health-impairing habits (e.g. smoking, eating a fat diet) or health protective behaviours (e.g. attending a health check). Decades of research indicate that knowledge and awareness is instrumental in how individuals choose to behave (Lashley, 1987, Champion, 1990, Rimer et al., 1991). However, further research has shown that awareness alone is insufficient. Individual beliefs, also known as health beliefs are fundamental in predicting behaviour change. Some of these health beliefs are identified as perceived self-efficacy, outcome expectancy and risk perception (Schwarzer, 2008). Bandura (1986) explained Perceived self-efficacy as 'one's belief in one's capabilities to organise and execute the sources of action required to manage prospective situations'. Outcome expectancies are defined as anticipated consequences (positive or negative) as a result of engaging in a behaviour (Reesor et al., 2017). Whilst, risk perception is a key health belief, concerning one's belief about the severity of a condition and individual vulnerability (Ogden, 2019).

Social-cognitive theories assume that an individual's intention to adopt a new behaviour is the best direct predictor of actual change. Notwithstanding this, people mostly do not act according to their intentions. Many factors account for this disparity in intent and behaviour (Luszczynska and Schwarzer, 2005). Unforeseen obstacles might arise, for example, people could give in to the temptations. Intent must, therefore, be complemented by the above-mentioned health beliefs that can facilitate the translation of intention into action. These beliefs also known as post intentional factors and help to bridge the intention-behaviour gap (Schwarzer, 2008). This has led to the use of behavioural strategies, specifically tailor-made interventions to improve patient adherence to treatment.

2.8.3. Continuum models versus Stage models of Health Behaviour Change

In recent decades, social-cognitive prediction models have mainly revealed the mechanisms of health self-regulation. Models of health behaviour change propose a sequence of variables that enhance motivation and would eventually facilitate behaviour change (Ogden, 2019). These models of behaviour can be categorised as stage or continuum models of health behaviour change. Stage models describe behaviour change as a dynamic process where individuals move through various stages, as they change their behaviour. Whilst, continuum models assume that a person's behaviour is the outcome of a conscious intention. Intention forming is seen as being determined by beliefs and attitudes (Lippke and Ziegelmann, 2008). They take inspiration from the subjective expected utility theory proposed by Edwards (1954), that any change in one's behaviour stems from weighing up the pros and cons of any action. The theory depicts individuals as 'rational informational processors' and emphasises on identifying a set of predictors that includes constructs such as, perceived barriers, social norms, disease severity, personal vulnerability, or perceived self-efficacy (Edwards, 1954). Similarly, continuum models also draw upon on the social cognition theory, which advocates that behaviour is guided by expectancies, incentives and social cognitions (Bandura, 2005). The integration of these factors facilitates the development of a prediction model for explaining changes in behavioural intention and behaviour change. The most widely applied continuum models are the theories of reasoned action, planned behaviour, and protection motivation theory (Weinstein, 2007, Abraham and Sheeran, 2013).

Despite the wide application of continuum models in health psychology, research has proposed major theoretical drawbacks. An overall drawback of continuum models is that they account more for intention variance than for behaviour variance. Additionally, the 'one-size-fits-all' intervention approach of continuum models suggests cognitive and behaviour change transpires in a linear process. This fails to account for the qualitative changes such as changing mind-sets, phase transitions, or relapse or discontinuation of the behaviour (Armitage and Arden, 2002). Accordingly, continuum models do not necessarily aim for

interventions to initially change perceived vulnerability, perceived consequences, or perceived self-efficacy. Thus, interventions are not expected to proceed in a structured sequence but can be applied randomly, or even concurrently. Furthermore, the continuum models exclude the post intentional phase, which bridges 'the intention-behaviour' gap', in which goals are translated into action (Armitage and Arden, 2002, Abraham and Sheeran, 2013) . The post-intentional phase relates to the interplay of various factors that can hinder or facilitate behaviour change. These factors or beliefs are identified as maintenance and recovery self-efficacy, as well as action and coping planning. Thus, motivation alone is not sufficient to bring about the desired behaviour change. The motivation phase must be followed by a subsequent action phase, that is more decisive for behaviour change (Luszczynska et al., 2007a). Therefore, it is implicitly assumed that behaviour change is the integration of two processes, a motivational one that ends with an intention, and a volitional one that ends with the desired behaviour change. Thus, any advancement of traditional continuum models in this course implicitly implements the idea of distinct processes, stages, or phases in health behaviour change (Schwarzer, 2008).

2.8.4. Health action process approach (HAPA): A model of adoption and maintenance of health behaviour change

The HAPA model of behaviour change explicitly includes the post-intentional factors to overcome the intention-behaviour gap, which are not taken into account by the traditional continuum models (Presseau et al., 2017). The purpose of such a model is twofold: It allows better prediction of behaviour and it reflects the assumed casual mechanism of behaviour change. HAPA constitutes a hybrid model in the sense that one can apply it either as a continuum model or a stage model. As a continuum model, it includes two mediators between intention and behaviour. As a stage model, it advocates a distinction between a) pre-intentional motivation processes that lead to a behavioural intention, and b) post-intentional volition processes that leads to the actual health behaviour (Schwarzer, 2008). These stages are comprised of different patterns of social-cognitive predictors (Schwarzer and Renner, 2000).

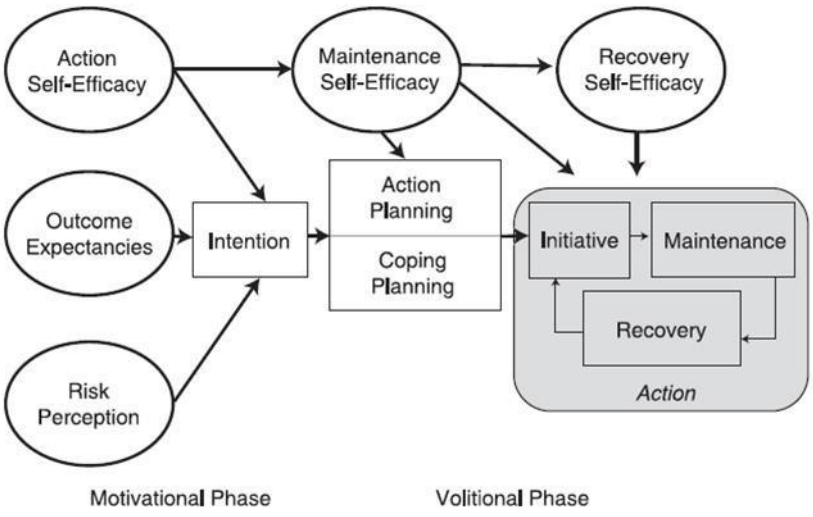


Figure 2.1 Generic diagram of Health Action Process Approach (HAPA)

In the motivational phase, a person develops an intention to act whilst risk perception is seen as a distal antecedent (e.g., I am at risk of cardiovascular disease). However, risk perception in itself is insufficient as it only sparks a contemplation process and further elaboration ofthoughts about consequences and competencies (Lippke et al., 2010). Positive outcome

expectancy is equally important to enable a person to form an intention in the motivation phase. It allows the individual to address the pros and cons of certain behavioural outcomes (e.g., If I use my sleep apnoea treatment every night, I will reduce my risk to cardiovascular diseases) (Luszczynska et al., 2007b). Consequently, perceived self-efficacy operates in combination with outcome expectancies to form an intention (Bandura, 1997). Perceived self-efficacy is one's belief in one's capability to perform a desired behaviour no matter what the obstacles (e.g., I am capable of adhering to my sleep apnoea treatment in spite of the discomfort). Once an intention is developed, detailed instructions on how to perform the behaviour facilitate the transformation of the intention into the desired action (Wilson et al., 2016). Furthermore, maintenance of this action encompasses self-regulatory skills and strategies. Hence, the post-intentional phase involves proximal factors, such as planning and recovery self-efficacy. Most social-cognition models do not explicitly acknowledge these factors (Luszczynska and Schwarzer, 2005).

2.8.4.1. Components of HAPA

2.8.4.1.1. Volitional factor: phase-specific self-efficacy beliefs

The rationale for the distinction between several phase-specific beliefs is that during the course of health-behaviour change, different tasks have to be mastered and different self-efficacy beliefs are required to master these tasks carefully (Scholz et al., 2005). Hence, the meaning of self-efficacy is context-specific and differs for individuals who may be more or less advanced in the change process e.g. a person might be confident in his or her capability to initiate sleep apnoea treatment (i.e. high action self-efficacy), but might not be very confident about resuming treatment after a setback (i.e. low recovery self-efficacy). Baer et al. (1995) emulated the difference between action self-efficacy, coping self-efficacy and recovery self-efficacy in the field of addictive behaviours (Baer et al., 1995).

Action self-efficacy (also called "pre-action self-efficacy") is involved in the motivational phase of behaviour change, in which an individual develops a motivation to act. It is an optimisticbelief during the pre-action phase (Schwarzer and Renner, 2000). Individuals high

in action self-efficacy anticipate success and potential outcomes of diverse strategies. Those with less self-efficacy imagine failure, harbour self-doubts, and tend to procrastinate.

As action self-efficacy is instrumental in the motivational phase, maintenance self-efficacy and recovery self-efficacy are instrumental in the subsequent volitional phase and can, therefore, be summarised under the heading of 'volitional self-efficacy' (Schwarzer, 2008). A new health behaviour might turn out to be much more difficult to adhere to than expected, but individuals with high maintenance self-efficacy invest more effort and persist longer than those who are less self-efficacious. Hence, maintenance self-efficacy (coping self-efficacy) refers to one's capability to deal with barriers that arise during the maintenance period (Scholz et al., 2005). If a lapse occurs, individuals tend to attribute their setbacks to internal, stable, and global causes, dramatise the event, and interpret it as a full-blown relapse (Baer et al., 1995). However, individuals with high recovery self-efficacy avoid this affect by attributing the setback to an external high-risk situation and by finding ways to control the damage and to restore hope. Thus, recovery self-efficacy refers to one's conviction to get back on track after being derailed (Schwarzer et al., 2007). Although there is a functional difference between the self-efficacy beliefs and how they operate, the constructs may be harboured at the same point in time. For example, recovery self-efficacy is most functional when it comes to resuming an interrupted chain of action, whereas action self-efficacy is most functional when facing a novel challenging demand (Luszczynska and Sutton, 2006, Luszczynska et al., 2007a).

A recent meta-analysis has demonstrated that action and maintenance self-efficacy have been observed to be persistent along the process of behaviour prediction and change (Zhang et al., 2019). Meta-analytic structural equation modelling revealed that action self-efficacy had the largest effects on health behaviour through intentions and maintenance self-efficacy. Whilst, effects of recovery self-efficacy on behaviour change were found to be less pervasive and more context-specific, specifically in situations more prone to behavioural lapses (Zhang et al., 2019). Hence, research has emphasised on behaviour change interventions that are highly context-sensitive (Bandura, 2004, Conroy and Hagger, 2018).

2.8.4.1.2. Action planning and coping planning

Research on action plans have observed that intentions can facilitate health behaviour change only when in combination with specific instructions on how to perform them. Action planning comprises of specific situation parameters ("when, where") and a sequence of action ("how") (Schwarzer, 2008, Pakpour et al., 2014). It is more effective than intentions when it comes to the likelihood and speed of performance, partly because behaviour might be elicited almost "automatically" when the relevant situational cues are encountered. As people do not forget their intentions easily when specified in a when, where, and how manner (Gollwitzer and Sheeran, 2006). After people contemplate the when, where, and how of action, they generate coping strategies for the foreseeable barriers. Coping with strategies, thus, comes on top of action planning. Planning is a variable which can be modified and easily communicated to individual with self-regulatory deficits. A number of randomised controlled trials have recently documented the evidence in favour of such planning interventions (Luszczynska, 2006, Luszczynska et al., 2007b). Similarly, meta-analysis of HAPA has shown that action and coping planning predicted behaviour and mediated effects of intentions and maintenance self-efficacy (Zhang et al., 2019).

2.8.4.3. Application of HAPA in interventions: An explicit stage model

Including planning and self-efficacy as volitional mediators renders the model into an implicit stage model because it implies the existence of two phases or stages, a motivational one and a volitional one (Schwarzer, 2008). However, when it comes to the design of interventions, the implicit stage model is transformed into an explicit stage model. This is achieved by identifying individuals who reside at either the motivational stage or the volitional stage (Gollwitzer and Sheeran, 2006). Then, each group becomes the target of a specific treatment that is tailored to this group. Moreover, it is theoretically meaningful and has been found useful to further subdivide the volitional group into those who perform and those who only intend to perform.

In the post-intentional pre-actional stage, individuals are labelled "intenders", whereas in the actional stage they are labelled "actors". Thus, a suitable subdivision within the health behaviour change process yields three groups: non-intenders, intenders and actors

(Luszczynska et al., 2007b). As individuals pass through different mind-sets during the course of behaviour change, interventions are more efficient when tailored to these particular mind-sets (Deng et al., 2013). For example, non-intenders will benefit from risk awareness and outcome expectancy communication. As this will help them to balance the pros and cons of the desired behaviour. However, intenders would benefit from planning to translate their intentions into actions. Similarly, actors do not need any intervention at all, unless one wants to improve their relapse prevention skills. As this can be done by teaching them to anticipate such situations and by acquiring the necessary levels of perceived recovery self -efficacy (Marlatt et al., 2011).

Several studies have examined the efficacy of HAPA as a staged-matched intervention in bringing about behaviour change and increasing patient adherence to treatment. As mentioned previously, HAPA differentiates between individuals who have not yet decided to change their behaviour and those who have decided to change or who have already implemented the changes and performed the target behaviour. Those who become active are the ones with higher volitional self-efficacy (Schüz et al., 2007). Similarly, a recent systematic review highlighted the use of goal setting, self-monitoring and planning as effective interventions for improving oral hygiene-related behaviour in patients with periodontal disease (Newton and Asimakopoulou, 2015). Interestingly, in the field of sleep medicine, Deng et al. (2013) conducted a randomized control trial to examine the efficacy of staged-match intervention, based on the HAPA model, on intention formation and 3-month adherence to CPAP. The study observed that a 3-month stage-matched intervention had a favourable influence on patients' intention formation, acceptance, and adherence to CPAP. These findings are in are in agreement with previous studies indicating that stage-matched intervention promotes stage progression (Lippke et al., 2004).

Furthermore, the current evidence on HAPA has demonstrated its universal applicability for a number of health behaviours and for diverse samples from various cultures (Bierbauer et al., 2017b, Presseau et al., 2017). The finding that a structural equation model fits the data, however, does not prove that the chosen model is the only one or the best one that fits. The question is whether this model appears to be empirically superior to alternative models. To test the validity of a model in comparison with other theories of health behaviour change, experimental studies are required (Weinstein et al., 1998a). To-date, studies that aim at comparing determinants from different theories are mainly correlational ones. Nevertheless, researchers tend to prefer heterogeneous approaches, such as selecting attractive elements from one model and implanting them into another one, which can also be seen as a means of theory evolution (Schwarzer, 2008, Bierbauer et al., 2017b).

2.8. MAA Adherence

Recent evidence concerning MAA adherence has observed that patient adherence is not associated with patient or disease dependant factors (Murphy et al., 2020, Pahkala and Suominen, 2021, Tallamraju et al., 2021). Furthermore, Pahkala and Suominen (2021) reported a positive correlation between reduction in snoring, and a negative correlation between mandibular retrognathia and patient-reported adherence. The authors also highlighted the need for 'a patient-tailored therapy in combination with objective monitoring of adherence' to optimise adherence to mandibular advancement therapy (Pahkala and Suominen, 2021).

Interestingly, Liu et al. (2022) evaluated the efficacy of a multifactorial intervention in enhancing patient adherence to mandibular advancement device. The study randomised 82 subjects into control and experimental groups, and monitored adherence objectively. Whilst, the control group received routine care, the experimental group received a single intervention to promote adherence. This single intervention entailed of educational counselling concerning the aetiology of OSA and risk of untreated OSA, tailored for the patient and his/her bed partner. Such counselling was reinforced by the clinicians at follow-up appointments. The intervention

also enabled the patients to communicate with the clinicians via phone messages, email or phone calls for follow-up communication. After 3-months of follow-up, results indicated no significant difference in the number of nights the appliance was worn between the two groups, however, the nightly adherence was significantly more in the experimental group than the control group ($p < 0.039$) (Liu et al., 2022). Although the study reported significant results, the multifactorial approach did fail to consider heath beliefs that govern adherence in patients with OSA (Stepnowsky et al., 2006, Carballo et al., 2016). In many chronic conditions, patient education is observed to be instrumental in improving patient adherence. Educational interventions have reported to be advantageous in increasing the risk awareness among patients concerning their conditions (Costa et al., 2015). Nevertheless, studies have observed that education alone is in an inadequate approach in enhancing patient adherence (Balkrishnan, 2005, Wozniak et al., 2014). A recent Cochrane review of educational support and behavioural interventions to improve usage of CPAP in adults with OSA concluded with high certainty that behavioural interventions produce a clinically significant increase in hourly CPAP usage (Askland, Wright et al. 2020). Behavioural interventions increased CPAP usage by 1 hour/night and increased the number of people who used CPAP for 4 hours or more per night (Rapelli, Pietrabissa et al. 2021). Thus, a unidimensional effort to improve patient adherence appears insufficient as adherence is influenced by a multitude of factors. Therefore, a multilevel patient intervention entailing tailored patient education, which is stage-specific and targets health beliefs such as risk perception, outcome expectancy and self-efficacy, is more likely to achieve optimum patient adherence to the prescribed treatment (Conroy and Hagger, 2018, Zhang et al., 2019).

2.10. Conclusion

Research in the field of sleep medicine has observed risk perception, outcome expectancy and self-efficacy, targeted by the HAPA model, as determinants of CPAP adherence (Stepnowsky and Dimsdale, 2002, de Zeeuw et al., 2003, Olsen et al., 2008, Deng et al., 2013). To-date, little research has been undertaken exploring these concepts in determining MAA adherence. Consequently, the current research aims to increase patient adherence to

MAA treatment, in adult patients with OSA, using the staged-matched behaviour change model of HAPA.

Chapter 3. A systematic review and meta-analysis of factors influencing adherence to oral appliance therapy in adults with obstructive sleep apnoea

3.1. Introduction

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder, characterized by the repeated episodic collapse of the upper airway during sleep, with resultant sleep deprivation (Banno and Kryger, 2007). Severe long-term effects of this disease include excessive daytime sleepiness, cognitive dysfunction, hypertension, impaired quality of life, and increased cardiovascular morbidity and mortality (Deng et al., 2013).

Based on the severity of OSA there are two main treatment modalities, continuous positive airway pressure (CPAP) and mandibular advancement appliances (MAA) (SIGN, 2003) . Both treatments are lifelong with sustained adherence to treatment of paramount importance. Successful treatment may lead to improvements in quality of life, considerable cost saving to the health provider and a reduction in the risk of motor vehicle collisions and cardiovascular disease (Rejon-Parrilla, 2014).

CPAP is mainly used for those suffering from moderate to severe OSA, being highly effective and regarded as the gold standard of treatment (Zozula and Rosen, 2001). However, side effects such as pressure sores, mask dislodgement, claustrophobia, air leakage, and nasal congestion have made it unpopular and intolerable among patients. According to a recent update of the American Academy of Sleep Medicine guidelines, MAA can be prescribed to those with mild to moderate OSA, particularly if they express a preference for it. MAA remains the second-line treatment of choice for patients who refuse or are unable to tolerate CPAP therapy (Ramar et al., 2015).

MAA reduces daytime sleepiness and improves the AHI by posturing the mandible and maintaining an open pharyngeal airway (Lim et al., 2004). However, studies have consistently demonstrated that CPAP is more effective than MAA at reducing sleep disordered breathing and achieving complete control of OSA (Sharples et al., 2016). Despite the greater effect of

CPAP on objective polysomnographic parameters, it does not appear to be more effective at achieving better health outcomes. It seems that the higher efficacy of CPAP is offset by greater MAA adherence. Adherence with CPAP is reportedly over 1 hour per night lower than with MAA (Phillips et al., 2013). This discrepancy may explain why, despite the superior efficacy of CPAP, as determined by the apnoea-hypopnoea index (AHI), no significant differences were observed in terms of quality of life, cognitive, and functional outcomes (Schwartz et al., 2018).

The short-term efficacy of MAA has been studied in many randomized controlled trials, with encouraging results in all age groups (Marklund et al., 2012, Dal-Fabbro et al., 2014, Sutherland et al., 2014, Marklund and Franklin, 2015, Marklund et al., 2015). However, long-term studies report an unchanged or only minor decrease in the efficacy of MAA (Marklund et al., 2001, Rose et al., 2002b, Ghazal et al., 2009, Aarab et al., 2011, Gauthier et al., 2011). Rose et al observed an increase in the mean AHI, from 4.2 to 8.3 after 2 years of MAA (Rose et al., 2002b). Deterioration in OSA severity and a loss of MAA efficacy were found in a small sample of patients (n = 9) treated continuously for more than 15 years (Marklund, 2016). However, MAA was reported to be effective in two-thirds of patients (n = 279) after three years of treatment (Attali et al., 2016). Despite the limited number of long-term studies, no significant changes appear to have been detected in the efficacy of MAA (Marklund et al., 2001, Ghazal et al., 2009, Gauthier et al., 2011). Notwithstanding this, a decrease in blood pressure is reported from MAA compared with a placebo and equivalent to that of CPAP, in the relatively small samples studied (Schwartz et al., 2018).

Adherence with MAA has until recently been limited to self-reported data, with the inherent risks of over-reporting. Based on this subjective reporting, adherence with MAA therapy appears to decline over time, Hoffstein et al. reported a wide range of adherence (4-76%) in the first year of appliance use. In a further study, adherence after one year was 83% (Dieltjens et al., 2013a) declining to 62-64% after 4 to 6 years (Walker-Engstrom et al., 2002, de Almeida et al., 2005). The ability to assess adherence objectively provides a more valid measure of a treatment modality's effectiveness. With CPAP therapy, the presence of an inbuilt adherence

monitor has provided valuable insight into the limitations of self-reported use, with patients overestimating by up to 1 hour (Kribbs et al., 1993). More recently, Vanderveken et al. and Johal et al. reported on the safety and feasibility, at 3- & 18-months respectively, of objective measurement techniques with MAA in the same cohort of patients, who demonstrated a range of sleep-disordered breathing, from snoring to OSA.

3.2. Objectives

The systematic review aimed to assess the factors influencing adherence to MAA in adults with obstructive sleep apnoea and the potential effectiveness of interventions to promote improved adherence.

3.3. Materials and methods

Following the registration of the protocol with the International Register of Systematic review (Prospero: CRD42019122615), a systematic review of the literature was undertaken to identify studies exploring the factors influencing adherence to oral appliance therapy in patients with obstructive sleep apnoea.

3.3.1. Search strategy

The search strategy was designed to access both published and unpublished materials and comprised three stages:

- A search of MEDLINE Ovid and Embase to identify relevant keywords contained in the title, abstract and subject descriptors.
- Terms identified in this way, and the synonyms used by respective databases were then used in an extensive search of the literature.
- Reference lists and bibliographies of the articles collected from those identified in stage two were searched.

The initial search terms were ‘obstructive sleep apnoea’, ‘oral appliance’ and ‘patient adherence’ and ‘Compliance’. Articles indexed in the following database with no restrictions in relation to the date of publication and language of the article were searched: Ovid, Embase, Scopus, Cochrane Library and Web of Science. Primary authors and experts in the field of

sleep and respiratory medicine were contacted. The additional literature search included Google Scholar to identify any other relevant published work. An example of the search strategy used is shown in Table 3.1.

Table 3.1. Search Strategy (MEDLINE OVID)

1	**Sleep Apnoea Syndromes/ or Sleep Apnoea, Obstructive/**	**30535**
2	Mandibular Advancement/	1736
3	Patient Compliance/	54886
4	Obstructive sleep apnoea.mp	3798
5	OSA.mp.	10389
6	Oral Appliance.mp.	486
7	Mandibular advancement appliance.mp.	0
8	Patient adherence.mp.	2838
9	Patient compliance.mp.	2838
10	1 or 4 or 5	34644
11	2 or 6	2098
12	3 or 8 or 9	63355
13	10 and 11 and 12	99

3.3.2. Selection criteria

The title and abstracts of the studies identified were assessed independently by two reviewers (HT, AJ) and were included or excluded based on the following PEO criteria:

1. Population: Adults with OSA receiving oral appliance therapy

2. Exposure of Interest: Disease characteristics, patient characteristics, appliance features, psychological and social factors
3. Outcome: Adherence

4. Study Design: Prognostic studies both retrospective or prospective observational in nature and randomized or non-randomized controlled trials

5. Exclusions: Studies comparing CPAP or surgical intervention with oral appliance therapy were excluded

3.4. Data collection and management

3.4.1. Study selection

The first two reviewers (HT, AJ) obtained full-text reports of studies meeting the selection criteria for screening, and any disagreement was resolved by consulting a third reviewer to reach a consensus (TN).

3.4.2. Data extraction

The influence of independent variables such as disease characteristics, patient characteristics, appliance features, and psychological and social factors on the outcome, i.e. adherence, reported in the included studies was recorded and categorized based on these factors (Table 3.2). The findings of the studies were synthesised in a narrative manner. Information regarding study design, sample size, participants and settings, type of oral appliance used, strategies or interventions employed to increase adherence, and method of adherence measurement (objective or self-reported) were recorded.

Table 3.2 Characteristics and principal outcomes of the included studies.

Sr.no.	Study	Study Design	Participants & Settings	Exposure (Patient or disease Characteristics, type of appliance, psychological or social factor)	Outcome (Increased/Decreased or No effect on adherence)	Appliance	Measurement of Adherence	Intervention for adherence
1	**Clark et al, 2000**	Retrospective observational study	Orofacial Pain & Oral medicine, University of California (n=53, M/F: 46/7, Mean age: 55.7 yrs, Mean AHI <30/hr)	Side effects	Decreased adherence	Herbst Appliance	Self-reported	Nil
2	**McGown et al, 2001**	Retrospective observational study	Middlesex Hospital, RNTNE Hospital, RLH (n=126, Mean AHI <30/hr)	Patient Characteristics Side effects Psychological (Self-perceived changes) and Social factors	No association with adherence Decreased adherence Increased adherence	Modified Adjustable Silensor and Herbst Device	Self-reported	Nil

3	**Rose et al, 2002**	Retrospective observational study	Respiratory Care, University Hospital of Freinburg, Germany (n=188, M/F: 168/23, Mean age: 54.4 yrs)	Patient & Disease Characteristics Side effects Psychological (Self-perceived Changes)	No association with adherence Decreased adherence Decreased adherence	Custom-made MAA (Esmarch IPG)	Self-reported	Nil
4	**De Almeida et al, 2005**	Retrospective observational study	University of British Columbia, Canada (n= 544, M/F: 202/49, Mean age: 49.9 yrs, Mean AHI: 30.25/hr)	Patient & Disease characteristics Side effects Social factors (Bed partners satisfaction) *	No association with adherence Decreased adherence Increased adherence	Oral Appliance	Self-reported	Nil
5	**Izci et al, 2005**	Retrospective observational study	Department of Sleep Medicine, Edinburgh University (n=144, M/F: 114/30, Mean age: 51 yrs, Mean AHI: 24/hr)	Patient characteristics Psychological factors (Marital Satisfaction) ** Side effects	No association with adherence Increased adherence Decreased adherence	Mandibular Repositioning Splint	Self-reported	Nil

6	**Bates et al, 2006**	Prospective observational study	Department of Orthodontics, Victoria Hospital (n=121, M/F: 83/38, Mean age: 49.55 yrs, Mean AHI: 18.21/hr)	Side effects	Decreased adherence	Mandibular Repositioning Splint	Self-reported	Nil
7	**Vanderveken et al, 2008**	Randomized Control trial	University of Antwerp, Belgium (n=35, M/F: 29/6, Mean age: 49 yrs, Mean AHI: 14/hr)	Appliance fabrication and titration procedure (Ready-made MAA vs Custom-made MAA)	Increased adherence with Custom-made MAA	Ready-made MAA (SnoreGuard Plus) and Custom-made MAA	Self-reported	Nil
8	**Ghazal et al, 2009**	Randomized Control trial	Respiratory Care, University Hospital of Freinburg, Germany (n=103, M/F: 48/55, Mean age: 50.5 yrs, Mean AHI: 34.5/hr)	Patient & Disease characteristics Appliance Fabrication (IST vs TAP)	No association with adherence Increased adherence with IST®	IST® and Thornton Anterior Positioner (TAP ™)	Self-reported	Nil

9	**Tsuda et al, 2010**	Prospective observational study	Kyushu Dental University, Japan (n= 47, M/F: 40/7, Mean age: 53.1 yrs, Mean AHI: 21.3/hr)	Patient & Disease Characteristics (BMI and ESS) Side effects	Decreased adherence in association with higher ESS and BMI Decreased adherence	Boil- Bite Appliance (TheraSnore)	Self-reported	Nil
10	**Cunali et al, 2011**	Randomized Control trial	Federal University of Sao Paulo, Brazil (n=29, M/F: 10/19, Mean age: 48.5 yrs, Mean AHI: 17/hr)	Intervention-Support Therapy	Increased adherence	MAA (Brazilian Repositioning device BRD ®)	Self-reported	Support Therapy (Mandibular Exercises)
11	**Brette et al, 2012**	Prospective observational study	Antoine-Beclere & Argenteuil Hospitals (n=140, M/F: 108/32, Mean age: 62 yrs, Mean AHI: 27/hr)	Patient & Disease Characteristics Social Support Appliance characteristics	Decreased adherence Decreased adherence Decreased adherence	Custom-made adjustable device (OPM4 J device)	Self-reported	Nil
12	**Freidman et al, 2012**	Case series	Advanced Centre for Specialty Care, Chicago (n=180, M/F: 130/50, Mean age: 61.5 yrs, Mean AHI: 33.9/hr)	Side effects Appliance Fabrication (Ready-made MAA vs Custom-made MAA)	Decreased adherence Increased adherence with Custom-made MAA	Ready-made MAA (SomnoGuard AP) and Custom-made MAA (Thornton Adjustable Positioner TAP)	Self-reported	Nil

13	**Zhou et al, 2012**	Randomized Control trial	Department of Orthodontics, Tongji University (n=16, M/F: 13/3, Mean age: 45.23 yrs, Mean AHI: 38/hr)	Appliance fabrication and titration procedure (Mono-bloc MAA vs two-piece MAA)	Increased adherence with Mono-bloc MAA	Mono-bloc MAA (Activator) and Bi-bloc MAA (Silent Nite)	Self-reported	Nil
14	**Dieltjens et al, 2013**	Case-control study	University of Antwerp, Belgium (n=82, M/F: 56/26, Mean age: 49.5 yrs, Mean AHI: 18/hr)	Psychological factors (Type D personality)	Decreased adherence	Custom-made Mono Bloc MAA and Custom-made Bi-bloc titratable MAA (RespiDent Butterfly ®)	Self-reported	Nil
15	**Ingman et al, 2013**	Retrospective observational study	Department of Oral & Maxillofacial Diseases, Helsinki University Hospital (n=96, M/F: 68/28, Mean age: 50.5 yrs, Mean AHI: 18.4/hr)	Patient characteristics (length of the maxilla, mandible and soft palate, oropharyngeal space, crepitation at TMJ)	Increased adherence with shorter mesio-distal length of the maxilla and mandible, and crepitation at right TMJ	Mandibular Advancement Splint	Self-reported	Nil
16	**Lee at al, 2013**	Non-randomized control trial	Department of Otorhinolaryngology, Seoul National University (n=153, M/F: 138/15, Mean age: 51.2 yrs, Mean	Appliance fabrication and titration procedure (Mono-bloc MAA vs Bi-bloc MAA)	Increased adherence with Bi-bloc MAA	Mono-bloc and Bi-bloc MAA	Self-reported	Nil

			AHI: 32.8/hr)					
17	**Quinnell et al, 2014**	Randomized Control trial	Papworth Hospital Sleep Centre, (n=90, M/F: 72/81, Mean age: 50.9 yrs, Mean AHI: 13.8/hr)	Appliance fabrication (Boil-Bite vs Semi-bespoke vs Be-spoke)	Increased adherence with the Be-spoke oral appliance	Boil-bite MAA (Sleep pro-1), Semi-bespoke MAA (Sleep pro 2), and Bespoke MAA	Self-reported	Nil
18	**Wang et al, 2014**	Randomized Control trial	Dept. of Otorhinology, Hospital of Anhui Medical University (n=22, M/F: 22/0, Mean age: 51.9 yrs, Mean AHI: 48.16/hr)	Appliance Type (Adjustable MAA vs Non-adjustable MAA)	Increased adherence with the adjustable MAA	Rod Type MAA (Erkodent Silensor) and Controllable appliance (Twin Bloc)	Self-reported	Nil
19	**Dieltjens et al, 2015**	Prospective observational study	Antwerp University Hospital, Belgium (n=51, M/F: 38/13, Mean age: 49.3 yrs, Mean AHI: 14.9/h, Mean AHI: 18.4/hr)	Patient (Anthropometric) & Disease characteristics (Polysomnographic measure) Side effects	No association with adherence Decreased adherence	Custom-made titratable MAA (RespiDent Butterfly ®)	Objective (Theramon Sensors)	Nil

20	**Prescinotto et al, 2015**	Retrospective observational study	Federal University of Sao Paulo, Brazil (n=28, M/F: 9/19, Mean age: 48.8 yrs, Mean AHI; 17.5/hr)	Patient characteristics (upper airway abnormalities)	No association with adherence	Custom-made	Self-reported	Nil
21	**Attali et al, 2016**	Prospective observational study	Pitié-Salpétrière, France (n=279, M/F: 98/81, Mean age: 58 yrs, Mean AHI: 26/hr)	Appliance factors Side effects Psychological factors	Decreased adherence Decreased adherence Decreased adherence	Ready-made MAA (Naval Resmed) and Custom-made MAA (Somnodent SomnoMed)	Self-reported	Nil
22	**Carballo et al, 2016**	Retrospective observational study	Veterans Affairs Medical Centre, Brazil (n=33, M/F: 32/1, Mean age: 71.4 yrs)	Psychological and social factors	No association with Adherence	Oral Appliance	Self-reported	Nil
23	**Makihara et al, 2016**	Retrospective observational study	Kyushu Dental University, Japan (n=48, M/F: 35/13, Mean age: 64.9 yrs)	Side effects Psychological factors	Decreased adherence Decreased adherence	Boil- Bite Appliance (TheraSnore)	Self-reported	Nil
24	**Nerfeldt et al, 2016**	Prospective intervention study	Department of Clinical Science, Karolinska Institute Stockholm, Sweden (n=66, M/F: 37/35, Mean Age: 48.5 yrs, Mean AHI: 16/hr)	Disease Characteristics (Arousers vs Desaturaters)	Increased adherence in arousers	Mono-bloc titratable MAA	Self-reported	Nil

25	**Vecchierini et al, 2016**	Prospective intervention study	Multicentre (n=369, M/F: 273/96, Mean age: 52.6 yrs, Mean AHI: 29.5/hr)	Side effects	Decreased adherence in the early stages of the treatment	Custom-made MAA (Narval)	Self-reported	Nil
26	**Al-Dharrab et al, 2017**	Randomized Control trial	Faculty of Dentistry, King Abdul-Aziz University (n=12, M/F: 2/10, Mean age: 46 yrs, Mean AHI: 26/hr)	Appliance fabrication and titration procedure (Titratable vs Non-titratable)	Increased adherence with Titratable appliance	Custom-made titratable MAA (Foresta Dent, Bite Jumping screw) and non-titratable MAA	Self-reported	Nil
27	**Gagnadoux et al, 2017**	Non-randomized control trial	University of Angers and Saint-Antoine Hospital, France (n=158, M/F: 104/54, Mean age: 54 yrs, Mean AHI: 27.7/hr)	Appliance fabrication and titration procedure (Ready-made MAA vs Custom-made MAA)	Increased adherence with Custom-made MAA	Ready-made MAA (BluePro) and Custom-made MAA (Somnodent and Amo Device)	Self-reported	Nil
28	**Haviv et al, 2017**	Mixed-methods	Department of Oral Medicine, Hebrew university (n=52, M/F: 48/4, Mean age: 56.75 yrs, Mean AHI ≤40/hr)	Side effects Psychological factors	Decreased adherence Decreased adherence	Herbst Device	Self-reported	Nil

29	**Johal et al, 2017**	Randomized Control trial	Royal London Dental Hospital, Queen Mary University of London, (n=35, M/F: 21/14, Mean age: 44.9 yrs, Mean AHI: 13.3/hr)	Appliance fabrication and titration procedure (Ready-made MAA vs Custom-made MAA)	Increased adherence with Custom-made MAA	Ready-made MAA (Snoreshield) and Custom-made MAA	Self-reported	Nil
30	**Nishigawa et al, 2017**	Retrospective observational study	Department of General Dentistry, Tokushima University Hospital Japan (n=40, M/F: 28/12, Mean age: 57.8 yrs)	Side effects Psychological factors	Decreased adherence Decreased adherence	Herbst Appliance	Self-reported	Nil
31	**Saglam-Aydinatay et al, 2018**	Retrospective observational study	Department of Orthodontics, Hacettepe University, Ankara, Turkey (n=69, M/F: 52/17, Mean age: 54.4 yrs, Mean AHI <30/hr)	Patient & Disease Characteristics Side effects Psychological (Self-perceived changes) and social factors	No association with adherence Decreased adherence Increased adherence	Mono-bloc MAA and Twin-bloc MAA	Self-reported	Nil

3.4.3. Risk of bias and quality assessment in Individual studies

Two authors independently assessed the risk of bias of the included studies (HT, AJ) and any disagreements were resolved by further discussion and consensus. Due to the diversity in the design of the included studies, two different tools were used to assess their quality. Randomized controlled trials were assessed using the Cochrane Collaboration's risk of bias tool (Higgins et al., 2019). The following five domains were considered: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting. The domain blinding of participants and personnel was not considered due to the nature of the questions addressed by this review. Observational studies were critically appraised using the QUIPS (Quality in Prognosis studies) tool (Hayden et al., 2013). This tool assesses the risk of bias in studies of prognostic factors and comprises of six domains: study participation, study attrition, prognostic factor management, outcome measurement, study confounding, and statistical analysis and reporting.

3.4.4. Meta-analysis

A meta-analysis was performed using Review Manager (RevMan; Version 5.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for studies with: low and /or unclear risk of bias, similar study design and comparing two types (ready-made vs custom-made) mandibular advancement appliances, prescribed for patients with OSA in regards to patient adherence. Results were analysed using forest plots with weighted mean differences between ready-made versus custom-made appliances in relation to patient adherence i.e. mean nightly (hours) use of the appliance. The studies were weighted using the inverse variance method and tested for heterogeneity using the Chi^2 test to assess the significance of heterogeneity and I^2 statistics to measure the diversity between studies. Pooled studies with $I^2 < 25\%$ were regarded as homogenous, and those with $I^2 > 75\%$ were considered to demonstrate high heterogeneity. A fixed-effects model was used and a P-value of less than

0.05 was considered statistically significant, reported along with the 95% confidence interval (CI).

3.5. Results

Following the removal of duplicates, 419 articles were considered eligible for screening of the title and abstract. The abstracts were assessed against the selection criteria, with 45 articles considered eligible for full-text screening. Subsequently, fourteen studies were excluded (Table 3.3), with a total of 31 studies included in the review, which consisted of eight RCTs, two CCTs, seven prospective cohorts, 11 retrospective cohorts, whilst the remaining three studies were a case-series, case-control and a mixed-methods study (Figure 3.1). All 31 included studies were subject to qualitative analysis, with four studies subject to a meta-analysis. All included studies were undertaken in academic medical centres or sleep centres.

Table 3.3 Excluded studies along with the reason for exclusion

Sr. no.	Study	Reason for Exclusion
1	Bachour et al, 2016	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
2	Banhiran et al, 2014	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
3	Basoglu et al, 2012	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
4	Bennett et al, 1998	Excluded (Wrong comparator- CPAP vs MAA)
5	Ferguson et al, 1996	Excluded (Wrong comparator- CPAP vs MAA)
6	Freidman et al, 2010	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
7	Gagnadoux et al, 2009	Excluded (wrong comparator –CPAP vs MAA)
8	Gindre et al, 2008	Excluded (wrong outcome –no information in regard to influence of variables on patient adherence)
9	Neill et al, 2002	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
10	Peled et al, 2009	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
11	Randerath et al, 2002	Excluded (Wrong comparator –CPAP vs MAA)
12	Tavares et al, 2009	Excluded- Full Text Not available
13	Tsai et al, 2004	Excluded (Wrong outcome –no information in regard to influence of variables on patient adherence)
14	Vanderveken et al, 2012	Excluded (Wrong study design)

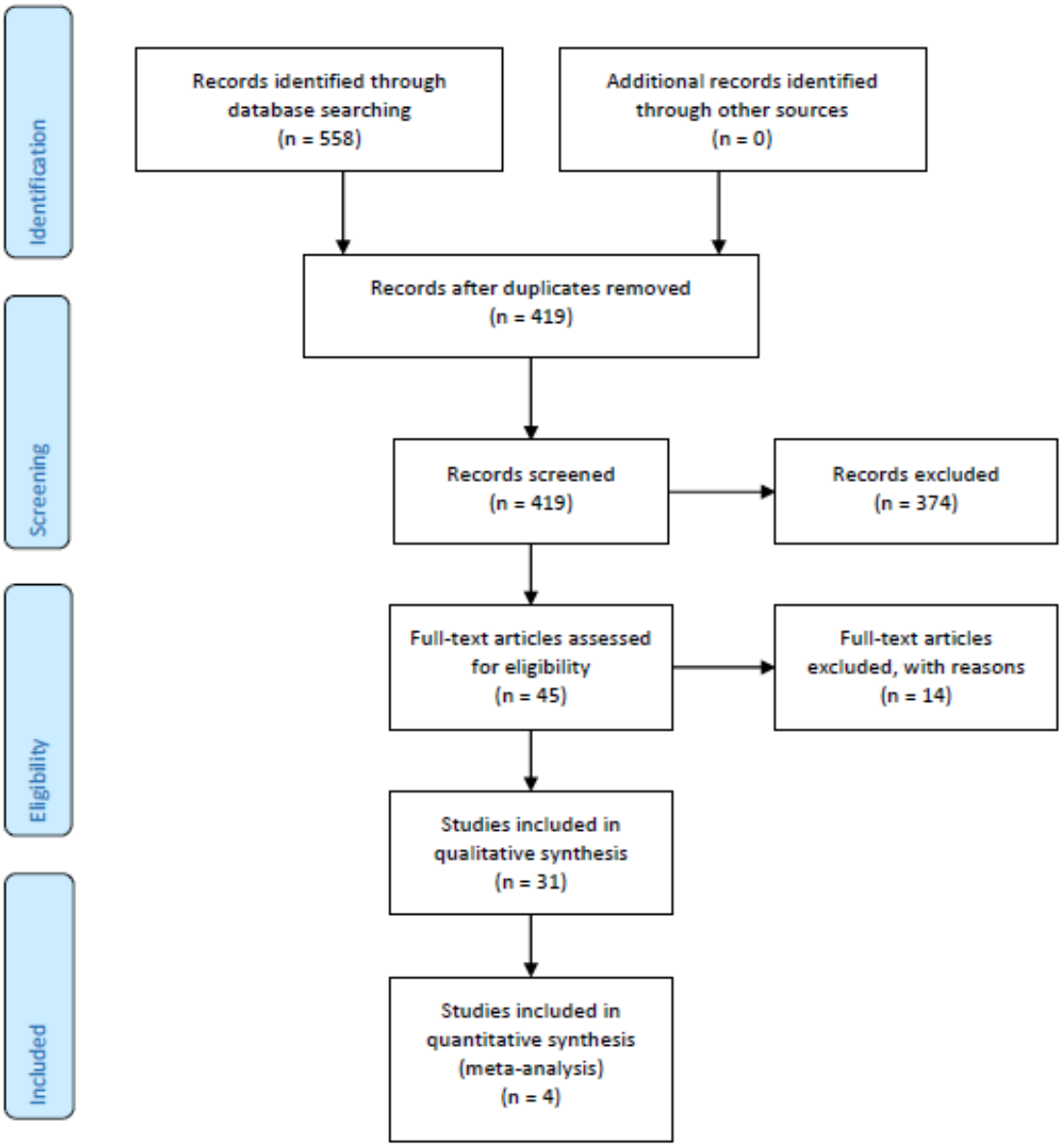


Figure 3.1 A PRISMA flow diagram shows the number of articles identified at each stage of the search.

3.5.1. Characteristics of included studies

The majority of the included studies investigated the influence of side effects (45%), disease and patient characteristics (41%) and appliance characteristics (32%) on patient adherence (Table 3.4). The efficacy of strategies or interventions to increase patient adherence to MAA in adult patients with OSA was only assessed in a single study (Cunali et al., 2011). Whilst a self-reported measure of adherence was used in the majority of included studies, objective monitoring of adherence was reported in just one study (Dieltjens et al., 2015). Studies which considered psychological and social factors (38%) focused on the impact of constructs, such as bed-partner satisfaction levels (improvement reported in the patient's snoring by their partner), self-perceived changes and type D personality (a combination personality type of negative affectivity and social inhibition) on oral appliance adherence.

Table 3.4 Categorisation of studies based on the influencing factor

Sr no.	Exposure of interest	Study
1	**Disease and Patient Characteristics**	De Almeida et al, 2005
		Dieltjens et al, 2013
		Ghazal et al, 2009
		Izci et al, 2005
		McGown et al, 2001
		Brette et al, 2012
		Dieltjens et al, 2015
		Ingman et al, 2013
		Nerfeldt et al, 2016
		Prescinotto et al, 2015
		Rose et al, 2002
		Saglam-Aydinatay et al, 2018
		Tsuda et al, 2010
3	**Appliance Fabrication and Titration Procedures**	Gagnadoux et al, 2017
		Johal et al, 2017
		Lee at al, 2013
		Wang et al, 2014
		Zhou et al, 2012
		Al-Dharrab et al, 2017
		Dieltjens et al, 2013
		Ghazal et al, 2009
		Quinnell et al, 2014
		Freidman et al, 2012
		Vanderveken et al, 2008
4	**Side Effects**	Attali et al, 2016
		De Almeida et al, 2005
		Izci et al, 2005
		Makihara et al, 2016
		McGown et al, 2001

		Bates et al, 2006
		Clark et al, 2000
		Freidman et al, 2012
		Dieltjens et al, 2015
		Haviv et al, 2017
		Nishigawa et al, 2017
		Rose et al, 2002
		Tsuda et al, 2010
		Vecchierini et al, 2016
5	**Psychological & Social Factors**	Attali et al, 2016
		Carballo et al, 2016
		De Almeida et al, 2005
		Dieltjens et al, 2013
		Izci et al, 2005
		Makihara et al, 2016
		McGown et al, 2001
		Brette et al, 2012
		Haviv et al, 2017
		Nishigawa et al, 2017
		Rose et al, 2002
		Saglam-Aydinatay et al, 2018

3.5.2. Risk of bias within studies

The risk of bias assessment for random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, selective reporting was assessed for the included RCTs (n = 8) and CCTs (n = 2). The majority of these studies demonstrated a low or unclear risk of bias for the above domains. Only two studies (Lee et al., 2013, Gagnadoux et al., 2017) demonstrated a high risk of bias for random sequence generation, otherwise a low risk of bias was assessed in relation to selective reporting for all included studies. In terms of allocation concealment, five studies (Ghazal et al., 2009, Zhou and Liu, 2012, Quinnell et al., 2014, Wang and Liu, 2014, Al-Dharrab, 2017) demonstrated an unclear risk of bias, three studies (Vanderveken et al., 2008, Cunali et al., 2011, Johal et al., 2017) indicated a low risk of bias and a high risk of bias was observed in two studies (Lee et al., 2013, Gagnadoux et al., 2017). Due to no clear description concerning blinding of outcome assessors, seven studies (Ghazal et al., 2009, Cunali et al., 2011, Zhou and Liu, 2012, Lee et al., 2013, Quinnell et al., 2014, Wang and Liu, 2014, Al-Dharrab, 2017) exhibited an unclear risk of bias and a low risk of bias was observed in the rest of the three studies (Vanderveken et al., 2008, Gagnadoux et al., 2017, Johal et al., 2017). High risk of bias for incomplete outcome data was observed in only one study (Gagnadoux et al., 2017) whereas the remaining nine studies (Vanderveken et al., 2008, Ghazal et al., 2009, Cunali et al., 2011, Lee et al., 2013, Quinnell et al., 2014, Wang and Liu, 2014, Al-Dharrab, 2017, Johal et al., 2017, Zhou and Liu, 2012) exhibited a low risk of bias. The findings along with the comments for the judgement are summarised in Table 3.5.

Similarly, observational studies (n = 21) were found to demonstrate a low or moderate risk of bias concerning study participation, study attrition, prognostic factor management, outcome management, study confounding and statistical analysis and reporting. Four studies (Prescinotto et al., 2015, Carballo et al., 2016, Nerfeldt and Friberg, 2016, Saglam-Aydinatay and Taner, 2018) exhibited a moderate risk of bias for study participation whereas the remaining studies (n = 17) indicated a low risk of bias. All studies demonstrated a low risk of bias for the domains-outcome measurement and, statistical analysis and reporting. In terms

of study attrition, three studies (Brette et al., 2012, Nerfeldt and Friberg, 2016, Nishigawa et al., 2017) exhibited a moderate risk of bias whilst a low risk of bias was observed in the remaining studies. Furthermore, eight studies (Tsuda et al., 2010, Brette et al., 2012, Ingman et al., 2013, Dieltjens et al., 2015, Prescinotto et al., 2015, Nerfeldt and Friberg, 2016, Vecchierini et al., 2016, Saglam-Aydinatay and Taner, 2018) demonstrated a low risk of bias for prognostic factor measurement and remaining studies exhibited a moderate risk of bias. The majority of the studies indicated a moderate risk of bias for study confounding while a low risk of bias was observed in two studies (Izci et al., 2005, Dieltjens et al., 2015) (Table 3.6).

Table 3.5 Risk of bias assessment for RCTs using Cochrane risk of bias tool

1	Al Dharrab 2017	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	"The patients were then simply randomised to treatment with either Type A or Type B appliance."
ii	Allocation Concealment (Selection Bias)	Unclear risk	No clear description
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	"No patients were dropped from the study for any reason."
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
2	Cunali 2011	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	"…study was a double-blind, Randomised, and controlled trial in which patients were distributed…"
ii	Allocation Concealment (Selection Bias)	Low risk	"The investigator who was blinded to the Randomisation has only applied all study instruments of evaluation such as the RDC, while a second investigator did the Randomisation and was responsible for explaining the exercises to the patients."
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	Small number of dropouts in both of the groups (Support therapy n=1 dropout vs Placebo Therapy n=2 dropout)
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
3	Gagnadoux 2017	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	High risk	"This prospective non Randomised study was conducted…"

ii	Allocation Concealment (Selection Bias)	High risk	Lack of Randomisation and allocation concealment
iii	Blinding of outcome assessment (Detection Bias)	Low risk	“Outcome assessors were unaware of the device assignment."
iv	Incomplete Outcome Data (Attrition Bias)	High risk	Large number of dropouts in both groups (Ready-made n=39 dropouts and Custom-made n= 23 dropouts) and imbalanced Randomisation (Ready-made n= 125 vs Custom-made n=95) due to lack of Randomisation.
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
4	Lee 2013	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	High risk	No description of Randomisation and allocation concealment. "Two groups of patients were included in the present study; one group of patients was prescribed mono-bloc MAD and the other group of patients was bi-bloc MAD."
ii	Allocation Concealment (Selection Bias)	High risk	No description of allocation concealment. "Two groups of patients were included in the present study; one group of patients was prescribed mono-bloc MAD and the other group of patients was bi-bloc MAD."
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	No dropouts or withdrawal as 153 patients were enrolled and 153 were analysed
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
5	Quinnell 2014	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	"This open-label, randomised, controlled, crossover trial was undertaken at a UK sleep centre."
ii	Allocation Concealment (Selection Bias)	Unclear risk	No clear description

iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	Small number of dropouts only in one group (n=3 lost to follow-up)
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
6	Vanderveken 2008	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	“Participants were randomly allocated (concealed Randomisation) to either treatment sequence A or B."
ii	Allocation Concealment (Selection Bias)	Low risk	"...allocated (concealed Randomisation) to either treatment sequence A or B."
iii	Blinding of outcome assessment (Detection Bias)	Low risk	“Sleep recordings were scored manually in a standard fashion by a qualified sleep technician blinded to the subject’s treatment status.”
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	No dropouts reported
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
7	Wang 2014	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	“Randomisation at the beginning of the study.”
ii	Allocation Concealment (Selection Bias)	Unclear risk	No clear description
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	Smaller no of dropouts (n=2 dropouts)
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
8	Zhou 2012	Risk of Bias	Support for judgement

i	Randomisation (Selection Bias)	Low risk	“The 16 patients enrolled were randomly divided into two groups…"
ii	Allocation Concealment (Selection Bias)	Unclear risk	No clear description
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	“All of the patients finished the treatment as expected…"
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
9	Johal 2017	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	"…random identification numbers were compiled from Altman's randomisation table to one of the two treatment groups, using a block randomisation method…"
ii	Allocation Concealment (Selection Bias)	Low risk	"Opaque envelopes to conceal the allocation were labelled with identification numbers only…"
iii	Blinding of outcome assessment (Detection Bias)	Low risk	“Data analysis, was undertaken blind to the intervention by a statistician with coded data, using SPSS."
iv	Incomplete Outcome Data (Attrition Bias)	Low risk	Balanced dropouts from both the groups (Ready-made n= 6 and Custom-made n=4), "intention to treat analysis demonstrated that dropouts did not affect the validity of the current study results."
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.
10	Ghazal 2009	Risk of Bias	Support for judgement
i	Randomisation (Selection Bias)	Low risk	“Enrolled patients were Randomised according to a computer-generated Randomisation list.”
ii	Allocation Concealment (Selection Bias)	Unclear risk	Not described
iii	Blinding of outcome assessment (Detection Bias)	Unclear risk	No clear description

iv	Incomplete Outcome Data (Attrition Bias)	Low risk	Balanced number of withdrawals from both the groups at follow-up 1 and 2.
v	Selective Reporting	Low risk	The authors reported all the pre-specified outcomes.

Table 3.6 Risk of bias tool for observational studies using the QUIPS tool

		Bias Domains					
Sr. no.	**Study ID**	**Study Participation**	**Study Attrition**	**Prognostic Factor Measurement**	**Outcome Measurement**	**Study Confounding**	**Statistical Analysis and Reporting**
1	**Attali 2006**	Low	Low	Moderate	Low	Moderate	Low
2	**Carballo 2016**	Moderate	Low	Moderate	Low	Moderate	Low
3	**De Almeida 2005**	Low	Low	Moderate	Low	Moderate	Low
4	**Izci 2005**	Low	Low	Moderate	Low	Low	Low
5	**Makihara 2016**	Low	Low	Moderate	Low	Moderate	Low
6	**McGown 2001**	Low	Low	Moderate	Low	Moderate	Low
7	**Bates 2006**	Low	Low	Moderate	Low	Moderate	Low
8	**Brette 2006**	Low	Moderate	Low	Low	Moderate	Low
9	**Clark 2000**	Low	Low	Moderate	Low	Moderate	Low
10	**Freidman 2012**	Low	Low	Moderate	Low	Moderate	Low
11	**Dieltjens 2013**	Low	Low	Moderate	Low	Moderate	Low
12	**Dieltjens 2015**	Low	Low	Low	Low	Low	Low
13	**Haviv 2017**	Low	Low	Moderate	Low	Moderate	Low
14	**Ingman 2013**	Low	Low	Low	Low	Moderate	Low
15	**Nerfeldt 2016**	Moderate	Moderate	Low	Low	Moderate	Low
16	**Nishigawa 2017**	Low	Moderate	Moderate	Low	Moderate	Low
17	**Prescinotto 2015**	Moderate	Low	Low	Low	Moderate	Low

18	**Rose 2002**	Low	Low	Moderate	Low	Moderate	Low
19	**Saglam-Aydinatay 2018**	Moderate	Low	Low	Low	Moderate	Low
20	**Tsuda 2004**	Low	Low	Low	Low	Moderate	Low
21	**Vecchierini 2016**	Low	Low	Low	Low	Moderate	Low

3.5.3. Qualitative study analysis

3.5.3.1. Patient and disease Characteristics

The findings of the qualitative analysis are summarised in table 3.7. The current review identified 13 studies exploring the influence of patient and disease characteristics, which reported neither supine-dependent OSA, age, obesity, sex, or sleepiness to be related to MAA tolerability (McGown et al., 2001, Rose et al., 2002a, de Almeida et al., 2005, Izci et al., 2005, Ghazal et al., 2009, Tsuda et al., 2010, Brette et al., 2012, Dieltjens et al., 2013b, Ingman et al., 2013, Dieltjens et al., 2015, Prescinotto et al., 2015, Nerfeldt and Friberg, 2016, Saglam-Aydinatay and Taner, 2018). There were no significant gender differences detected in relation to the cessation of appliance use. Neither disease severity or baseline sleepiness was found to be a predictor of MAA adherence (de Almeida et al., 2005). Whilst the above-reported studies relied upon self-reported adherence, a further single study found no correlation between objective adherence and anthropometric characteristics, polysomnographic parameters or excessive daytime sleepiness (Dieltjens et al., 2015). Furthermore, among the 13 studies included, one study found no significant association between adherence and the following patient anatomical characteristics: upper-airway or facial skeletal abnormalities, such as pharyngeal alterations ($p = 0.62$), retrognathia ($p = 0.34$), Class II dental occlusion ($p = 0.64$), craniofacial alterations ($p = 0.44$) or nasal alterations ($p = 0.38$) (Prescinotto et al., 2015). Although the findings are not statistically significant, these should be viewed carefully as the authors relied upon self-reported adherence, rather than objective adherence.

3.5.3.2. Appliance fabrication and titration

In terms of appliance factors, 11 studies examined the influence of appliance fabrication and titration on MAA adherence (Vanderveken et al., 2008, Ghazal et al., 2009, Friedman et al., 2012, Zhou and Liu, 2012, Dieltjens et al., 2013b, Lee et al., 2013, Gagnadoux et al., 2017, Al-Dharrab, 2017, Johal et al., 2017, Quinnell et al., 2014, Wang and Liu, 2014). One study compared the modified Herbst appliance (IST®) with the Thornton anterior positioner (TAP™), which differed in their ability to open the mouth during sleep in a protrusive position (Ghazal et

al., 2009). Although the TAP™ was more effective in treating OSA, its long term acceptance was less than that of the IST® (Ghazal et al., 2009).

Three Studies comparing mono-bloc MAA with bi-bloc MAA, with regards to their adherence have reported rather conflicting results (Zhou and Liu, 2012, Dieltjens et al., 2013b, Lee et al., 2013). Zhou and Lou suggested that mono-bloc appliance should be considered, as almost half of the patients preferred the appliance to the bi-bloc device. However, the findings were based on a very small sample size (n = 16) (Zhou and Liu, 2012). On the contrary, a large prospective single-centre study, with a sample size of 153 patients, observed an adherence rate of 83.3% with the Bi-Bloc MAA and 68.8% with the Mono-Bloc MAA, at 1 year (P = 0.04). The authors concluded that the relatively free mandibular movement may explain the difference in adherence rates (Lee et al., 2013). Similarly, Dieltjens et al. whilst examining the association between Type D personality (a combination personality type of negative affectivity and social inhibition) and MAA adherence, observed a higher discontinuation rate with monobloc MAA in comparison to bi- or duo-bloc appliance (95% CI, 1.77 - 47.09; p = 0.008) when adjusted for Type D personality, age, gender and decrease in AHI (Dieltjens et al., 2013b). However, the findings of the above studies should again be interpreted with caution as they failed to assess adherence using an objective measure and the marked differences in study designs.

Seven studies evaluating the impact of ready-made (non-adjustable/ non-titratable) and custom-made MAA, observed an overwhelming patient-reported preference for custom-made MAA in comparison to ready-made devices (Vanderveken et al., 2008, Friedman et al., 2012, Quinnell et al., 2014, Wang and Liu, 2014, Al-Dharrab, 2017, Gagnadoux et al., 2017, Johal et al., 2017). The adherence was higher with the custom-made MAA despite more reported dental discomfort (p = 0.03) (Gagnadoux et al., 2017). In a further RCT, with a crossover design, Johal et al. reported a response rate of only 24% with a ready-made MAA versus the 64% in the custom-made MAA. It has to be acknowledged that adherence was assessed from self-reports and can be at risk of bias. More recently, the addition of objective adherence

monitors has served to confirm the reported levels of self-reported adherence with MAA (Vanderveken et al., 2013, Johal et al., 2016).

3.5.3.3. Side effects

Side effects, such as dental pain, muscular pain and excessive salivation associated with MAA may prevent early acceptance of the device and contribute to non-adherence (Bates and McDonald, 2006). Moreover, side effects arising from long-term MAA use, such as bite change may also lead to poor patient adherence (Clark et al., 2000, McGown et al., 2001, Dieltjens et al., 2015, Attali et al., 2016). The current review identified 14 studies examining the influence of early and long-term side effects on MAA adherence (Clark et al., 2000, McGown et al., 2001, Rose et al., 2002a, de Almeida et al., 2005, Izci et al., 2005, Bates and McDonald, 2006, Tsuda et al., 2010, Friedman et al., 2012, Dieltjens et al., 2015, Attali et al., 2016, Makihara et al., 2016, Vecchierini et al., 2016, Haviv et al., 2017, Nishigawa et al., 2017).

The most common self-reported reason for discontinuing the treatment was a lack of treatment effect or discomfort or pain on MAA use, consistent with other reported studies (Clark et al., 2000, Bates and McDonald, 2006, Izci et al., 2005, Attali et al., 2016, Saglam-Aydinatay and Taner, 2018). Furthermore, early discontinuation (< 2 years) of treatment was observed due to side effects, discomfort and inefficacy. In contrast, patients discontinued treatment due to no specific reasons after 2 or more years (Attali et al., 2016). Additionally, the higher rates of treatment discontinuation with ready-made MAA was found to be associated with higher reported side effects in comparison to the custom-made MAA (Vanderveken et al., 2008, Quinnell et al., 2014, Gagnadoux et al., 2017, Johal et al., 2017).

3.5.3.4. Psychological and Social factors

Among the 31 included studies, twelve studies (de Almeida et al., 2005, Attali et al., 2016, Carballo et al., 2016) examined the influence of the psychological and social factors on MAA adherence. One study reported low rates of perceived effectiveness, self-efficacy, and social support for MAA as a cohort (n = 39) of older patients had low expectation for positive outcomes (Carballo et al., 2016). However, given that other included studies identified psychological factors, such as a lack of perceived benefits by the patients and their bed partner, and cognitive perceptions such as complete symptom resolution as influential on MAA

adherence, the above findings are highly contentious (Rose et al., 2002a, de Almeida et al., 2005, Izci et al., 2005, Dieltjens et al., 2013b, Attali et al., 2016, Haviv et al., 2017, Nishigawa et al., 2017). Likewise, two studies identified that social factors, such as poor marital satisfaction (marital quality and bed sharing frequency) ($p < 0.04$), support from their partner and shame caused by the disease symptoms, to be associated with continued usage of MAA (Izci et al., 2005, Saglam-Aydinatay and Taner, 2018). Nevertheless, the above findings should be viewed carefully due to marked differences in study designs and lack of objective assessment of adherence.

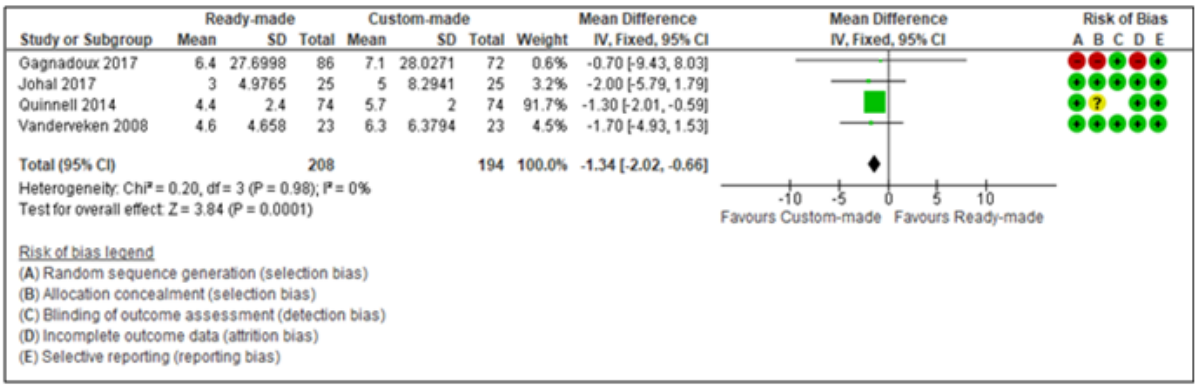
Table 3.7. Factors of influence on MAA adherence

Factors	Decreased adherence	Increased adherence	No significant association with adherence	Caveat
Patient and disease characteristics			Anthropometric characteristics (Age, Sex, obesity)	
			Disease severity	
			Baseline Sleepiness	
			Polysomnographic parameters	
			Anatomical characteristics (length of the maxilla, mandible and soft palate, oropharyngeal space, crepitation at TMJ)	
			Upper airway or facial skeletal abnormalities	
	Desaturaters (patients with oxygen desaturations)	Arousers (Patients with respiratory arousals)		Significant improvement in the ESS among the arousers
		MAA therapy as the first line of treatment		Strong predictor for treatment continuation
		Complete symptom resolution		Contributes to the perception of OSA but not a strong predictor alone
	Mono-bloc MAA	Bi-Bloc MAA		Relatively free mandibular movement

Appliance Fabrication and Titration	Ready-made (Non-titratable) MAA	Custom-made (Titratable) MAA		More reported side-effects with ready-made as compared to custom-made
Side effects	Dental, Muscular and TMJ pain Excessive salivation Bite change			Prevents early acceptance of the device and weak but consistent factors for discontinuation Non-users reported more side-effects than users
	Patients not using the MAA for > 2 years			More likely to discontinue the treatment
		Regular dental follow-up		Helps in minimising early side-effects which lead to early discontinuation of the treatment
Psychological and social factors	Lack of perceived benefits			Leads to early discontinuation of the treatment, consistent factor
		Support from their bed partners		Improved sleep quality of the bed partner with MAA use is associated with increased adherence

3.5.4. Quantitative analysis

A meta-analysis was undertaken in relation to the use of ready-made MAA versus custom-made MAA with regards to patient adherence (Figure 3.2). Based on these studies (Vanderveken et al., 2008, Quinnell et al., 2014, Gagnadoux et al., 2017, Johal et al., 2017), increased adherence was observed with custom-made appliances, with a pooled mean difference of -1.34 (-2.02 to -0.66b), with low levels of heterogeneity (I^2 = 0%).



The forest plot demonstrates four studies that indicate increased patient adherence with custom-made appliances in comparison to ready-made appliances. The squares represents the point estimate of the corresponding studies. The area of the each square is proportional to the study's weight in the meta-analysis and the lateral points (horizontal line) indicate the confidence intervals of the respective study. The overall effect or the summary estimate is plotted as a diamond and the lateral points demonstrate the confidence intervals of the estimate. A mean difference of zero (vertical line) indicates no effect; studies with confidence intervals crossing the vertical line are inconclusive. Powerful studies have narrower confidence intervals.

In the above graph the Quinnell study and the overall effect estimate have narrow confidence intervals that do not cross zero, indicating that the meta-analysis could be considered as statistically significant.

Figure 3.2 Forest plot of patient reported adherence for custom-made MAA and ready-made MAA.

3.5. Discussion

Given that mandibular advancement appliances are removable and have to be used indefinitely, adherence to treatment is of utmost importance for achieving successful therapy (Ramar et al., 2015). However, adherence to MAA for obstructive sleep apnoea is highly variable (Sutherland et al., 2014). The current review observed that the relationship between MAA adherence and patient and disease characteristics such as age, sex, obesity, AHI, daytime sleepiness is relatively weak. Furthermore, no association was observed between objective adherence and anthropometric characteristics, polysomnographic parameters, and excessive daytime sleepiness. It also appears that disease severity and sleepiness may not be associated with MAA adherence. The majority of the included studies, exploring the impact of patient and disease characteristics were retrospective in nature and highly heterogeneous in terms of study participants.

Dieltjens et al. conducted a prospective clinical trial to identify the determinants of objective adherence to MAA in patients with OSA. Previous studies on MAA adherence have relied upon patient-reported adherence which is subject to overestimation (de Almeida et al., 2005, Marklund and Franklin, 2007). Moreover, objective compliance monitors with MAA have only been introduced recently (Vanderveken et al., 2013). The trial (n = 51) observed no correlation between objective adherence and anthropometric characteristics, polysomnographic parameters and excessive daytime sleepiness. Nevertheless, the authors did emphasize the influence of socially disturbing snoring, reporting objective adherence correlated significantly with a decrease in socially disturbing snoring, as reported by the partner compared with baseline visual analogue scale scores (VAS) for snoring without the appliance (Dieltjens et al., 2015). Nerfeldt and Friberg investigated the difference between ‘arousers (patients with respiratory arousals) and ‘desaturaters’ (patients with oxygen desaturations) in terms of adherence rates the authors observed that patients with greater numbers of arousal showed higher adherence (85%) than among the ‘desaturaters’ (55%; p=0.034). It was reasoned that the above difference in adherence rate was due to a significant improvement in the Epworth sleepiness score (ESS) among the ‘arousers’ (ESS

≥ 10) which was not seen among the 'desaturaters' (Nerfeldt and Friberg, 2016). Furthermore, MAA as a first-line treatment was reported to be a strong predictor (OR 1.77, 95% CI 1.03-3.03; p = 0.0375) for treatment continuation (Attali et al., 2016). Similarly, complete symptom resolution (OR 1.78, 95% CI 1.03-3.03, p = 0.0384) was also a strong predictor for MAA adherence (Attali et al., 2016). These findings support an important role for disease chronicity in terms of patient adherence, which was similar to those reported for other chronic diseases (Iglay et al., 2015). They also reinforce the link between disease chronicity and long-term treatment persistence, whilst indicating that patients intolerant of or non-adherent with CPAP are more likely to discontinue MAA (Attali et al., 2016). However, Izci et al. in a large sample (n=144) of patients with OSA demonstrated that usage of MAA was not significantly affected by whether a patient was a CPAP failure or refuser (p>0.3) (Izci et al., 2005). Nonetheless, the findings of the above studies should be interpreted with caution, as the studies failed to provide an objective measure of adherence and also due to the marked differences in study design and participant settings with regards to race and ethnicity. However, Johal et al. demonstrated excellent long-term objective adherence with MAA in a sample of 42 patients with OSA, who were CPAP intolerant.

Nonetheless, it is interesting to evaluate these findings in the context of CPAP adherence. A weak association between patient and disease characteristics such as disease severity, AHI, oxygen desaturation and ESS on CPAP adherence has been observed (Engleman et al., 1994, Reeves-Hoche et al., 1994, Sin et al., 2002). Although nasal resistance influences initial CPAP acceptance, nasal anatomy, not necessarily patient-reported nasal complaints, may be influential on CPAP adherence (Li et al., 2005, Morris et al., 2006, Sugiura et al., 2007). Furthermore, initial CPAP adherence appears to be closely associated with higher neighbourhood socioeconomic factors, independent of individual demographic and clinical factors (Platt et al., 2009). These findings suggest that socio-environmental factors are important in terms of patient adherence among patients with OSA. Studies have also examined race as influential on CPAP adherence, all of which have reported lower CPAP adherence in African-Americans compared with Caucasian users (Scharf et al., 2004,

Budhiraja et al., 2007). Factors such as race and ethnicity-based differences in MAA adherence were not examined, as no studies have been published exploring such factors. Similarly, a low socio-economic index is only considered a barrier to accessing MAA, as its influence on treatment adherence is yet to be explored (Fleury et al., 2015). Thus, further studies are needed to understand and help characterise the individual considerations needed for initiating and managing MAA treatment within diverse patient groups.

In terms of appliance characteristics, both patient-reported adherence and preference favoured the use of custom-made appliances. The preference was not only reflected in the higher number of nights per week but also the number of hours per night that the appliance was used (Vanderveken et al., 2008, Johal et al., 2017). The findings are consistent with a recent systematic review and meta-analysis (Johal and Agha, 2018). Moreover, as MAA for OSA is entirely dependent on patient behaviour, patient preference or acceptance cannot be disregarded. However, the majority of the studies were limited to self-reported use and lacked an objective adherence measurement. This reflects the relatively recent introduction of objective adherence monitors (Vanderveken et al., 2013). Notwithstanding this, a lack of retention with the ready-made MAA was the most frequently cited reason for discomfort and non-adherence (Vanderveken et al., 2008, Tsuda et al., 2010, Friedman et al., 2012, Quinnell et al., 2014, Johal et al., 2017).

In relation to side effects, non-users experienced one or more adverse effects and tend to discontinue the treatment earlier i.e. within the first three months, whereas those who use the device for longer periods experienced milder problems (McGown et al., 2001, Makihara et al., 2016). In a questionnaire-based retrospective study, non-users reported a higher average number of side effects than users (McGown et al., 2001). Similarly, Makihara et al. reported that one-third of the non-users discontinued the MAA within the first month and 40% within in the next 3 months (Makihara et al., 2016). The most common reasons for discontinuation of treatment were discomfort or lack of treatment effects (Clark et al., 2000, McGown et al., 2001, de Almeida et al., 2005). Specifically, pain originating from the masticatory muscles or the temporomandibular joints may be one of the main reasons for poor adherence or

abandonment (Cunali et al., 2011). Consequently, Cunali et al. randomized 29 OSA adult patients with Temporomandibular disorders into two groups: the exercise support therapy (ST) and placebo therapy (PT) and were evaluated prior to and 120 days after MAA. The authors observed higher treatment adherence in the ST group ($p < 0.05$) as comparison to the PT group, as there was a significant reduction of pain intensity in the former group ($p < 0.05$), but not in the latter (Cunali et al., 2011). Long-term occlusal changes may occur with MAA (de Almeida et al., 2005), as such, dental follow-up may be useful in encouraging adherence while limiting possible side effects and the risk of cessation of treatment in long-term MAA users. In terms of the influence of gender, in a retrospective study (n=251), women experienced and reported more side effects and seemed to have a greater tendency to abandon treatment than males, as 46.8% of the women who answered a questionnaire based survey had discontinued the use of MAA compared to the 32.8% of males (de Almeida et al., 2005). However, given that the study was retrospective, with data collection from patients at different time intervals, the findings should be interpreted with caution (de Almeida et al., 2005).

Psychological and social factors, such as mood and perception of treatment benefits, and bed partner satisfaction levels were significantly correlated with MAA use (Izci et al., 2005). Dieltjens et al. identified that self-reported adherence to MAA was significantly lower for adults with OSA and Type D personality, a combination personality type of negative affectivity and social inhibition, as compared to patients with OSA without the said personality. These findings are in agreement with similar observations reported by Brostrom et al. in regards to lower CPAP adherence with type D personality (Brostrom et al., 2007). Objective adherence was found to be significantly correlated with a more pronounced decrease in socially disturbing snoring (Dieltjens et al., 2015). Research shows that adoption of new health behaviour, like a new physical activity routine or adhering to a prescribed medication regimen, is a challenging endeavour involving a variety of social, emotional, and cognitive factors (Schwarzer and Luszczynska, 2008). However, evidence in terms of psychological and social factors with regards to MAA adherence is highly underrepresented, which

contrasts with the volume of literature concerning CPAP adherence. Efforts to enhance patient education ranging from telephone support to home visits, motivational enhancement, or augmented support (Chervin et al., 1997, Hui et al., 2000) have been shown to improve CPAP adherence when compared to standard care. It has also been suggested in a recent Cochrane review that educational, supportive and behavioural interventions may increase CPAP usage to varying degrees (Wozniak et al., 2014). However, no studies evaluating the efficacy of the above-mentioned interventions in relation to MAA adherence were identified in this review. Evidence concerning the impact of psychological factors, such as patient's perceptions, self-efficacy, and social support on MAA adherence is highly underrepresented in the field of sleep medicine in comparison to various sleep apnoea treatments. Therefore, further research is imperative for the development of tailor-made interventions to enhance adherence in patients with low mood and/or psychological disorders.

3.5.1. Strengths and limitations

This is the first systematic review to assess the factors influencing adherence or non-adherence in adult patients with OSA on MAA. In order to limit publication bias, comprehensive search strategies were implemented along with the use of Covidence, a core component of Cochrane's review toolkit. The review followed the PRISMA reporting guidelines and the Cochrane Handbook of systematic review was used for risk of bias assessment for the included RCTs.

In terms of limitations, the search yield was limited to eight RCTs demonstrating low or unclear risk of bias. Furthermore, the application of a meta-analysis in non-randomized controls trials leads to bias arising from methodological issues and marked differences in study designs. Another possible limitation is the limited evidence identified concerning the impact of psychological and social factors, and the effect of strategies or interventions to improve MAA adherence.

3.6. Conclusion

A weak relationship was observed between objective MAA adherence and patient and disease characteristics such as age, sex, obesity, AHI, daytime sleepiness. Non-adherent patients reported more side effects than users and tended to discontinue treatment within the first three months. Increased patient adherence was identified with custom-made MAA in comparison to ready-made MAA. The review identified limited evidence concerning the influence of psychological and social factors on MAA adherence. Given that majority of the studies relied upon patient-reported adherence, the review observed a considerable lack of objective adherence monitoring.

Further research would be beneficial to describe the determinants of adherence, such as risk perception, self-efficacy, and outcome expectancy and to facilitate patient education and development of tailor-made interventions to enhance adherence to MAA. Similarly, the lack of objective adherence monitoring necessitates the need for future studies that assess adherence objectively.

Chapter 4. Intervention to enhance adherence to mandibular advancement appliance in patients with obstructive sleep apnoea: a randomised clinical trial

4.1. Introduction

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder characterised by the repeated episodic collapse of the upper airway during sleep, resulting in sleep deprivation, giving rise to apnoeas and hypopnoeas (Banno and Kryger, 2007).

An overnight sleep study is required to establish a diagnosis of OSA and provides the apnoea-hypopnoea index (AHI), which is the sum of the average number of apnoea (complete airflow cessation) and hypopnoea (partial airflow cessation) events per hour of sleep. The AHI has been classified into the following severity grades: mild (5 -15), moderate (16 - 30) and severe (> 30) (Medicine, 2005).

Based on the severity of OSA, there are two primary treatment modalities: continuous positive airway pressure (CPAP) and mandibular advancement appliance (MAA) therapy (Network, 2003, McDaid et al., 2009). CPAP is prescribed to those suffering from moderate to severe OSA. According to the current NICE guideline, MAA therapy is recommended to in individuals diagnosed with Mild OSA and symptoms that affect their usual daytime activities. The guidelines also prescribe MAA therapy to those with moderate or severe OSA intolerant to CPAP treatment as a second-line of treatment (NICE, 2021). It was noted that MAA reduces daytime sleepiness and improves the AHI by protruding the mandible and thereby maintaining an open pharyngeal airway (Lim et al., 2004). However, studies have consistently demonstrated that CPAP is more effective than MAA at reducing sleep- disordered breathing and achieving complete control of OSA (AHI < 5) (Sharples et al., 2016). Despite the greater effect of CPAP on objective polysomnographic parameters (e.g. AHI), it does not appear to be more effective at achieving better health outcomes. It seems that the higher efficacy of CPAP is offset by greater MAA adherence. Phillips et al. (2011) showed that CPAP and MAA

achieved similar improvements in excessive daytime sleepiness and quality of life. Average MAA adherence was 6.5 hours/night compared to 5.2 for CPAP ($p < 0.0001$) (Phillips et al., 2011). These findings are consistent with the results of a recent systematic review and meta-analysis, which demonstrated that adherence was significantly lower with CPAP than MAA by 1.1 hours per night ($p = 0.004$) (Schwartz et al., 2018).

Although initial subjective treatment adherence to MAA therapy is relatively high, it appears to decline over time. A phone-based survey of 69 patients with mild to moderate OSA prescribed MAA, reported a 32 per cent adherence rate after 4 years of therapy, indicating a high level of non-adherence (Saglam-Aydinatay and Taner, 2018). The study also suggested the prevention of barriers, associated with MAA therapy adherence, to improve the efficiency of the appliance and disease outcome. In a systematic review, Hoffstein et al. (2007) reported a wide range (4 -76 per cent) of adherence rates in the first year of appliance use and further studies have highlighted that adherence decreases with time (Hoffstein, 2007): 83 per cent after 1 year (Dieltjens et al., 2013b), and 62 - 64 per cent after 4 - 6 year (Walker-Engström et al., 2002, de Almeida et al., 2005).

MAA adherence might differ depending on the type of the appliance, custom-made or ready-made, disease severity, and patient management (Haviv et al., 2017). In a recent systematic review, patient-reported adherence (6.4 – 7 nights per week and 5 – 6.3 hours per night) and preference ($p \leq .001$) were strongly associated to custom-made MAA in comparison to ready-made MAA (Johal and Agha, 2018). Subjective side effects such as dry mouth, excessive salivation, tooth discomfort, muscle tenderness, and jaw stiffness, were not reported to lead to treatment discontinuation (Pantin et al., 1999, Fritsch et al., 2001, McGown et al., 2001, Clark et al., 2000). In addition, tooth movement and occlusal changes have been noted after 1 to 4 years of follow-up, but these changes again do not appear to be related to treatment withdrawal (Bondemark, 1999, Fransson et al., 2003, Ringqvist et al., 2003, Robertson et al., 2003, Marklund et al., 2004).

As mentioned in chapter 3, Dieltjens et al. (2013) were the first to investigate the impact of type D personality disorder on adherence to MAA therapy. Individuals with Type-D personality often possess a negative outlook towards life and are overwhelmed with emotions such as stress, anxiety, and anger. The study assessed 113 patients using two questionnaires: type D scale 14 and a postal questionnaire addressing side effects and adherence to MAA. The study included 83 patients with a baseline type D personality and reported a 45 per cent non-adherence rate amongst them (Dieltjens et al., 2013b). Patients with a type D personality had a higher discontinuation rate and lower adherence. These findings are in agreement with similar observations reported by Brostrom et al. (2007) in regard to lower CPAP adherence with type D personality (Broström et al., 2007). Nevertheless, the study has some limitations. The first being the relatively small sample size (sample bias) and the non-meaningful comparison groups, which may reduce the generalisability of the findings. The second is the subjective assessment of adherence and perceived side effects rather than employing objective means of adherence measurement. A further limitation is that the characteristic negative reporting trait of the type D patients may cause them to over-estimate their non-adherence (Dieltjens et al., 2013b).

Research shows that adoption of a new health behaviour, like a new physical activity routine or adhering to a prescribed medication regimen, is a challenging endeavour involving a variety of social, emotional, and cognitive factors (Schwarzer and Luszczynska, 2008). A multicentre study examined perceived effectiveness, self-efficacy and social support among 122 adult patients with OSA aged ≥ 65 years prescribed for MAA therapy (Carballo et al., 2016). The study reported a very low(30%) response rate (n = 39), in which the authors showed low rates of perceived effectiveness, self-efficacy and social support, highlighting the lack of self-efficacy, expectations for positive outcomes and social support experienced by the older patients in the sample. These findings are questionable, as literature has identified psychological and social factors and cognitive perceptions as determinants of CPAP adherence, including patients' risk perceptions, treatment outcome expectations, locus of control, and self-efficacy (Stepnowsky Jr and Dimsdale, 2002, De Zeeuw et al., 2007, Olsen

et al., 2010). Another possible limitation of the study is that the questionnaires were mailed to the participants, who were only contacted once by the authors explaining the poor response rate (Carballo et al., 2016). As a result, further research involving larger samples of men and women incorporating modes, which increase the response rate, is necessary to gain a better understanding of the patient's perception of MAA therapy. In turn, this understanding could be implemented for the development of interventions enhancing patient's adherence and experience to MAA treatment.

Interestingly, previous studies in the field of Sleep Medicine have featured an aspect of enhanced patient education ranging from telephone support to home visits, motivational enhancement, or augmented support (Chervin et al., 1997, Hui et al., 2000), which have been proven to effectively improve CPAP adherence when compared to usual care. Bakker et al. (insert ref number not year) conducted a randomised controlled trial of CPAP use with motivational enhancement (ME) versus CPAP only in 83 participants, with moderate to severe OSA. The trial demonstrated a clinically significant increase in CPAP adherence in the intervention arm (CPAP with ME), supporting the use of a motivational enhancement approach to optimise the management of OSA (Bakker et al., 2016).

A recent Cochrane review has also emphasised the efficiency of interventions in enhancing adherence to CPAP by stating that educational, supportive and behavioural interventions increase CPAP usage to varying degrees (Wozniak et al., 2014). Stage theories such as the Health Action Process Approach (HAPA), a social cognition model for behaviour change, can be used to identify factors to target in an intervention and their interrelationships. The model-based approach often uses a quantitative, questionnaire-based approach to assess a small set of factors linked within a model specifying how the factors are related to behaviour and to one another. It includes self-efficacy, outcome expectancies, and risk-perception as distal predictors, intention as a middle-level mediator, and volitional factors (such as action planning) as the most proximal predictors of behaviour. All are considered as determinants of adherence in CPAP therapy (Sawyer et al., 2011, Dzierzewski et al., 2016).

A number of randomised controlled trials within medicine have examined the concept of stage-matched interventions based on HAPA, for example in the context of dietary behaviours (Wiedemann et al., 2009), physical activity (Lippke et al., 2010), and dental hygiene (Schüz et al., 2009). In order to investigate the efficiency of interventions on CPAP adherence, 110 OSA (AHI ≥ 15 events/h) patients were randomly assigned into staged-match intervention care (SMC) and standardised care (SC) groups (Deng et al., 2013). The staged-match intervention care design, following the principles of HAPA, significantly improved CPAP adherence whilst facilitating intention formation and enhancing treatment self-efficacy. Although the evidence for stage theories is somewhat inconsistent, a meta-analysis (Noar et al., 2007) suggests that tailoring interventions to behavioural stages is more effective than a generic, non-staged-tailored approach.

The above stage theory advocates that behaviour intervention takes account of the stages of change. Individuals are presumed to progress through an ordered set of stages while contemplating, initiating, and maintaining health behaviour change (Weinstein et al., 1998b). Risk perception is an antecedent, that forms an intention to adopt a precautionary action or treatment (Deng et al., 2013). After a treatment intention develops, it transforms into detailed action plans and these plans may promote moving further into action and/or a maintenance stage (Prochaska et al., 1992), which implies that understanding behaviour change over time, on dynamic variables instead of static variables, would achieve maximum intervention effectiveness (Deng et al., 2013). This feature differentiates stage theories from social cognition theories, such as the theory of planned behaviour (TPB), which interpret behaviour change as a continuous process.

The approach also recommends a distinction between pre-intentional motivational processes and post-intentional volitional processes (Schüz et al., 2009). The motivational phase comprises of growing risk perception and outcome expectancies, leading to the development of an intention. Although risk perception is the initial step for developing an intention, it alone is deficient and outcome expectancies, characterised by the advantages and disadvantages of the health behaviour in context are essential to promote intention formation. For example,

the more a patient feels vulnerable to the possible health threats of long-term untreated OSA (hypertension, cardiovascular diseases), the more he or she will expect from the MAA therapy.

In the volitional phase, Intention and behaviour implementation (adherence to MAA) would be mediated through action planning (Presseau et al., 2017). Action planning consists of specifying when, where and how to perform the behaviour (Pakpour et al., 2014). Self-efficacy is an important construct to consider for behaviour change (Wilson et al., 2016) and facilitates maintenance of action (Presseau et al., 2017). For example, after a patient has been provided MAA treatment, he or she would make concrete plans concerning the commencement and continuation of the treatment, while overcoming the difficulties. Highly self-efficacious individuals are more confident in coping with setbacks and easily tackle unanticipated difficulties, as opposed to individuals with low self-efficacy (insert ref number not year). Since patients with OSA experience different mind-sets from initiation to long-term adherence, it is imperative to frame interventions to optimise adherence, tailor-made to the patients' specific psychological variables at different stages of therapy (Deng et al., 2013). In summary, research on increasing adherence to mandibular advancement appliances in obstructive sleep apnoea patients in underrepresented, which is in sharp contrast to the literature regarding CPAP adherence. The current NICE guidelines have highlighted the need of further research to enhance adherence to MAA therapy (NICE, 2008). Thus, we aim to address this shortfall by identifying the factors influencing adherence to MAA in patients with OSA and simultaneously assess the effectiveness of stage theories/stage-matched intervention on subjective and objective adherence, using the HAPA model.

4.2. Objectives

4.2.1. Aims and research questions:

The aim and primary outcome of this study is

- To assess the effectiveness of stage-matched intervention on adherence to mandibular advancement appliances (MAA) in patients with obstructive sleep apnoea (OSA).

4.2.2. Secondary objectives:

The secondary outcomes are:

- To identify the psychosocial and socio-economic indicators enhancing adherence of MAA in patients with OSA.
- Use of the indicators to develop a psychological and socio-economic predictor model.

4.2.3. Null hypothesis:

- Stage-matched intervention does not enhance adherence to MAA in patients with OSA compared to standardised care.

4.3. Methodology

The study was undertaken at the Royal London Dental Hospital, Bart's Health NHS Trust in line with the CONSORT reporting guidelines.

4.3.1. Selection criteria

4.3.1.1. Inclusion criteria

- Adult (≥ 40 years old)
- Confirmed diagnosis of OSA (AHI ≥ 5)
- Referred for MAA therapy
- Must be able to understand, read and write English; with the assistance of a translator

4.3.1.2. Exclusion criteria

- Insufficient teeth for MAA fabrication
- Poor dental or periodontal health
- Symptomatic temporomandibular disorder (TMD)
- Previously used an MAA
- Patients with uncontrolled epilepsy

4.3.2. Sample size

The study's sample size was based on the non-adherence rate of 30.45 percent and clinical wearing time of more than four hours demonstrated by previous research (Deng et al., 2013). A minimum sample size of 51 patients distributed in two groups, was proposed for given α (0.01), power (0.8) and between-group variance of $\eta^2 \approx 0.1$. Finally, assuming a maximum of 15 per cent dropout, a total number of 58 patients is required for 2 randomly assigned groups, intervention care (n = 24) and (n = 24).

4.3.3. Recruitment

As part of the routine care for patients presenting with sleep-related breathing disorders, they are all diagnosed with OSA, based on an overnight sleep study, performed in sleep clinics. Patients requiring mandibular advancement appliance (MAA) therapy are then referred to specific dental sleep clinics for treatment, as part of a multi-disciplinary approach to care. Patients, with a confirmed diagnosis of OSA, that were specifically referred for MAA

therapy to Barts' Health NHS Trust and met the studies selection criteria were approached for recruitment.

4.3.4. Trial design

The study was a single-centre, superiority, two-arm, parallel-group, individually randomised clinical trial, with 1:1 allocation, designed to test the effectiveness of stage-matched intervention in enhancing patient adherence to MAA therapy in patients with OSA.

Ethical approval (Appendix 3) was obtained from the Greater Manchester West Research ethics committee (REC ref: 19/LO/0972 & 19/NW/0391). Additionally, the study protocol was also accepted for publication in Trials 2021 22:699 issue https://trialsjournal.biomedcentral.com/articles/10.1186/s13063-021-05582-1 (Appendix 4). Furthermore, the study was registered in the international database, Clinicaltials.gov (Study ID: NCT04092660).

Patients meeting the eligibility criteria were provided with a participant information leaflet (Appendix 5) explaining the study. Written informed consent (Appendix 6) was then obtained, after which they were randomly assigned into two groups: intervention care (IC) and standardised care (SC). Only the investigator and chief investigator (CI) were aware of the participant's allocation.

Participants were provided with a sleep diary (Appendix 7) to record their hours of sleep and MAA wear-time, which provided a subjective record of the adherence (duration of usage of MAA). The TheraMon®, a micro-sensor was included in the MAA design (Figure 4.1), to provide objective data of MAA adherence. TheraMon® calculates the actual wear time by measuring temperature every 15 minutes and then transforms this information into wear time when the temperature ranges between two specific values. Vanderveken et al. and Johal et al. reported on the safety and feasibility, at 3- & 18-months respectively, of objective measurement techniques with MAA therapy in the same cohort of patients, who demonstrated a range of sleep-disordered breathing, from snoring to OSA (Vanderveken et al., 2013, Johal et al., 2016) . In the present study, this range is defined as 28°C to 38°C,

which includes the vast majority of intraoral temperature values observed in an individual under normal conditions. At baseline (T0), routine clinical subject demographics were collected which included age, gender, body mass index (BMI), and neck circumference (Table 4.1). The AHI was also recorded during the initial screening. Following an oral examination, upper and lower alginate impressions were taken along with the participant's bite. In addition, participants were asked to complete the following questionnaires (Table 4.1):

- Epworth sleepiness scale (ESS) (Johns, 1991) (Appendix 1)
- Self-efficacy measure for sleep apnoea (SEMSA) modified for oral appliance (Weaver et al., 2003) (Appendix 8)
- Pittsburgh sleep quality index (PSQI) (Buysse et al., 1989) (Appendix 9)
- EuroQol-5 Dimension (EQ-5D) (EuroQol, 2009) (Appendix 10)
- Socio-economic position questionnaire (NS-SEC, 2010) (Appendix 11)
- Social support questionnaire (Stepnowsky et al., 2002) (Appendix 12)

The above questionnaires provided information concerning the participant's daytime sleepiness, personality, quality of sleep, health-related quality of life, socio-economic status and social support, respectively.

At Fit appointment (T1), participants underwent the initial fitting of the MAA and were provided instruction on appliance use and care.

Both IC and SC groups were called for follow-up at 3- (T2), and 6- (T3) months. Any problems that the patients were experiencing regarding MAA use was attended to at these appointments. However, patients were offered a sooner appointment if there were any issues before their follow-up visits. In addition, data indicating adherence was collected and evaluated at the appointments both subjectively and objectively by downloading the data from the sensor using dedicated software.

Furthermore, at T2, participants completed the SEMSA questionnaire, whilst at T3, participants completed the ESS, SEMSA, PSQI and EQ-5D questionnaires.

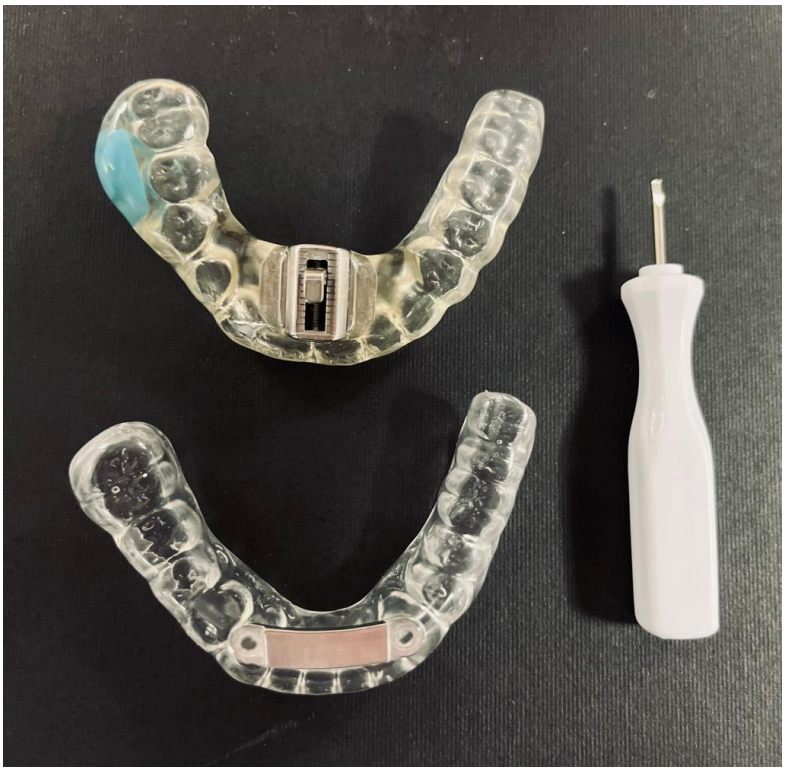
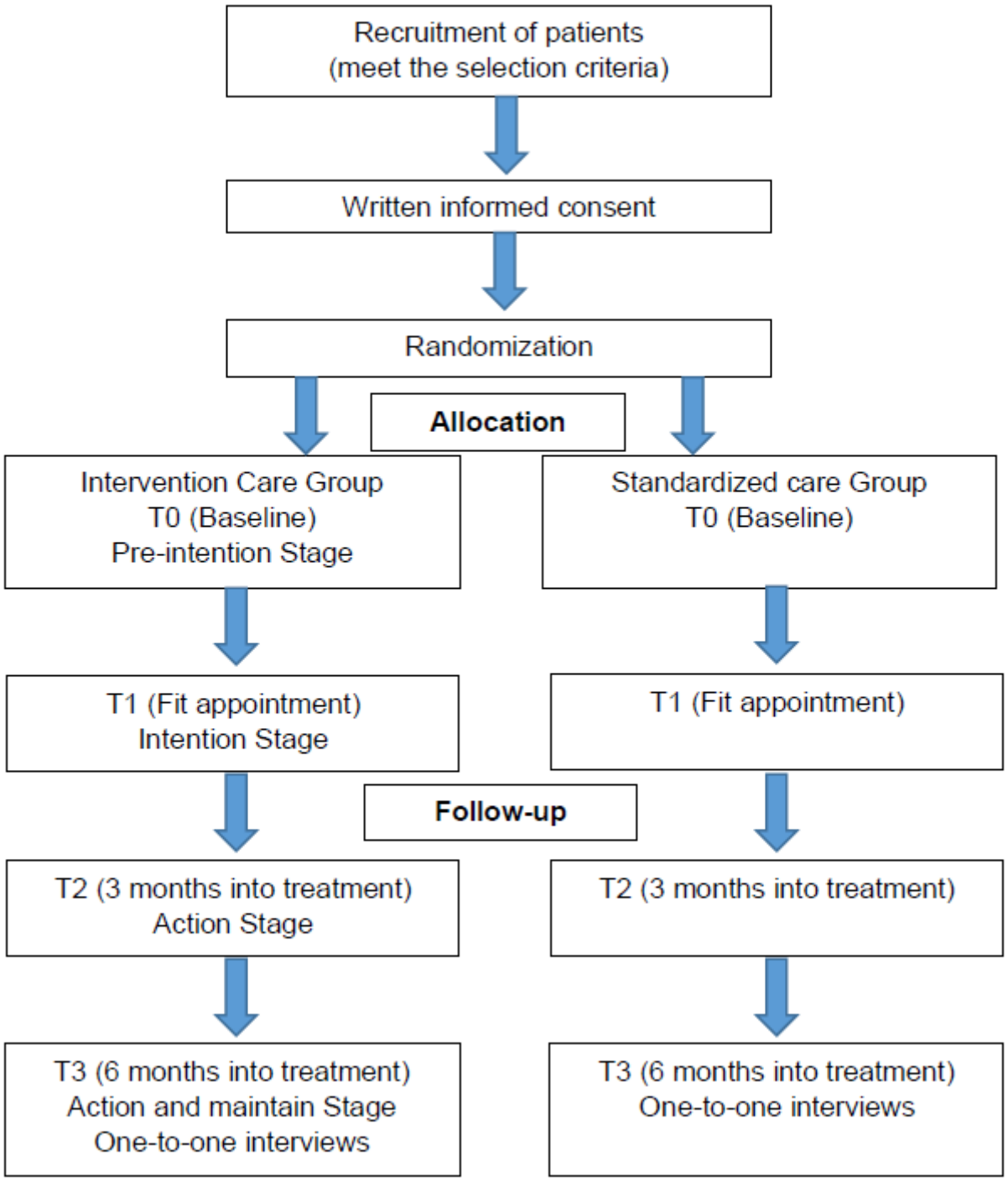


Figure 4.1 Mandibular advancement appliance (MAA), with attached micro sensor and adjustment key.

Table 4.1 Schedule of assessment

ASSESSMENT	Baseline (T0)	Fit appointment (T1)	3- months (T2)	6- months (T3)
Questionnaires				
Epworth Sleepiness Scale (ESS)	X			X
Self-Efficacy Measure for Sleep Apnoea (SEMSA)	X		X	X
Pittsburgh Sleep Quality Index (PSQI)	X			X
EQ-5D	X			X
Socio-Economic Questionnaire	X			
Social Support Questionnaire	X			
Age	X			
Gender	X			
Body Mass Index (BMI)	X			
Neck Circumference	X			
Objective Measure of Adherence			X	X
Subjective Measure of Adherence			X	X
One-to-one Interviews				X

Figure 4.2. Study schematic diagram



4.3.5. Allocation and concealment

A simple computer-generated randomisation method was performed using a restricted (10-number block) random number sequence (www.graphpad.com/quickcalcs/randomn2.cfm) to ensure equivalence of numbers in each group. Participants were stratified by OSA severity. In every 10-number block from the random table, the sequence was checked to ensure the even numbers were equal to the odd numbers. Each number in the random table were given a study number and assigned into one of the study groups. The allocation number of the participants were sealed in an opaque envelope from the investigator.

4.3.6. Blinding

The participants were precluded from blinding due to the nature of trial and intervention. Only the research student (HT) and CI will have access to the Master file and patient allocation. Patients were anonymised and allocated a unique study number and the data then blinded to the statistician, for analysis.

4.3.7. Measurements

4.3.7.1. MAA adherence

Participants were provided with a sleep diary to record their hours of sleep and MAA wear-time, which provided a subjective record of the adherence (duration of usage of MAA). The TheraMon®, a micro-sensor included in the MAA design, was used for the objective documentation of MAA adherence. TheraMon® calculates the actual wear time by measuring temperature every 15 minutes and then transforms this information into wear time when the temperature ranges between two specific values. In the present study, this range was defined as 28°C to 38°C, which includes a wide range of intraoral temperature values observed in an individual under normal conditions. Adherence was assessed at 3- and 6-month follow- up.

4.3.7.2. Epworth sleepiness scale

The Epworth Sleepiness Scale (ESS) assesses subjective sleep propensity by asking the subject to rate his or her chance of dozing in eight different sedentary situations (Phillips et al., 2011). Likert scale ratings for each of the eight items are scored on a scale of 0–3.

Summed scores range from 0 to 24, and scores ≥10 suggest excessive daytime sleepiness. The ESS has strong internal consistency (Cronbach's alpha = 0.81) and half-split reliability (*r* = 0.82) (Johns, 1991). Excessive daytime sleepiness was assessed at baseline and at 6-month follow-up (T2).

4.3.7.3. Self-efficacy measure for sleep apnoea

The Self-Efficacy Measure for Sleep Apnea (SEMSA) is a 27- item questionnaire assessing adherence-related cognitions (Weaver et al., 2003). It contains three subscales: risk perception, outcome expectancy, and self-efficacy. Items are rated on a Likert scale ranging 1–4, with higher scores indicating greater risk perception, higher outcome expectancies with treatment, and greater treatment self-efficacy, respectively. The SEMSA has strong internal consistency (Cronbach's alpha = 0.89) and half-split reliability (r = 0.80) (Olsen et al., 2010). The SEMSA was evaluated at baseline, 3- and 6-months of follow-up.

4.3.7.4. Pittsburgh sleep quality index

The Pittsburgh Sleep Quality Index (PSQI) questionnaire is a well-validated instrument to evaluate subjective sleep quality over a 1-month time interval (Buysse et al., 1989). The scale has seven components: (1) subjective quality, (2) sleep onset latency, (3) sleep duration, (4) sleep efficiency, (5) presence of sleep disturbances, (6) use of hypnotic–sedative medication, and (7) presence of daytime disturbances. The total scores of the PSQI are from 0 to 21, and higher the scores, poorer is the quality of sleep. The PSQI has strong internal consistency (Cronbach's alpha = 0.85) and test–retest reliability after 2 weeks (*r* = 0.81) (Buysse et al., 1989). Sleep quality was measured at baseline and 6-months of follow-up.

4.3.7.5. EuroQol-5 Dimension

The EuroQol five-dimensions – 3-level (EQ-5 D) is a versatile quality of life (QOL) instrument with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) and a visual analogue scale (EuroQol, 2009). The instrument demonstrates good internal consistency (Cronbach's alpha = 0.76) and test-retest reliability

after 2 weeks (*r* = 0.72) (Tripathy et al., 2015). Quality of life was measured at baseline and 6-month follow-up.

4.3.7.6. Socio-economic position

The National Statistics Socio-economic Classification (NS-SEC) scale was employed to assess the socio-economic position of the participants, which is the official classification system in the United Kingdom (NS-SEC, 2010).

4.3.7.6. Social support questionnaire

The social support questionnaire (SSQ) develop by Stepnowsky et al. (ref number) was used to evaluate the social support variable in the participant's life. The tool demonstrates good internal consistency with a Cronbach's alpha of 0.70 (Stepnowsky et al., 2002). Furthermore, as the variable is considered dynamic and specific time, context and subject, a test-retest reliability was not deemed appropriate by the authors. Social support was evaluated at baseline.

4.3.8. Stage-matched intervention

Participants in the IC group received additional support in the form of behaviour change intervention (Table 4.2). The behaviour change intervention based on the HAPA model entails delivering interventions in a staged manner. The intervention that was delivered are described in table 4.3, along with the time point.

Table 4.2 Intervention care content specified by behaviour change techniques and linked to constructs of the HAPA model

Intervention component	Behaviour change technique	HAPA construct targeted	Content
Pamphlet	Information about consequences	Risk perception and outcome expectancy	The health pamphlet (Appendix 13), based on HAPA, divided into 6 sections, systematically provides information about the risk, benefits and treatment of OSA. Section 2 and 4 of the pamphlets provides spaces for the participants to discuss about risks and benefits that concern them the most. Section 3 explains the various treatments available and a brief explanation of the mechanism of the treatment.
	Action Planning	Task Self-efficacy	Section 5 and 6 provided valuable information for participants on how to begin with using the appliance and to continue using it regularly. Patients were advised that is normal to struggle at time when starting with a new habit and setting short-term attainable goals will aid them in their struggles to adjust. The section suggests participants to seek feedback from their family, especially their sleeping partner regarding their improvement. This type of support motivates the patient to work more towards achieving their goals.
	Goal Setting		
	Problem Solving		

	Social support (unspecified)		
	Self-reward	Coping and Recovery Self-efficacy	In section 6, participants were told about the importance of rewarding themselves about the effort they put in to achieve their goals.
	Relapse prevention	Recovery Self-efficacy	Section 6 also advises the participants to focus on the positives and think about situations that effect their capability and then about options to avoid/cope with these situations.
Video	Credible Source	Risk perception, Outcome expectancy and Task & Coping Self-efficacy	Patients were shown a video (QMUL, 2019) of an OSA patients who are undergoing treatment, so that they can to relate to someone who is going through the same condition as him/her. The video consists of patients talking about how OSA effected their life and its negative consequences. The patients were encouraged to discuss about what motivated them to start the treatment, how has it changed their life and what helps them use the appliance regularly. It also consisted of a specialist in the field of Dental sleep medicine, briefly talking about the ill effects of untreated OSA and the specific oral appliance treatment available.
	Social Comparison		
	Information about the negative and positive consequences		
	Demonstration of Behaviour		
	Feedback on the behaviour		
	Social Support (Emotional & Practical)		
Counselling	Information about health consequences	Risk perception, Outcome expectancy and Task Self-efficacy	Participants were given an initial counselling session in person along with their partner if they wish. During the session i.e. structured to fit the participants needs…

	Social Support (unspecified and emotional)		• Their knowledge regarding OSA was assessed • The above video was shown • Using the information provided on the pamphlets the risks of untreated OSA and the benefits of the treatment were discussed • If the partner was present at the appointment, they were asked to complete a section of the pre-screening questionnaire (Appendix 14), which is part of the routine clinical examination. In the questionnaire, the partner was asked to indicate their and the participant's quality of sleep. In addition, the partner was asked to indicate the severity of the participant's snoring and whether it had an influence on their sleep.
	Verbal persuasion about capability		
Follow up at sleep clinic	Monitoring the behaviour and the outcome	Coping and Recovery Self-efficacy	Participants were required to visit the sleep clinic for follow up at month 3 and 6. Their MAA usage was assessed both objectively and subjectively by downloading the data from the micro-sensor chip embedded in the appliance and by recording the hours from their daily sleep log respectively.
	Focus on Past success and Verbal persuasion about capability	Coping and Recovery Self-efficacy	Feedback would be provided depending on the participant's usage. Their planning sheets would be discussed, and appropriate feedback will be provided whilst encouraging them to set more active goals and plans.
	Social Comparison	Coping and Recovery Self-efficacy	To increase their emotional support other patient's feedbacks and successful treatment would be shared.
	Problem solving	Coping and Recovery Self-efficacy	Additionally, participants will be prompted to identify common factors that act as barriers for them in using the appliance and will be helped to find solutions to overcome such factors tailored to the participants needs.

Booster phone calls	Verbal persuasion about capability	Coping and Recovery Self-efficacy	Participants will receive calls at weeks 3,6,18 and 21 approximately 10-15 mins in duration, prompting them to keep working towards their goals and stating that they are capable of achieving them.
	Social support unspecified	Coping and Recovery Self-efficacy	Participant's partner's experience of the treatment will also be discussed by asking them to share their thoughts on the participant's improvement.
	Problem solving	Coping and Recovery Self-efficacy	Additionally, participants will be prompted to identify common factors that act as barriers for them in using the appliance and will be helped to find solutions to overcome such factors tailored to the participants needs.

Table 4.3. Intervention and standardised care components

Time Point	Intervention Care Group	Standardised Care Group
T0 (Baseline)	• Questionnaires -ESS, SEMSA (Modified for Oral Appliance) PSQI, EQ-5D, Socio-Economic Position and Social Support	• Questionnaires -ESS, SEMSA, PSQI, EQ-5D, Socio-economic position, Social Support scale
T1 (Fit appointment)	• Providing instruction about how to use the MAA • Health pamphlet based on HAPA theory • Assessment of knowledge of OSA and involvement of the partner in education • A brief education focusing on the benefits associated with MAA • 10-min video education about OSA, emphasising the negative consequences if OSA is untreated • Risk perception communication • Setting Goals and action planning (steps to facilitate the use of MAA)	• Providing instruction about how to use the MAA • Health pamphlet about OSA and MAA
T2 (3-months into treatment)	• Phone calls to be made at 3 and 6 weeks -Problem Solving -Evaluation of the patient and partner perception of treatment -Verbal Encouragement -Setting attainable goals and action planning • Follow up at Sleep Clinic -Assessment of MAA use -Problem Solving -Verbal Encouragement	• Follow up at Sleep Clinic -Problem Solving -Assessment of MAA use • Questionnaires -SEMSA

	-Sharing other Patient's Feedbacks and successful treatment experiences • Questionnaire -SEMSA	
T3 (6-months into treatment)	• Phone calls to be made at 18 and 21 weeks -Problem Solving -Partner involvement in treatment and family support -Verbal Encouragement -Setting attainable goals and action planning • Follow up at Sleep Clinic -Assessment of MAA use -Problem Solving -Verbal Encouragement -Sharing other Patient's Feedbacks and successful treatment experiences • Questionnaires -ESS, SEMSA, PSQI, EQ-5D One-to-one interviews	• Follow up at Sleep Clinic -Problem Solving -Assessment of MAA Use • Questionnaires ESS, SEMSA, PSQI, EQ-5D • One-to-one Interviews

4.3.9. Outcomes

4.3.9.1. Primary outcome

Adherence i.e. the number of the hours the patient uses their appliance every night was measured objectively at 3-months to assess the effectiveness of the interventions in enhancing adherence to MAA.

4.3.9.2. Secondary outcome

Self-efficacy, risk perception, outcome expectancy, socio-economic status, and social support was measured to assess the ability of these variables in predicting adherence.

4.3.10. Statistical analysis

Both objective and subjective data of adherence i.e. duration of the usage of the appliance was collected at 3- and 6-months was analysed to assess the effectiveness of Intervention care in comparison with standardised care.

Comparison of pre- and post-treatment scores of ESS, SEMSA, PSQI, and EQ-5D, for both the groups, aided in identifying significant differences in terms of improvement.

Statistical evaluations were undertaken to assess the ability of the variables -self-efficacy, risk perception, outcome expectancy, social support, and socio-economic position, to predict patient adherence at 3- and 6-months.

Assuring random assignment to groups, tests were undertaken as to whether the observations differed in any of the time zero measurements. Indifference meant there was no allocation bias.

T-tests were applied for each of the following variables between SC and IC

1. Risk perception
2. Outcome expectancy
3. Self-efficacy
4. ESS -T0
5. PSQI – T0
6. EQ5D – T0
7. Social support
8. Socio-economic (ordinal) – chi-square test

In any case of violation of the t-test assumption (normality of the error term), Wilcoxon tests were subsequently implemented.

In order to assess the aims of the study, each of the repeated measures was tested first by themselves, using a repeated measures ANOVA, controlling for groups:

1. Adherence - subjective at T2, T3 difference T2-T3

2. Adherence - objective at T2, T3 difference T2-T3

3. ESS - T3, difference T0-T6

4. PSQI - T3, difference T0-T6

5. EQ5D- T3, difference T0-T6

6. Risk perception - T2, T3, difference T0-T2, T0-T3, T2-T3

7. Outcome expectancy - T2, T3, difference T0-T2, T0-T3, T2-T3

8. Self-efficacy - T2, T3, difference T0-T2, T0-T3, T2-T3

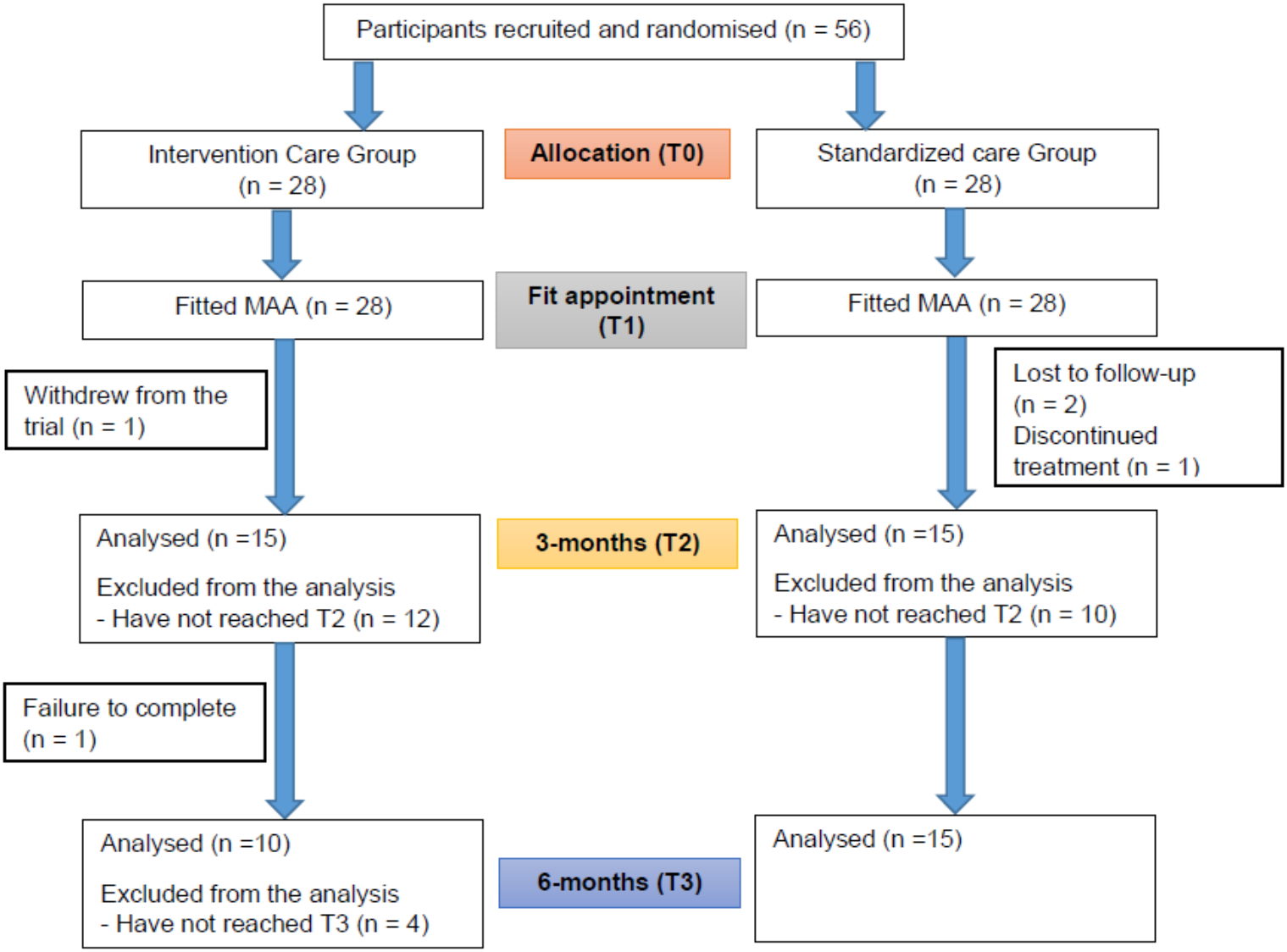
Once the trends in the data were analysed, a multiple regressions model for Adherence variables was constructed. These were the final measurements from T3 or the differences between them and previous time points i.e. T0 and T3. In these models, the psychosocial variables and socio-economic position were used as predictors, beyond the group classification.

4.4. Results

4.4.1. Participants flow

Fifty-six OSA patients who satisfied the selection criteria were recruited in this study after written informed consent. The participants were then randomised into IC (n = 28) and SC (n = 28) groups. In SC group, two patients were lost to follow-up and one patient discontinued treatment. Whilst one patient withdrew from the trial and one patient failed to complete treatment in the IC group. Figure 4.3 illustrates the flow of the participants through the trial.

Figure 4.3 Consort flow



4.4.2. Participant characteristics

Table 4.4 summarises the clinical and demographic characteristics of the participants. The sample consists of 34 (60%) males, with the mean age of the overall sample 55 years (SD = 10.72). There were no significant differences in gender, age, BMI, neck circumference and AHI between the two groups ($p > 0.05$) at baseline (T0). The results demonstrate that the study groups were comparable.

Table 4.4 Clinical and demographical characteristics

	Overall sample (n = 56)	**IC group (n = 28)**	**SC group (n = 28)**
Gender, n (%)			
Male	34 (60%)	15(52%)	19(69%)
female	22(40%)	13(48%)	9(31%)
Mean age in years (SD)	55 (10.72)	56.86 (8.65)	54.46 (12.51)
BMI (kg/m²), mean (SD)	30.78 (6.63)	31.53 (5.49)	29.9 (7.83)
Mean neck circumference (cm) (SD)	38.85 (3.23)	38.9 (3.07)	38.7 (3.42)
AHI (events/h) (SD)	19.16 (13.06)	19 (12.97)	19.32 (13.39)

4.4.3. MAA adherence

The overall mean objective adherence for the whole sample was 2.34 ± 2.59 hours/night and 2.87 ± 3.02 hours/night at T2 (n = 30) and T3 (n = 23), respectively. Inspecting the difference between groups, at T2 the mean adherence ranged from 2.0.2 ± 2.59 hours/night in the IC group to 2.63 ± 2.57 hours/night in the SC group. Whilst the mean adherence at T3 ranged from 2.42 ± 2.59 hours/night for the IC group to 3.21 hours/night in the SC group. Furthermore, no statistical difference was detected for adherence amongst the two groups at T2 (p = 0.5296, x^2 = 1.56) and T3 (p = 0.5344, x^2 = 0.12) (Table 4.5).

In addition, 28% of the participants in the IC group (n = 14) wore their MAA for at least 4 hours/night compared with 31% of the SC group (n = 16) at T2. Whilst 30% of the participants in the IC group (n = 10) wore their MAA for at least 4 hours/night compared with 46% of the SC group (n = 13) at T3.

Linear regression results of adherence over the two time points i.e. T2 and T3, demonstrate a significant positive relationship (Table 4.6). The coefficient is essentially equal to a unit indicating the adherence readings were almost identical over time.

Concerning the relationship between the SEMSA constructs (risk perception, self-efficacy and outcome expectancy), mean adherence was positively correlated with risk perception (p = 0.0352, r^2 = 0.16) and outcome expectancy at T2 (Table 4.6).

Table 4.5 Difference in adherence i.e. (hours/night) between the groups at 3- (T2) and 6- (T3) months.

Dependent	Time point	Group	N	Mean	SD	Pvalue >|t|
Adherence	T2	IC	15	2.02	2.68	0.5296
		SC	15	2.63	2.57	
Adherence	T3	IC	10	2.42	2.59	0.5344
		SC	13	3.21	3.37	

Table 4.6 Linear regression scores for adherence at 3-months (T2) by adherence at 6 months (T3) and mean adherence by risk perception, outcome expectancy and self-efficacy. representing the mean of Likert scores 1 to 4. Higher scores indicate greater perceived susceptibility, higher outcome expectancy and greater perceived self-efficacy

Dependent	Independent	Estimate (B)	Pvalue > |t|	R^2	N
Adherence T3	Adherence T2	0.96	<.0001	0.754	22
	Intercept	0.38	0.4325		
Mean Adherence	Mean Risk perception	1.84	0.0211	0.170	31
	Intercept	-2.07	0.2774		
Mean Adherence	Mean Outcome Expectancy	2.07	0.0175	0.180	31
	Intercept	-3.47	0.1518		
Mean Adherence	Mean Self Efficacy	2.46	0.0625	0.115	31
	Intercept	-4.89	0.2053		

4.4.4. Effect of stage-matched intervention

SEMSA questions were averaged per constructs, namely: risk perception, outcome expectancy and self-efficacy. Cronbach's alpha was used to test the reliability for each item. Reliability measurements were estimated in the range between 0.92 – 0.80 which was considered high and sufficient for aggregating the items.

The results for SEMSA constructs: risk perception, outcome expectancy, self-efficacy at baseline (T0), 3- (T2) and 6- (T3) months follow-up is summarised in table 4.7. The scores demonstrated no significant differences concerning the three constructs between the IC and SC groups at baseline (T0), 3- (T2) and 6- (T3) months follow-up.

Table 4.7 Scores for risk perception, outcome expectancy and self-efficacy at baseline (T0), 3- (T2) and 6- (T3) months representing the mean of Likert scores 1 to 4. Higher scores indicate greater perceived susceptibility, higher outcome expectancy and greater perceived self-efficacy

Dependent	Time point	Group	N	Mean	SD	Pvalue>|t|	χ^2
Risk perception	T0	IC	28	2.63	0.8	0.2053	1.16
		SC	28	2.38	0.68		
	T2	IC	15	2.53	0.83	0.6464	0.06
		SC	15	2.65	0.63		
	T3	IC	10	2.4	0.48	0.8438	0.13
		SC	15	2.36	0.49		
Outcome expectancy	T0	IC	27	2.86	0.65	0.3278	2.33
		SC	28	2.69	0.6		
	T2	IC	15	2.79	0.72	0.3491	0.84
		SC	15	3.03	0.61		
	T3	IC	10	2.92	0.73	0.6416	0.17
		SC	15	3.04	0.43		
Self-efficacy	T0	IC	27	2.83	0.56	0.6432	0.01
		SC	28	2.9	0.6		
	T2	IC	15	2.95	0.4	0.4379	0.14
		SC	15	3.07	0.48		
	T3	IC	10	2.89	0.52	0.7955	0.03
		SC	15	2.94	0.28		

4.4.4.1. Risk perception

Concerning risk perception, no significant effect was observed in regard to the 2 groups (p = 0.8438, x^2 = 0. 13). Similarly, no significant effect of time was demonstrated (p = 0.1563, x^2 = 1.43) and no significant effect of time X group was observed, at T2 – T0 (p = 0.7262, x^2 = 0.08) and at T3 – T0 (p = 0.9385, x^2 = 0.13). The findings are summarised in Table 4.8 and 4.9.

4.4.4.2. Outcome expectancy

In terms of outcome expectancy, there was no significant effect was observed between the two groups at T2 (p = 0.3491, x^2 = 0.84) and at T3 (p = 0.6416, x^2 = 0.71). Similarly, no significant effect of time was observed (p = 0.2677, x^2 = 1.81). However, whilst no significant effect was observed of time X group at T2 – T0 (p = 0.717, x^2 = 0.28), a significant effect was demonstrated at T3 – T0 (p = 0.0318, x^2 = 3.47). Although, participants of both the groups received the same treatment, participants in the IC group had higher outcome expectancy than the SC group participants after the intervention. The findings are summarised in Table 4.8 and 4.9.

4.4.4.3. Self-efficacy

In terms of self-efficacy, no significant effect was observed between the groups at T2 (p = 0.4379, x^2 = 0.14) and T3 (p = 0.7955, x^2 = 0.03). Similarly, no significant effect of time was observed (p = 0.7424, x^2 = 0.01). Although, similar to outcome expectancy, a significant effect of time X group at T3 – T0 (p = 0.0252, x^2 = 4.48) was observed with self-efficacy but no significant effect was demonstrated at T2 – T0 (p = 0.1642, x^2 = 2.91). Hence, after intervention, participants in the IC group had higher self-efficacy than those in the SC group. The findings are summarised in Table 4.8 and 4.9.

Table 4.8 Scores of risk perception, outcome expectancy and self-efficacy over time by treatment groups representing the mean of Likert scores 1 to 4. Higher scores indicate greater perceived susceptibility, higher outcome expectancy and greater perceived self-efficacy.

Dependent		Group	N	Mean	SD	Pvalue>|t|	χ^2
Risk perception	T2-T0	IC	15	0.02	0.78	0.7262	0.08
		SC	15	0.11	0.63		
	T3-T0	IC	10	-0.15	1.12	0.9385	0.13
		SC	15	-0.18	0.66		
Outcome Expectations	T2-T0	IC	14	0.11	0.68	0.717	0.28
		SC	15	0.19	0.48		
	T3-T0	IC	9	0.49	0.33	0.0318	3.47
		SC	14	0.08	0.53		
Self-Efficacy	T2-T0	IC	14	0.32	0.67	0.1642	2.91
		SC	15	-0.05	0.72		
	T3-T0	IC	9	0.41	0.64	0.0252	4.48
		SC	14	-0.23	0.53		

Table 4.9 Scores for risk perception, outcome expectancy and self-efficacy over time representing the mean of Likert scores 1 to 4. Higher scores indicate greater perceived susceptibility, higher outcome expectancy and greater perceived self-efficacy

Dependent	Group	N	Mean	SD	Pvalue>|t|	χ^2
Mean Risk perception	IC	28	2.62	0.69	0.1563	1.43
	SC	28	2.37	0.61		
Mean Outcome Expectancy	IC	28	2.92	0.56	0.2677	1.81
	SC	28	2.75	0.57		
Mean Self Efficacy	IC	28	2.9	0.41	0.7424	0.01
	SC	28	2.86	0.47		

4.4.5. Excessive sleepiness

At 6-months, ESS scores demonstrated statistically significant improvement across the whole sample (t = -3.51, p = 0.002). However, the ESS change over time across treatment groups showed no significant difference. Furthermore, the relationship between mean adherence and ESS at baseline demonstrated no significant correlations (p = 0.242, r^2 = 0.047).

4.4.6. Quality of sleep

The mean PSQI for the whole sample ranged from 8.48 ± 4.11 to 6.08 ± 4.12 at baseline and 6-months, respectively. No significant differences were observed over time between IC and SC groups (p = 0.5483, x^2 = 0.41). Whilst a significant negative correlation was demonstrated (B = -0.6, p = 0.04) between quality of sleep and adherence at T3. In addition, adherence at T2 showed a negative association with change in PSQI over time i.e. T0-T3 (B = -0.56, p = 0.035).

4.4.7. Socio-economic position

The distribution of SEP in the sample includes a majority (n=43; 82%) managerial, administrate and professionals. In estimating the difference in mean adherence by SEP category, no significant differences were detected regarding adherence (p = *0.96,* x^2 = 0.398).

4.4.8. Quality of life

The quality-of-life scores had an overall mean of 69.8 (SD=15.72) and 68.32 (SD=12.17) at T0 and T3 respectively across the sample. The difference over time was -1.36 (SD=12.5). Inspecting the difference between groups at each time point results indicate a statistically significant difference at T3 while not at T0. At T3, the mean quality of life scores for the IC and the SC group was 62.5 (SD=10.34) and 72.2 (SD=12.03) (t=2.15, p=0.04) (χ^2 = 4.53, P=0.03), respectively.

4.4.9. Social support

Across the whole sample, the mean social support score was 4.04 (SD=0.78). The social support score was measured by averaging the nine items from SSQ. The overall reliability, as measured with Cronbach's α, was estimated at 0.927, which was high and sufficient for aggregating. Very little differences were evident in SSQ by groups, with averages ranging between 3.88 ± 0.84 and 4.22 ± 0.70. No statistical difference was detected ($p = 0.1024$, $x^2 = 2.84$). Linear regression between adherence and social support showed no significant correlations ($p = 0.5252$, $r^2 = 0.014$).

4.5. Discussion

Previous literature in the field of sleep medicine has highlighted the need for a multifaceted patient-tailored intervention associated with objective monitoring of usage to enhance adherence to mandibular advancement appliance therapy (Saglam-Aydinatay and Taner, 2018, Pahkala and Suominen, 2021). Similarly, the current NICE guidelines have reiterated the above need (NICE, 2021). Thus, the current study aimed to assess the impact of a stage-matched intervention specific to patient needs on adherence to MAA, through a randomised clinical trial. The trial recruited 56 participants into intervention and standard care groups in a 1:1 ratio. Due to the Covid-19 pandemic, recruitment and data collection were temporarily paused for eight months. Hence, only thirty participants had completed the data collection at three months (T2), whilst 25 had completed six months (T3) of treatment.

4.5.1. Effect of stage-matched intervention: Risk perception, outcome expectancy and self-efficacy

The current study is the first to implement a stage-matched intervention to enhance patient adherence to mandibular advancement appliance therapy. The findings of the study to-date indicate that the stage-matched intervention demonstrates no improvement in adherence to MAA. The intervention delivered at 3- and 6- months was designed based on the health action process approach (HAPA), a behaviour change model. The dual-phase model identifies three social-cognitive constructs in behaviour initiation and maintenance: risk perception, outcome expectancy and self-efficacy (Schwarzer, 2008). Research has consistently identified these constructs as predictors of behaviour change and determinants of adherence in OSA patients (Carballo et al., 2016). In addition, studies have demonstrated positive correlations between these constructs and behaviour change (Hattar et al., 2016, Maher and Conroy, 2016, Bierbauer et al., 2017a). Consequently, a positive association was observed between adherence and risk perception. Risk perceptions are beliefs regarding personal risk or susceptibility to conditions or outcomes. Similarly, the study found that patients who perceived a higher risk of untreated OSA were more adherent than those who did not. Therefore,

the ability of risk perception to determine adherence should not be underestimated in OSA patients, as they are at an increased risk of chronic diseases and treatment of their condition alleviates immediate symptoms (e.g. excessive daytime sleepiness, snoring, gasping and fatigue). Furthermore, health psychologists have regarded risk perception as an important facilitator for intention development (Lippke et al., 2004). Accordingly, the stage- matched intervention entailed strategies for risk awareness at T1 such as risk perception communication and a brief 10-minute video emphasising the negative consequences of untreated OSA (Table 4.2 and 4.3). This aided the participants to move from the pre-intention to the intention stage. This is consistent with previous research that considers perceptions of health threat to be the most obvious prerequisite for the motivation to adopt a health behaviour (Ruiter et al., 2001). However, the findings of the present study indicated no significant differences in terms of risk perception between the groups. This could be attributed to the limited number of observations available to-date for analysis. Additionally, the findings of a meta-analysis have demonstrated negligible effects of risk perception on behaviour initiation and indirectly on behaviour change across studies implementing the HAPA, with the authors argued that risk perception has a relatively minimal role in determining health-related behaviour (Zhang et al., 2019). Thus, risk perception might be less evident if no clear, explicit and proximal link is established between health-related behaviour and reduced risk (Ferrer and Klein, 2015). Nonetheless, research has emphasised on testing the collaborative effects of self-efficacy and risk perception on health behaviour, which may provide further insight into the process by which risk perception determines action (Zhang et al., 2019).

The current study also observed outcome expectancy as one of the drivers for adherence, with a positive correlation observed between outcome expectancy and adherence. Outcome expectancies reflect beliefs about whether engaging in the behaviour will result in desired outcomes (Strecher et al., 1986). Consistent with the HAPA model, participants who were more aware about the advantages of MAA therapy were more adherent than those who were not. Although risk perception is considered as a facilitator to pursue treatment, however, is

insufficient on its own to instil a behaviour change (Ferrer and Klein, 2015). Thus, the benefits perceived from MAA therapy and the alleviation of the symptoms are the key features that appear to drive individuals to initiate treatment. Hence, the intervention at T1 also entailed strategies that made patients more aware about the benefits of MAA therapy through education about the advantages of initiating treatment (Table 4.2 and 4.3). Moreover, the brief 10-minute video also contained testimonials of OSA patients talking about the benefits they have received from long-term MAA therapy (Table 4.2 and 4.3). Accordingly, the present study observed that participants in the IC group had a higher outcome expectancy in relation to the SC group over time i.e. T3 – T0. Hence, the stage-matched intervention appeared to have a favourable influence on participants' outcome expectancy. This is in consistent with previous research concerning CPAP adherence that has demonstrated positive outcome expectancies of initial CPAP to be related to subsequence adherence and regarded the first month of therapy to be a transition period for adaptation to treatment (Drake et al., 2003, Aloia et al., 2004). However, the transition from the motivational phase to volitional (action) phase requires planning (Schwarzer, 2008). Thus, the intervention also emphasised on setting attainable goals and action planning at T1, T2 and T3 (Table 5.2 and 5.3). In addition, the 'booster' phone calls undertaken at 3-, and 6- weeks attempted to deliver the same. Previous research has observed that early side effects to treatment can lead to treatment discontinuation (Attali et al., 2016). Hence, the 'booster' phone calls made at 3- and 6- weeks also helped patients in problem solving. Furthermore, studies have observed that individuals would normally imagine circumstances that would prevent them from performing the desired behaviour and this would lead to the development of coping strategies (Aloia et al., 2007, Deng et al., 2013). Participants in the IC group who demonstrated a higher outcome expectancy in the first 3 months of treatment, identified techniques that aided in their usage of MAA. These involved designating a specific place (e.g. bedside table or bathroom) for the MAA or incorporating the MAA into their night-time routine (after brushing their teeth or after applying night cream), which would function as a reminder for them to wear the MAA before going to bed. The study also observed

that setting short-term attainable goals such as setting targets for increasing the wearing time gradually helped participants to perform and maintain the behaviour.

As described in HAPA, the volitional (action) phase consists of two components that facilitate in the enactment of the intentions: self-efficacy and maintenance. Self-efficacy is described to be phase-specific as action self-efficacy is relevant during intention-formation, whilst maintenance (coping), and recovery self-efficacy is attributed to the enactment and maintenance of behaviour (Schwarzer and Renner, 2000). Consistent with the model, the intervention consisted of action planning, goal setting and problem solving at T1 to increase the participant's action self-efficacy (Table 5.2 and 5.3). Whilst the subsequent 'booster' phone calls and follow-up visits focused on increasing the participant's maintenance and recovery self-efficacy. This is in agreement with previous research concerning CPAP, which has demonstrated that frequent and regular follow-up, telephone calls, tailored education, and social support during the initial months of therapy can enhance long-term adherence to treatment (Fletcher and Luckett, 1991, Chervin et al., 1997, Hoy et al., 1999). Accordingly, participants in the IC group demonstrated a significantly higher self-efficacy in comparison to the SC group over time (T3 – T0). Nonetheless, no correlations were observed between adherence and self-efficacy. This is in sharp contrast to previous studies, which have observed that participants with higher self-efficacy reported a stronger correlation between CPAP usage and symptom improvement (Baron et al., 2011b). The lack of association in the present study may be a consequence of the limited data available for analysis. Action self-efficacy, described as an individual's capacity to perform the desired behaviour whilst overcoming the potential barriers seems to have a persistent effect on the health behaviour (Schwarzer, 2008). Furthermore, Action self-efficacy is a constant predictor of maintenance self-efficacy, and maintenance self-efficacy mediates action self-efficacy effects on behaviour, illustrating that the individual's estimates of their capacity to engage in health behaviour in future align closely with their estimates to maintain that behaviour (Schwarzer and Renner, 2000). Given that, adherence to MAA is variable and long-term adherence is observed in the literature to decline

(Sutherland et al., 2014). Further research is needed to assess ways to enhance self-efficacy in patients with OSA. In addition, the role of recovery self-efficacy, which is observed to be relevant only in situations of relapse (Schwarzer and Renner, 2000), cannot be underestimated, with participants on MAA therapy finding it challenging to maintain the therapy over a longer duration. Moreover, early side effects have resulted in early discontinuation of the treatment (Attali et al., 2016). Hence, future research comparing the role of recovery self-efficacy in determining behaviour in specific contexts where behavioural lapses are likely (e.g. situations where there is high opportunity to participate in rewarding, counter-intentional behavioural options) may demonstrate the context-specific value of this construct (Zhang et al., 2019).

4.5.2. Effect of Up-stream factors

Additionally, the current study also aimed to assess the role of up-stream factors such as excessive daytime sleepiness, quality of sleep, socio-economic position, quality of life and social support in predicting adherence.

4.5.2.1. Excessive daytime sleepiness

The results of disease characteristic such as excessive daytime sleepiness demonstrated no correlation with adherence. This is in agreement with the results of a systematic review that observed no association between objective adherence and anthropometric characteristics, polysomnographic parameters, and excessive daytime sleepiness (see Chapter 4 section 4.6). Although, consistent with previous research, a significant reduction in daytime sleepiness was observed across the whole sample at T3 (Saglam-Aydinatay and Taner, 2018, Pahkala and Suominen, 2021).

4.5.2.2. Quality of sleep

In line with previous studies, findings for quality of sleep demonstrated a negative association with adherence at T3 (Deng et al., 2013, Dieltjens et al., 2015, Pahkala and Suominen, 2021). Hence, this indicates that increase in adherence was related to an improvement in the quality of sleep. However, no relationship can be drawn between quality of sleep at baseline and

adherence at T3. The findings can be attributed to the limited data available for analysis at T3. Nonetheless, the findings are consistent with previous research concerning both CPAP and MAA adherence (See chapter 4 section 4.5).

4.5.2.3. Socio-economic position

In terms of socio-economic position, majority of the participants belonged to the managerial, administrative professional group, representing the upper middle class and middle-class strata of the society. To-date, low socioeconomic index is only considered a barrier to accessing MAA therapy (Fleury et al., 2015). The current study to-date indicates no specific socio-economic category to be associated to adherence. However, previous research concerning CPAP adherence suggests that socio-environmental factors are important in terms of patient adherence among patients with OSA (Platt et al., 2009). The lack of association in this can be implicated to the availability of limited data for analysis. Hence, further research with robust data is needed to explore the influence of socio-environmental factors on adherence to MAA therapy.

4.5.2.4. Quality of life

The findings of the present study do not demonstrate a significant improvement in relation to quality of life at the end of 6 months. Again, the results can be attributed to the limited data analysed. However, the findings agree with Marklund et al. (2015) who reported no significant improvements in daytime sleepiness and quality of life from baseline to follow- up with MAA therapy when compared with a placebo device. Nonetheless, studies evaluating the quality of life benefits of MAA therapy vs placebo devices have observed positive effects on energy, fatigue, and vitality domains in patients with moderate and severe OSA (Johal, 2006, Petri et al., 2008, Doff et al., 2013b). Doff et al. (2013) showed that several subjective parameters (SF-36 and FOSQ) significantly improved with MAD therapy in the short-term (2 months) and long-term (2 years) follow-up. Similarly, Johal (2006) demonstrated a significant improvement in the physical functioning, role limitation-physical, social functioning, vitality and general health perception domains of the SF-36 QoL questionnaire. Nevertheless, quality of life and

excessive daytime sleepiness are subject to a multitude of factors, such as severity of OSA, underlying chronic disease, mental illness etc. Hence, in situations as such, adequate treatment might be insufficient to precipitate a considerable change in these parameters.

4.5.2.5. Social factors

Previous research has demonstrated that social factors such as involvement of family and bed partners' satisfaction levels correlate significantly with MAA adherence (see Chapter 4 section4.5). Dieltjens et al. (2015) observed that objective adherence was significantly correlated to socially disturbing snoring. However, the results of the current study do not corroborate with the above findings. No significant association was observed between social support and adherence. Carballo et al (2016) reported similar findings; however, this should not be interpreted as an indication that social support plays no role in MAA adherence, given that the benefits of MAA therapy, in all proportions, are not only limited to patients but also extend to their bed partners. Therefore, further research is needed with robust data to explore ways of implementing social support as a resource to improve MAA adherence.

4.5.3. Study design

As mentioned above, the current study is the first to assess the efficacy of a stage-matched intervention in enhancing adherence to MAA therapy. Only recently has Liu et al. (2022) evaluated the efficacy of a multifactorial intervention in enhancing patient adherence to mandibular advancement appliance. However, the effectiveness of stage-matched intervention has only been evaluated in relation to CPAP adherence. Hence, the current study's sample size was based on the non-adherence rates and clinical wearing time reported by Deng et al. (2013). Although Liu et al. (2022) had a greater sample size than the current study, both the studies exhibited similar powers. However, the multifactorial approach adopted by Liu et al. (2022) failed to consider heath beliefs (risk perception, outcome expectancy and self-efficacy) that govern adherence in patients with OSA (Stepnowsky et al., 2006, Carballo et al., 2016). Moreover, the authors delivered the intervention as a whole, rendering it difficult to assess which intervention was more effective in relation to the others. In addition, no

consideration was given to the ordered set of stages that individuals are presumed to progress while contemplating, initiating, and maintaining health behaviour change during intervention delivery.

Furthermore, in the current study, two patients were lost to follow-up, one patient discontinued treatment, one patient withdrew from the trial and one patient failed to complete treatment. The sample size was inflated to account for 15% dropouts, however due to time restraints (as a consequence of the Covid-19 pandemic) recruitment was stopped once 56 participants were enrolled in the study. Nevertheless, previous research in relation to enhancing MAA adherence has observed similar dropout rates (Pahkala and Suominen, 2021, Liu et al., 2022).

The present study enrolled individuals with a confirmed diagnosis of OSA (AHI ≥ 5), who were 40 years-old or above and referred for MAA therapy. Individuals with poor periodontal health, insufficient teeth for MAA fabrication, TMJ disorders, uncontrolled epilepsy and past MAA users were excluded. The prevalence of OSA is known to increase with advancing age, hence patients above 39 years age were considered eligible for the study. Nonetheless, recent survey of 493 healthy individuals ranging from 18-25 years of age indicated that 17.3% (n = 73) of participants were at increased risk of OSA using the STOP BANG questionnaire (Aggarwal et al., 2021). Therefore, further research is needed to screen for the prevalence of OSA in younger adults.

4.5.4. Limitations

The main limitation of the current study is the limited quantity of data that was available for the analysis. As highlighted previously, eight months of recruitment and data collection time was lost due the COVID-19 pandemic. Hence, the data might lack the robustness needed to assess the aims of the study.

Additionally, the consequence of presenting interim data, as not all the participants have completed the trial might increase the chances of type 2 error that often results from small sample sizes.

Nevertheless, the study did demonstrate results that were consistent with previous research concerning CPAP adherence (Stepnowsky et al., 2002, Deng et al., 2013). In addition, the current study does plan to follow-up the patients for over a longer period. However, further research with robust data, longer follow-up period devoid of any interruptions is imperative to explore effective ways to enhance adherence to MAA therapy.

4.6. Conclusion

The rationale for the current study was to help address the current shortfall in the literature in relation to methods that could be adopted to optimise MAA adherence in OSA. The current stage-matched intervention trial, to-date could not demonstrate any significant improvement in relation to MAA adherence.

However, whilst the findings of the present study should be interpreted with caution, the study did observe:

- A positive correlation between risk perception and outcome expectancy.
- Participants in the IC group had higher self-efficacy than those in the SC group

Nevertheless, future research is needed to further define the role of risk perception, outcome expectancy and self-efficacy in MAA adherence.

Chapter 5. Behaviour change techniques to enhance adherence to Mandibular advancement appliance in Patients with Obstructive Sleep Apnoea: A Qualitative study

5.1. Introduction

It is recognised that patient adherence to treatment in chronic conditions declines considerably after 6 months of therapy (Jin et al., 2008, Fernandez-Lazaro et al., 2019). Similarly, adherence to mandibular advancement therapy varies from 76 to 95%, while the range of MAA adherence after 33 months of use is 56–68%, and after 4 years use, declines to 32% (Hoffstein, 2007). Given that mandibular advancement appliances are removable and must be used indefinitely, adherence to treatment is of utmost importance for successful outcomes. Furthermore, adherence to treatment in patients with obstructive sleep apnoea is influenced on a multitude of factors (Tallamraju et al., 2021).

Adoption of new health behaviour, like a new physical activity routine or adhering to a prescribed medication regimen, is a challenging endeavour involving a variety of social, emotional, and cognitive factors (Schwarzer and Luszczynska, 2008). However, evidence in terms of psychological and social factors with regards to MAA adherence is highly limited in contrast with the volume of literature concerning CPAP adherence. Efforts to enhance patient education ranging from telephone support to home visits, motivational enhancement, or augmented support have been shown to improve CPAP adherence when compared to standard care (Chervin et al., 1997, Hui et al., 2000). It has also been suggested in a recent Cochrane review that educational, supportive and behavioural interventions may increase CPAP usage to varying degrees (Wozniak et al., 2014). However, no studies evaluating the efficacy of the interventions in relation to MAA adherence were identified in this review. Therefore, the aim of this study is to explore and understand the experiences of obstructive sleep apnoea (OSA) patients in relation to mandibular advancement appliance (MAA) therapy through a qualitative approach

5.2. Hypothesis

No hypotheses are required to undertake this study, since the qualitative nature of the study means they are generated once the gathered data has been interpreted and understood.

5.3. Aim

To identify behaviour change techniques influencing adherence to mandibular advancement therapy in obstructive sleep apnoea patients.

5.4. Methodology

5.4.1. Study design

Qualitative methodology with semi-structured, one-to-one interview of participants and analysis of data using the behaviour change taxonomy of Cane et al., (2012).

5.4.2. Ethical approval

Ethical approval (Appendix 3) for this study was obtained from Northwest – Greater Manchester West Research Ethics Committee (REC reference: 16/NW/0391 or 19/LO/0972), prior to the recruitment of participants.

5.4.3. Participant recruitment

Participants for this study were recruited from a randomised controlled trial at the Institute of Dentistry, the Barts and The London School of Medicine and Dentistry. The parent trial was undertaken to investigate the efficacy of behaviour change interventions in enhancing adherence to MAA therapy in patients with obstructive sleep apnoea.

5.4.4. Selection Criteria

5.4.4.1. Inclusion criteria

Adults (≥40 years old)

Confirmed diagnosis of OSA (AHI ≥ 5)

Referred for MAA therapy

Must be able to understand, read and write English; with the assistance of a translator

5.4.4.2. Exclusion criteria

Insufficient teeth for MAA fabrication

Poor dental and/or periodontal health

Symptomatic Temporomandibular disorder

Previously used an MAA

Patients with Epilepsy

Participants in this study were invited to take part in the interview, with verbal and written explanations provided (Appendix 15). Patients interested in participation had a week to consider, before confirming their interest with written consent (Appendix 16).

5.4.5. Sampling technique

A purposive sampling matrix was used and checked throughout the study to ensure that similar number of participants from both the groups, – intervention care and standardised care were interviewed. This enabled the collection of data both from adherent and non- adherent participants within both the groups (Table 5.1).

Group	Adherent	Non-adherent	**Total**
Intervention care	2	2	**4**
Standardised care	2	2	**4**
Total	**08**	**08**	**08**

Table 5.1. The sampling matrix table

5.4.6. Interview setting and procedure

In view of the COVID-19 pandemic, the interviews were undertaken on an online platform (Microsoft® Teams). However, if the participants were comfortable to attend in person, the interview was to be carried out in a private seminar room. Two designated researchers conducted the interview (TN, HT). TN has previous experience in qualitative interviews, whilst HT undertook formal training and initial supervision by TN for quality assurance purposes.

On the day of interview, the interview format was briefly explained to the participants at the start. All participants were asked a standard list of questions from the topic guide (Appendix 17) to address the following topics:

- Patient's awareness of risks of OSA and the benefits of treatment
- Barriers and facilitators of MAA therapy

The interviews were recorded and transcribed by a third party service- Essential Secretary Ltd. Depending on the response, the interviewer was also permitted to ask additional questions outside the topic guide to clarify or explore their response(s) in greater details. In addition to voice recording of the interview , a notepad was used by the researchers to write down additional observations and discussions, which are otherwise not captured.

5.8. Results

The behaviour change taxonomy of Cane et el., (2012) comprising of sixteen clusters and 93 individual behaviour change techniques (BCTs) was employed as the coding framework to identify the influence of BCTs on adherence. The BCTs identified in the transcripts and their influence on patient adherence is summarised in tables 5.2 and 5.3

5.8.1. Participant characteristics

A total of eight participants were recruited for the one-to-one interviews. The sample consists of five (62.5%) males, with the mean age of 55 years (SD = 9.97) and with a mean AHI of 21.54/hours (SD = 14.80).

Table 5.2 Behaviour change techniques (BCTs) identified in the interviews.

Sr. no.	Behaviour change Technique cluster	Behaviour change techniques defining the cluster	Examples from the interviews of factors that enhance adherence	Examples from the interviews of factors that decrease adherence
1	Reward and Threat	Reward Outcome	Decrease in snoring Improved quality of sleep Decreased night sweating Less waking up in the night to go to the toilet Decreased headaches Decreased daytime fatigue	
2	Repetition and Substitution	Habit formation	Incorporate into night-time routine Wearing the splint before night cream	Disruption of routine (e.g. weekends, falling asleep before putting it in)
3	Antecedents	Distraction		Alcohol consumption
		Restructuring the physical environment		Left the device somewhere else other than its usual place
4	Associations	Prompts and cues	Leave device on bedside table Wearing the splint before night cream	

6	Natural consequences	Information of Health consequences	Started the treatment because of the negative consequences of not starting treatment	
		Salience of consequences	Impact on health on not using the MAA	
7	Feedback and monitoring	Feedback on behaviour and Self-monitoring of behaviour	Snoring apps giving feedback	
9	Social support	Social support (emotional)	Positive feedback from the partner	
10	Comparison of outcomes	Pros and cons	Aware of the negative impact on sleep of not using the MAA	
		Comparative imagining of future outcomes	Impact on snoring on not using the MAA Positive consequences of using it	

Table 5.3 Excerpts from the interview drawing upon the specific behaviour change techniques

Behaviour change techniques	Excerpts from the interviews promoting adherence	Excerpts from the interviews promoting non-adherence
Reward Outcome	"… when I've got the mouth guard in, um, I don't snore, or I don't snore like I, I do when I have… haven't got it in." (Interviewee no.1) "The quality of the sleep has improved a lot." (Interviewee no 3) "Er, yes. Er, ah, one thing I have to say, is I just remember, sorry, so I don't forget. I used to go toilet a lot. And now I'm not going to toilet as before, maximum once." (Interviewee no 8) "But I do remember it was a long time, and, um, er, when I woke up I, I realised how well I slept because I was like fresh, not yawning, and things like this, you know. And in the daytime, when I was driving the bus, I never sort of felt sleepy at all, which I could be, er, with the vibration of the bus, for example, the monotonous, er, that is hypnotising in itself, and that, even that wasn't doing anything to me at the time." (Interviewee no 4) "I've certainly been much more awake during the afternoons and that sort of thing, feeling a lot better from that." (Interviewee no 7)	
Habit formation	"Like a regimented routine, of a weekend it sort of goes to pot a little bit. Um, er … " (Interviewee no. 1) "Create a routine, I would create a routine and put it very visual place like you always look in the night so you don't forget." (Interviewee no 3)	"… I miss it more of a weekend, I tend to miss it more of a weekend than opposed to a work day. If, if you look for any sort of pattern in that, that's …" (Interview no.1)

	"It's just habit, it's just habit, and you just do it before you put your cream on." (Interviewee no 5)	"I think keep to the side of my bed is, is helping but sometimes I keep it sofa, something like that, and then changing the routine."(no 3)
Distraction		"Mm, normally when I drink too much or …" (no 3)
Restructuring of the physical environment		"The only other reason I can think of, is just laziness, if I've left, washed it downstairs and it's late, and I need to sleep and I'm tired." (Interviewee 8)
Prompts and cues	"Oh, that's on my bedside table." (Interviewee no. 1) "You just need a night time ritual, you need to have it on your bedside table or next to your toothbrush or something, so you remember." (Interviewee 2) "Er, what I do, I leave the, er, the little box, white box you, er, gave to me, in my, er, the side of my bed." (Interviewee no 3) "It's just habit, it's just habit, and you just do it before you put your cream on." (Interviewee no 5)	
Information of Health consequences **Salience of consequences**	"… I'm using the second device much more than I'm using the first device, er, that is, that is a definite thing. Um, part of that is, um, I, I've had it explained to me how it takes a lot of, or takes some stress off your heart with breathing. These micro sort of, um, interruptions and your sleep, it actually sort of, it's almost you're, you're waking up almost with a start, and that's not good for your ge… your health in general. So, that is one thing that, um, I, I do bear in mind, and that has made, that has made me make a conscious effort to, to, to be, er, more diligent with using, using the mouth guard." (Interviewee no 1) "I thought it was normal. And, er, few times, like, well, quite a lot of time you have conversation about I feel so tired, and my	

	partner said that's not normal, you think it's but it's not normal. But for me it was not normal, being tired all the time. I thought it was about, about the job or anything else, I could not make a link once the sleep apnoea, once I found out." (Interviewee no 3) "I tolerated it quite easily because I actuallt wanted to use this device, because I knew that I had a problem…")Interviewee no. 4)	
Feedback on behaviour and Self-monitoring of behaviour	"So on occasion I check it and it's much lower, so I think a high score for me is like 120 or 130 and so it goes down to 60 or 40, or even lower with the device in." (Interviewee no 2) "I'm using the snore App, to help monitor my sleep and um, I could see there is a good pattern and this morning, it's completely gone down and I'm now sort of into single figures of the snore score and it's just slightly, on the odd day, maybe double digits in the twenties, early twenties, but nothing like it was before." (Interviewee no 5)	
Pros and cons **Comparative imagining of future outcomes**	"I'm worried that I would wake up feeling dreadful." (Interviewee no. 2) "So, now I can't sleep without the appliance, because I know if I don't use it the next day, I won't be as awake and alert and functioning, so, that you know, I do use it every night." (Interviewee no 5) "And I have experimented without it, using it, and it's just, it's like in double digits, like nineties or something." (Interviewee no. 5) " And, er, I remember the first time I used it I, I don't know … er, yeah, it has to be the, the device, I had, er, the first time I had a long sleep, continuous sleep without waking up in the middle of	

	the night, and that's when I knew that this thing is working for me (Interviewee no 4)	

5.8. Discussion

The study aimed to explore drivers for adherence to mandibular advancement therapy in patients with obstructive sleep apnoea. Given that adherence to a new treatment, is similar to the adoption of a new health behaviour. The Behaviour change taxonomy by Crane et al. (2012) was used to identify and compare active behaviour change techniques from the one-to-one interviews. The behaviour change taxonomy is a reliable validated tool developed, in the field of health psychology. It is used to explore and identify elements that direct behaviour change. This enabled systematic and efficient identification of specific BCTs that appeared most effective in enhancing patient adherence to treatment across the interviews.

5.8.1. Reward and threat

The BCT Reward (outcome) belonging to the Reward and Threat cluster to emerged in the majority of the interviews undertaken. Patient adherence was influenced by treatment benefits such as the decrease in snoring, improved quality of sleep, decreased night sweating, less waking up in the night to go the toilet, decreased headaches, and decreased daytime fatigue. The participants disregarded early side effects such as jaw ache, dryness of the mouth or excessive salivation once they started to perceive the benefits of the treatment. This is consistent with value-expectancy theories of behaviour which hypothesise that adherence to mandibular advancement therapy is enhanced if patients perceive therapy to be effective (Saglam-Aydinatay and Taner, 2018). Nevertheless, perceived effectiveness was observed to be low among an older population of obstructive sleep apnoea patients (Carballo et al., 2016). However, these findings are debatable, as studies concerning adherence to continuous positive airway pressure have reported perceived effectiveness i.e. outcome expectancy as a determinant of adherence (Stepnowsky Jr and Dimsdale, 2002, De Zeeuw et al., 2007, Olsen et al., 2010). Therefore, the issue of low perceived efficacy of the treatment should be addressed in a clinical setting as it could hamper treatment adherence.

5.8.2. Repetition and substitution

Previous studies in the field of health psychology have observed that if a specific behaviour is performed repeatedly in the same contextual cues, a habit will develop (Lally et al., 2010, Gardner et al., 2012). Similarly, we observed that patients used the MAA daily by incorporating it into an activity (context) that is performed regularly. This draws upon the BCT Habit formation from the Repetition and Substitution cluster. As summarised in Table 5.2 and 5.3, participants would often create a night-time routine (consistent context) that helped them to remember to wear the MAA whilst also ensuring repetition of the behaviour and enhanced treatment adherence. Therefore, any disruption of the routine translated to decreased patient adherence. Hence, studies have hypothesised that the behaviour is more likely to happen if repeated in a consistent context (Verplanken, 2005, Wood and Neal, 2007, Gardner et al., 2012). Furthermore, reviews have also regarded that repetition of behaviours in the same contextual cues may also occur in the absence of motivation, conscious control or deliberation (Ouellette and Wood, 1998, Webb and Sheeran, 2006, Gardner, 2015).

5.8.3. Antecedents

In terms of antecedents, restructuring of the physical or social environment such as moving the MAA from its usual place was associated with non-adherence to treatment. Additionally, break in the routine such as weekends or alcohol consumption also lead to non-adherence. The concept of relapses and missed opportunity have been addressed in previous studies (Lally et al., 2010). In particular over a 12-week period lapses in performing the behaviour predicted poorer future performance, particularly within the first (Armitage, 2005). Therefore, habit formation may be best aided by consistent repetition of behaviour when the cue is encountered, but it is not necessary to imply that participants should give up if an occasional relapse occurs (Lally and Gardner, 2013).

5.8.4. Associations

The majority of the participants made use of BCT Prompts and cues belonging to the Associations cluster in order to remember to wear the MAA every night. Hence, visual cues such as leaving the MAA on the bedside table or wearing it after applying night cream influenced habit formation

promoting adherence. Therefore, recognisable cues in the context in which a behaviour is performed consistently can come to ingrain habits (Verplanken, 2005, Wood and Neal, 2009).

5.8.5. Natural consequences

In terms of the impact of wearing or not wearing the MAA, the awareness and education concerning the negative consequences of treatment discontinuation lead to increased patient adherence. This draws upon two BCTs from the natural consequences cluster, namely information about health consequences and salience of consequences. In many chronic conditions, patient education to be instrumental in improving patient adherence. Educational interventions may be advantageous in increasing the risk awareness among patients concerning their conditions (Costa et al., 2015). However, clinical trials have not demonstrated robust improvements in adherence with educational strategies solely (Wiese et al., 2005, Golay et al., 2006, Meurice et al., 2007). Hence, including a therapeutic multifaceted intervention, addressing misconceptions about OSA and barriers to treatment is necessary to enhance patient adherence to treatment (Zhang et al., 2019).

5.8.6. Feedback and monitoring

Research concerning adherence to CPAP demonstrated improved patient adherence due to automated feedback services (Hwang et al., 2018). Similar trends were observed in the current study drawing upon the BCTs Feedback on behaviour and Self-monitoring of the behaviour belonging to the Feedback and monitoring cluster. Patients were able to receive feedback from mobile snoring applications which help monitor snoring. A visible reduction in the snoring level aided in treatment continuation and maintenance. A reduction in snoring is perceived by patients as a sign of therapeutic efficacy and therefore seems to promote treatment adherence (Dieltjens et al., 2015). However, further research is needed to assess the accuracy of the sleep monitoring application in relation to standard assessment techniques.

5.8.7. Social support

Among the cluster, social support, positive feedback from the patient's bed partner or members of the family promoted adherence to treatment. Whilst lack of feedback from family was observed to have a neutral effect on adherence. Previous studies have reported similar observations with regard to both CPAP and MAA adherence. (McArdle et al., 2001, Attali et al., 2016). Furthermore,

research concerning adherence to CPAP has observed that if the intention to seek medical intervention was not the patient's but the bed partner's, adherence is negatively influenced as the patient may not be ready to commit to therapy. Nevertheless, involving partners and members of the family in the patient's treatment, especially when treatment is patient-dependent and adherence is crucial, can have a favourable effect on the prognosis of the treatment. Given, that the benefits of OSA treatment is not only limited to the patient but also extends to their bed partner (Weaver and Grunstein, 2008).

5.8.8. Comparison of outcomes

The outcome of performing a behaviour has always reinforced the continuation or discontinuation of a behaviour. Accordingly, the BCTs 'Pros and Cons' and 'Comparative imaging of future outcomes' such as the negative impact on the quality of sleep of not wearing the MAA persuaded the participants to continue with the treatment despite minor inconveniences. These observations are consistent with previous studies that have demonstrated a significant positive relationship between outcome expectancy and CPAP usage at 1 month (Baron et al., 2011a, Deng et al., 2013). Hence, participants who perceive benefits at an early stage of treatment tend to be more adherent as compared to those who do not.

5.8.9. Limitations

A potential limitation of this study is the selection of participants for interview. Only 25 individuals had completed the treatment giving a small pool of potential recruitments and it is possible that those who had completed treatment and volunteered to be interviewed had a more positive experience of the intervention than those not recruited.

5.9. Conclusion

A varied range of behaviour change techniques was observed in the current study that aided participants in the initiation, enactment and maintenance of the behaviour. Further research is needed to better understand the application of these techniques in a clinical setting to enhance MAA adherence.

Chapter 6. Overall conclusions and future recommendations

A mixed-methods approach was adopted in order to assess the research questions, which entailed the undertaking of a systematic review, randomised clinical trial and a qualitative study.

I. The findings of the systematic highlighted the existence of a weak relationship between objective MAA adherence and patient and disease characteristics such as age, sex, obesity, AHI, and daytime sleepiness. Non-adherent patients reported more side effects than users and tended to discontinue treatment within the first 3 months. Increased patient adherence was identified with custom-made MAA in comparison to ready-made MAA. The review identified limited evidence concerning the influence of psychological and social factors on MAA adherence. Given that majority of the studies relied upon patient reported adherence, the review observed a considerable lack of objective adherence monitoring.

II. The results of the randomised clinical trial indicate that the adoption of a stage-matched intervention does not appear to improve adherence to MAA. However, a positive correlation was observed between objective adherence and health beliefs such as risk perception and outcome expectancy.

III. The qualitative study observed a varied array of behaviour change techniques which aided patients in the initiation, enactment and maintenance of the behaviour. These included reward & threat, repetition & substitution, restructuring of the physical or social environment, associations, consequences of untreated OSA, social support, feedback & monitoring and comparison of outcomes.

The observations of the above methods align closely and emphasise the importance of health psychology in enhancing MAA adherence.

The findings of the present study have paved the way for the following studies to further address the current shortcomings in the literature, in relation to optimising adherence to mandibular advancement appliance (MAA) therapy.

I. Completion of recruitment and follow-up of the current clinical trial to further help define the role of health beliefs such as risk perception, outcome expectancy and self -efficacy with longer follow-up duration.
II. Studies assessing ways to minimising long-term risk of tooth movement from MAA therapy.
III. Observational studies exploring the influence of race, age and ethnicity on adherence to mandibular advancement appliance therapy.
IV. Studies assessing adherent and non-adherent patients in relation to patient's facial phenotype.

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Appendices

Appendix 1 Epworth sleepiness scale

Epworth Sleepiness Scale

Participant identification Number for this study: _____ Date: _____

Age (Years):_____ Gender (Male = M, Female = F): _____

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 have not 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

M.W. Johns 1990

Appendix 2 Published systematic review

JCSM | Journal of Clinical Sleep Medicine

REVIEW ARTICLES

Factors influencing adherence to oral appliance therapy in adults with obstructive sleep apnea: a systematic review and meta-analysis

Harishri Tallamraju, BDS[1]; J. Tim Newton, PhD[2]; Padhraig S. Fleming, PhD[1]; Ama Johal, PhD[1]

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Study Objectives: The review aimed to identify the factors influencing adherence to oral appliance therapy in adults with obstructive sleep apnea.
Methods: The protocol was initially registered with the International Register of Systematic Reviews (Prospero: CRD42019122615) prior to undertaking a comprehensive electronic search of databases and references without language and date restrictions. Quality assessment was undertaken using the Cochrane Collaboration's risk of bias tool and Quality in Prognosis Studies (QUIPS) tool.
Results: Studies exhibited low or unclear risk of bias for the domains assessed by the respective quality assessment tools. The influence of independent variables such as disease characteristics, patient characteristics, appliance features, and psychological and social factors on adherence levels was also assessed. There was a total of 31 included studies, which consisted of 8 randomized controlled trials, 2 controlled clinical trial, 7 prospective cohorts, 11 retrospective cohorts, and the remaining 3 studies were a case-series, case-control, and a mixed-methods. All 31 included studies were subject to qualitative analysis, with only 4 studies included in the quantitative analysis. Results of the meta-analysis demonstrated increased adherence with custom-made appliances, with a pooled mean difference of −1.34 (−2.02 to −0.66) and low levels of heterogeneity (I^2 = 0%).
Conclusions: A weak relationship was observed between objective adherence and patient and disease characteristics, such as age, sex, obesity, apnea-hypopnea index, and daytime sleepiness, to oral appliance therapy. Nonadherent patients reported more side effects with oral appliance therapy than users and tended to discontinue the treatment within the first 3 months. Custom-made oral appliances were preferred and increased adherence reported in comparison to ready-made appliances. Further research is imperative to examine the relationship between psychosocial factors and adherence to oral appliance therapy.
Keywords: obstructive sleep apnea, patient adherence, oral appliance therapy, dental sleep medicine
Citation: Tallamaraju H, Newton JT, Fleming PS, Johal A. Factors influencing adherence to oral appliance therapy in adults with obstructive sleep apnea: a systematic review and meta-analysis. *J Clin Sleep Med*. 2021;17(7):1485–1498.

INTRODUCTION

Obstructive sleep apnea (OSA) is a sleep-related breathing disorder characterized by the repeated episodic collapse of the upper airway during sleep, with resultant sleep deprivation.[1] Severe long-term effects of this disease include excessive daytime sleepiness, cognitive dysfunction, hypertension, impaired quality of life, and increased cardiovascular morbidity and mortality.[2]

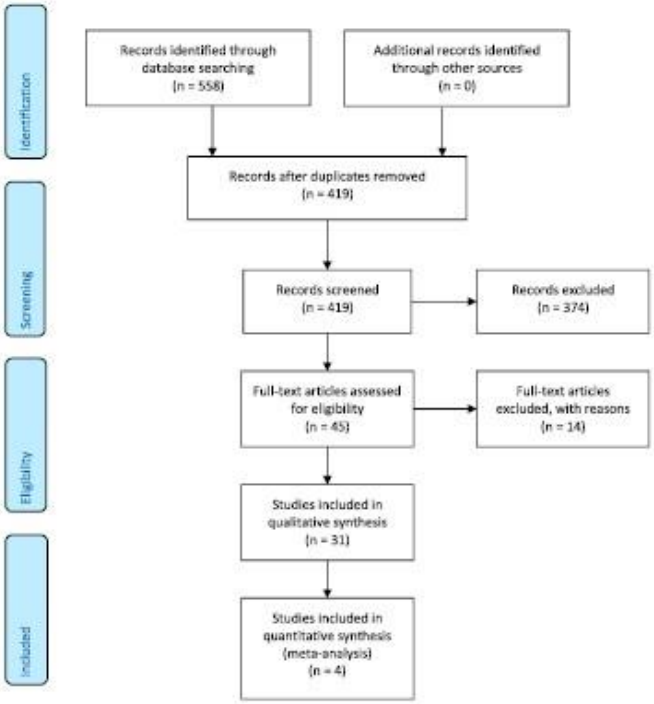
Based on the severity of OSA there are 2 main treatment modalities, continuous positive airway pressure (CPAP) and oral appliances (OA)[3]. Both treatments are lifelong, with sustained adherence to treatment of paramount importance. Successful treatment may lead to improvements in quality of life, considerable cost saving to the health provider, and a reduction in the risk of motor vehicle collisions and cardiovascular disease.[4]

CPAP is mainly used for those with moderate to severe OSA and highly effective and regarded as the gold standard of treatment.[5] However, side effects such as pressure sores, mask dislodgement, claustrophobia, air leakage, and nasal congestion have made it unpopular and intolerable among patients. According to a recent update of the American Academy of Sleep Medicine guidelines, OA therapy (OAT) can be prescribed to those with mild to moderate OSA, particularly if they express it as a preference. OAT remains the second-line treatment of choice for patients who refuse or are unable to tolerate CPAP therapy.[6]

OAT reduces daytime sleepiness and improves the apnea-hypopnea index (AHI) by posturing the mandible and maintaining an open pharyngeal airway.[7] However, studies have consistently demonstrated that CPAP is more effective than OAT at reducing sleep-disordered breathing and achieving complete control of OSA.[8] Despite the greater effect of CPAP on objective polysomnographic parameters, it does not appear to be more effective at achieving better health outcomes. It seems that the higher efficacy of CPAP is offset by greater OAT adherence. Adherence with CPAP is reportedly over 1 h/night lower than with OA.[9] This discrepancy may explain why, despite the superior efficacy of CPAP, as determined by the AHI, no significant differences were observed in terms of quality of life and cognitive and functional outcomes.[10]

The short-term efficacy of OAT has been studied in many randomized controlled trials (RCTs), with encouraging results in all age groups.[11–15] However, long-term studies report an unchanged or only minor decrease in the efficacy of OAT.[16–20] Rose et al[19] observed an increase in the mean AHI, from 4.2 to 8.3 events/h after 2 years of OAT. Deterioration in OSA severity

Figure 1—A PRISMA flow diagram shows the number of articles identified at each stage of the search.



and a loss of OA efficacy were found in a small sample of patients (n = 9) treated continuously for more than 15 years.[21] However, OAT was reported to be effective in two-thirds of patients (n = 279) after 3 years of treatment.[22] Despite the limited number of long-term studies, no significant changes appear to have been detected in the efficacy of OAT.[17,18,20] Notwithstanding this, a decrease in blood pressure is reported from OAT compared with a placebo and equivalent to that of CPAP in the relatively small samples studied.[24–27]

Adherence with OAT has until recently been limited to self-reported data, with the inherent risks of overreporting. Based on this subjective reporting, adherence with OA therapy appears to decline over time, Hoffstein et al reported a wide range of adherence (4–76%) in the first year of appliance use[23]. In a further study, adherence after 1 year was 83%[24] declining to 62–64% after 4 to 6 years.[25,26] The ability to assess adherence objectively provides a more valid measure of a treatment modality's effectiveness. With CPAP therapy, the presence of an inbuilt adherence monitor has provided valuable insight into the limitations of self-reported use, with patients overestimating by up to 1 hour.[27] More recently, Vanderveken et al[28] and Johal et al[29] reported on the safety and feasibility, at 3 and 18 months, respectively, of objective measurement techniques with OAT in the same cohort of patients who demonstrated a range of sleep-disordered breathing from snoring to OSA.

Thus, the current review aims to assess the factors influencing adherence to OAT in adults with obstructive sleep apnea and the potential effectiveness of interventions to promote improved adherence.

METHODS

Following the registration of the protocol with the International Register of Systematic Review (Prospero: CRD42019122615), a systematic review of the literature was undertaken to identify studies exploring the factors influencing adherence to oral appliance therapy in patients. The search strategy was designed to access both published and unpublished materials and comprised three stages:

1. A search of MEDLINE Ovid and Embase to identify relevant keywords contained in the title, abstract, and subject descriptors.
2. Terms identified in this way and the synonyms used by respective databases were then used in an extensive search of the literature.
3. Reference lists and bibliographies of the articles collected from those identified in stage 2 were searched.

The initial search terms were "obstructive sleep apnea", "oral appliance", and "patient adherence" and "compliance." Articles indexed in the following database with no restrictions in relation to the date of publication and language of the article were searched: Ovid, Embase, Scopus, Cochrane Library, and Web of Science. Primary authors and experts in the field of sleep

Table 1—Characteristics and principal outcomes of the included studies.

Sr. No.	Study	Study Design	Participants & Settings	Exposure (Patient or Disease Characteristics, Type of Appliance, Psychological or Social Factor)	Outcome (Increased/ Decreased or No effect on Adherence)	Appliance	Measurement of Adherence	Intervention for Adherence
1	Clark et al, 2000[57]	Retrospective observational study	Orofacial Pain & Oral medicine, University of California (n = 53, M/F: 46/7, Mean age: 55.7 y, Mean AHI < 30 events/h)	Side effects	Decreased adherence	Herbst Appliance	Self-reported	Nil
2	McGown et al, 2001[52]	Retrospective observational study	Middlesex Hospital, RNTNE Hospital, RLH (n = 126, Mean AHI < 30 events/h)	Patient Characteristics	No association with adherence	Modified Adjustable Silensor and Herbst Device	Self-reported	Nil
				Side effects	Decreased adherence			
				Psychological (Self-perceived changes) and Social factors	Increased adherence			
3	Rose et al, 2002[53]	Retrospective observational study	Respiratory Care, University Hospital of Frieburg, Germany (n = 188, M/F: 168/23, Mean age: 54.4 y)	Patient & Disease Characteristics	No association with adherence	Custom-made OA (Esmarch IPG)	Self-reported	Nil
				Side effects	Decreased adherence			
				Psychological (Self-perceived Changes)	Decreased adherence			
4	De Almeida et al, 2005[26]	Retrospective observational study	University of British Columbia, Canada (n = 544, M/F: 202/49, Mean age: 49.9 y, Mean AHI: 30.25 events/h)	Patient & Disease characteristics	No association with adherence	Oral Appliance	Self-reported	Nil
				Side effects	Decreased adherence			
				Social factors (Bed partners satisfaction)*	Increased adherence			
5	Izci et al, 2005[51]	Retrospective observational study	Department of Sleep Medicine, Edinburgh University (n = 144, M/F: 114/30, Mean age: 51 y, Mean AHI: 24 events/h)	Patient characteristics	No association with adherence	Mandibular Repositioning Splint	Self-reported	Nil
				Psychological factors (Marital Satisfaction)**	Increased adherence			
				Side effects	Decreased adherence			
6	Bates et al, 2006[56]	Prospective observational study	Department of Orthodontics, Victoria Hospital (n = 121, M/F: 83/38, Mean age: 49.55 y, Mean AHI: 18.21 events/h)	Side effects	Decreased adherence	Mandibular Repositioning Splint	Self-reported	Nil
7	Vanderveken et al, 2008[41]	Randomized Control trial	University of Antwerp, Belgium (n = 35, M/F: 29/6, Mean age: 49 y, Mean AHI: 14 events/h)	Appliance fabrication and titration procedure (Ready-made OA vs Custom-made OA)	Increased adherence with Custom-made OA	Ready-made OA (SnoreGuard Plus) and Custom-made OA	Self-reported	Nil

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Table 1—Characteristics and principal outcomes of the included studies. (continued)

Sr. No.	Study	Study Design	Participants & Settings	Exposure (Patient or Disease Characteristics, Type of Appliance, Psychological or Social Factor)	Outcome (Increased/ Decreased or No effect on Adherence)	Appliance	Measurement of Adherence	Intervention for Adherence
8	Ghazal et al, 2009[20]	Randomized Control trial	Respiratory Care, University Hospital of Freinburg, Germany (n = 103, M/F: 48/55, Mean age: 50.5 y, Mean AHI: 34.5 events/h)	Patient & Disease characteristics	No association with adherence	IST and Thornton Anterior Positioner (TAP)	Self-reported	Nil
				Appliance Fabrication (IST vs TAP)	Increased adherence with IST			
9	Tsuda et al, 2010[49]	Prospective observational study	Kyushu Dental University, Japan (n = 47, M/F: 40/7, Mean age: 53.1 y, Mean AHI: 21.3 events/h)	Patient & Disease Characteristics (BMI and ESS)	Decreased adherence in association with higher ESS and BMI	Boil- Bite Appliance (TheraSnore)	Self-reported	Nil
				Side effects	Decreased adherence			
10	Cunali et al, 2011[32]	Randomized Control trial	Federal University of Sao Paulo, Brazil (n = 29, M/F: 10/19, Mean age: 48.5 y, Mean AHI: 17 events/h)	Intervention- Support Therapy	Increased adherence	OA (Brazilian Repositioning device BRD)	Self-reported	Support Therapy (Mandibular Exercises)
11	Brette et al, 2012[46]	Prospective observational study	Antoine-Beclere & Argenteuil Hospitals (n = 140, M/F: 108/32, Mean age: 62 y, Mean AHI: 27 events/h)	Patient & Disease Characteristics	Decreased adherence	Custom-made adjustable device (OPM4 J device)	Self-reported	Nil
				Social Support	Decreased adherence			
				Appliance characteristics	Decreased adherence			
12	Freidman et al, 2012[55]	Case series	Advanced Centre for Specialty Care, Chicago (n = 180, M/F: 130/50, Mean age: 61.5 y, Mean AHI: 33.9 events/h)	Side effects	Decreased adherence	Ready-made OA (SomnoGuard AP) and Custom-made OA (Thornton Adjustable Positioner TAP 3)	Self-reported	Nil
				Appliance Fabrication (Ready-made OA vs Custom-made OA)	Increased adherence with Custom-made OA			
13	Zhou et al, 2012[39]	Randomized Control trial	Department of Orthodontics, Tongji University (n = 16, M/F: 13/3, Mean age: 45.23 y, Mean AHI: 38 events/h)	Appliance fabrication and titration procedure (Monobloc OA vs two-piece OA)	Increased adherence with Monobloc OA	Monobloc OA (Activator) and Bibloc OA (Silent Nite)	Self-reported	Nil
14	Dieltjens et al, 2013[54]	Case-control study	University of Antwerp, Belgium (n = 82, M/F: 56/26, Mean age: 49.5 y, Mean AHI: 18 events/h)	Psychological factors (Type D personality)	Decreased adherence	Custom-made Mono Bloc OA and Custom-made Bibloc titratable OA (RespiDent Butterfly)	Self-reported	Nil

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Table 1—Characteristics and principal outcomes of the included studies. (continued)

Sr. No.	Study	Study Design	Participants & Settings	Exposure (Patient or Disease Characteristics, Type of Appliance, Psychological or Social Factor)	Outcome (Increased/ Decreased or No effect on Adherence)	Appliance	Measurement of Adherence	Intervention for Adherence
15	Ingman et al, 2013[48]	Retrospective observational study	Department of Oral & Maxillofacial Diseases, Helsinki University Hospital (n = 96, M/F: 68/28, Mean age: 50.5 y, Mean AHI: 18.4 events/h)	Patient characteristics (length of the maxilla, mandible and soft palate, oropharyngeal space, crepitation at TMJ)	Increased adherence with shorter mesio-distal length of the maxilla and mandible, and crepitation at right TMJ	Mandibular Advancement Splint	Self-reported	Nil
16	Lee at al, 2013[35]	Nonrandomized control trial	Department of Otorhinolaryngology, Seoul National University (n = 153, M/F: 138/15, Mean age: 51.2 y, Mean AHI: 32.8 events/h)	Appliance fabrication and titration procedure (Monobloc OA vs Bibloc OA)	Increased adherence with Bibloc OA	Monobloc and Bibloc OA	Self-reported	Nil
17	Quinnell et al, 2014[37]	Randomized Control trial	Papworth Hospital Sleep Centre, (n = 90, M/F: 72/81, Mean age: 50.9 y, Mean AHI: 13.8 events/h)	Appliance fabrication (Boil- Bite vs Semibespoke vs Be-spoke)	Increased adherence with the Be-spoke oral appliance	Boil-bite OA (Sleep pro 1), Semibespoke OA (Sleep pro 2), and Bespoke OA	Self-reported	Nil
18	Wang et al, 2014[38]	Randomized Control trial	Dept. of Otorhindology, Hospital of Anhui Medical University (n = 22, M/F: 22/0, Mean age: 51.9 y, Mean AHI: 48.16 events/h)	Appliance Type (Adjustable OA vs Nonadjustable OA)	Increased adherence with the adjustable OA	Rod Type OA (Erkodent Silensor) and Controllable appliance (Twin Bloc)	Self-reported	Nil
19	Dieltjens et al, 2015[33]	Prospective observational study	Antwerp University Hospital, Belgium (n = 51, M/F: 38/13, Mean age: 49.3 y, Mean AHI: 14.9/h, Mean AHI: 18.4 events/h)	Patient (Anthropometric) & Disease characteristics (Polysomnographic measure)	No association with adherence	Custom-made titratable OA (RespiDent Butterfly)	Objective (Theramon Sensors)	Nil
				Side effects	Decreased adherence			
20	Prescinotto et al, 2015[44]	Retrospective observational study	Federal University of Sao Paulo, Brazil (n = 28, M/F: 9/19, Mean age: 48.8 y, Mean AHI: 17.5 events/h)	Patient characteristics (upper airway abnormalities)	No association with adherence	Custom-made OA	Self-reported	Nil
21	Attali et al, 2016[22]	Prospective observational study	Pitié-Salpétrière, France (n = 279, M/F: 98/81, Mean age: 58 y, Mean AHI: 26 events/h)	Appliance factors	Decreased adherence	Ready-made OA (Naval Resmed) and Custom-made OA (Somnodent SomnoMed)	Self-reported	Nil
				Side effects	Decreased adherence			
				Psychological factors	Decreased adherence			
22	Carballo et al, 2016[42]	Retrospective observational study	Veterans Affairs Medical Centre, Brazil (n = 33, M/F: 32/1, Mean age: 71.4 y)	Psychological and social factors	No association with Adherence	Oral Appliance	Self-reported	Nil
23	Makihara et al, 2016[58]	Retrospective observational study	Kyushu Dental University, Japan (n = 48, M/F: 35/13, Mean age: 64.9 y)	Side effects	Decreased adherence	Boil- Bite Appliance (TheraSnore)	Self-reported	Nil
				Psychological factors	Decreased adherence			

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Table 1—Characteristics and principal outcomes of the included studies. (continued)

Sr. No.	Study	Study Design	Participants & Settings	Exposure (Patient or Disease Characteristics, Type of Appliance, Psychological or Social Factor)	Outcome (Increased/ Decreased or No effect on Adherence)	Appliance	Measurement of Adherence	Intervention for Adherence
24	Nerfeldt et al, 2016[43]	Prospective intervention study	Department of Clinical Science, Karolinska Institute Stockholm, Sweden (n = 66, M/F: 37/35, Mean Age: 48.5 y, Mean AHI: 16 events/h)	Disease Characteristics (Arousers vs Desaturaters)	Increased adherence in arousers	Monobloc titratable OA	Self-reported	Nil
25	Vecchierini et al, 2016[50]	Prospective intervention study	Multicenter (n = 369, M/F: 273/96, Mean age: 52.6 y, Mean AHI: 29.5 events/h)	Side effects	Decreased adherence in the early stages of the treatment	Custom-made OA (Narval)	Self-reported	Nil
26	Al-Dharrab et al, 2017[38]	Randomized Control trial	Faculty of Dentistry, King Abdul-Aziz University (n = 12, M/F: 2/10, Mean age: 46 y, Mean AHI: 26 events/h)	Appliance fabrication and titration procedure (Titratable vs Nontitratable)	Increased adherence with Titratable appliance	Custom-made titratable OA (Foresta Dent, Bite Jumping screw) and nontitratable OA	Self-reported	Nil
27	Gagnadoux et al, 2017[34]	Nonrandomized control trial	University of Angers and Saint-Antoine Hospital, France (n = 158, M/F: 104/54, Mean age: 54 y, Mean AHI: 27.7 events/h)	Appliance fabrication and titration procedure (Ready-made OA vs Custom-made OA)	Increased adherence with Custom-made OA	Ready-made OA (BluePro) and Custom-made OA (Somnodent and Amo Device)	Self-reported	Nil
28	Haviv et al, 2017[59]	Mixed-methods	Department of Oral Medicine, Hebrew University (n = 52, M/F: 48/4, Mean age: 56.75 y, Mean AHI ≤ 40 events/h)	Side effects	Decreased adherence	Herbst Device	Self-reported	Nil
				Psychological factors	Decreased adherence			
29	Johal et al, 2017[40]	Randomized Control trial	Royal London Dental Hospital, Queen Mary University of London, (n = 35, M/F: 21/14, Mean age: 44.9 y, Mean AHI: 13.3 events/h)	Appliance fabrication and titration procedure (Ready-made OA vs Custom-made OA)	Increased adherence with Custom-made OA	Ready-made OA (Snoreshield) and Custom-made OA	Self-reported	Nil
30	Nishigawa et al, 2017[47]	Retrospective observational study	Department of General Dentistry, Tokushima University Hospital Japan (n = 40, M/F: 28/12, Mean age: 57.8 y)	Side effects	Decreased adherence	Herbst Appliance	Self-reported	Nil
				Psychological factors	Decreased adherence			
31	Saglam-Aydinatay et al, 2018[45]	Retrospective observational study	Department of Orthodontics, Hacettepe University, Ankara, Turkey (n = 69, M/F: 52/17, Mean age: 54.4 y, Mean AHI < 30 events/h)	Patient & Disease Characteristics	No association with adherence	Monobloc OA and Twin-bloc OA	Self-reported	Nil
				Side effects	Decreased adherence			
				Psychological (Self-perceived changes) and social factors	Increased adherence			

*Improvement reported by the partner in the patient's snoring. ** Marital quality and bed sharing. AHI = apnea-hypopnea index, BMI = body mass index, F = female, M = male, OA = oral appliance, TAP = Thornton anterior positioner.

Table 2—Factors of influence on oral appliance adherence.

Factors	Decreased Adherence	Increased Adherence	No Significant Association with Adherence	Caveat
Patient and disease characteristics			Anthropometric characteristics (age, sex, obesity)	
			Disease severity	
			Baseline sleepiness	
			Polysomnographic parameters	
			Anatomical characteristics (length of the maxilla, mandible and soft palate, oropharyngeal space, crepitation at TMJ)	
			Upper airway or facial skeletal abnormalities	
	Desaturaters (patients with oxygen desaturations)	Arousers (patients with respiratory arousals)		Significant improvement in the ESS among the arousers
		OA therapy as the first line of treatment		Strong predictor for treatment continuation
		Complete symptom resolution		Contributes to the perception of OSA but not a strong predictor alone
Appliance fabrication and titration	Monobloc OA	Bi-Bloc OA		Relatively free mandibular movement
	Ready-made (Nontitratable) OA	Custom-made (Titratable) OA		More reported side-effects with ready-made as compared to custom-made
	Patients not using the OA for > 2 years			More likely to discontinue the treatment
		Regular dental follow-up		Helps in minimizing early side-effects which lead to early discontinuation of the treatment
Psychological and social factors	Lack of perceived benefits			Leads to early discontinuation of the treatment, consistent factor
		Support from their bed partners		Improved sleep quality of the bed partner with OA use is associated with increased adherence

ESS = Epworth Sleepiness Scale, OA = oral appliance, TMJ = temporomandibular joint.

and respiratory medicine were contacted. The additional literature search included Google Scholar to identify any other relevant published work. An example of the search strategy used is shown in **Table S1** in the supplemental material.

The title and abstracts of the studies identified were assessed independently by 2 reviewers (H.T., A.J.) and were included or excluded based on the following PEO criteria:

1. Population: Adults with OSA receiving oral appliance therapy
2. Exposure of interest: Disease characteristics, patient characteristics, appliance features, and psychological and social factors
3. Outcome: Adherence
4. Study design: Prognostic studies both retrospective or prospective observational in nature and randomized or nonrandomized controlled trials
5. Exclusions: Studies comparing CPAP or surgical intervention with oral appliance therapy were excluded

The first 2 reviewers (H.T., A.J.) obtained full-text reports of studies meeting the selection criteria for screening, and any disagreement was resolved by consulting a third reviewer to reach a consensus (T.N.).

Risk of bias and quality assessment in individual studies

Two authors independently assessed the risk of bias of the included studies (H.T., A.J.; **Figure 1**, and any disagreements were resolved by further discussion and consensus. Due to the diversity in the design of the included studies, 2 different tools were used to assess their quality. RCTs were assessed using the Cochrane Collaboration's risk of

bias tool.[30] The following 5 domains were considered: random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, and selective reporting. The domain blinding of participants and personnel was not considered due to the nature of the questions addressed by this review. Observational studies were critically appraised using the Quality in Prognosis Studies (QUIPS) tool.[31] This tool assesses the risk of bias in studies of prognostic factors and comprises 6 domains: study participation, study attrition, prognostic factor management, outcome measurement, study confounding, and statistical analysis and reporting.

Data items and collection

The influence of independent variables such as disease characteristics, patient characteristics, appliance features, and psychological and social factors on the outcome, ie, adherence, reported in the included studies was recorded and categorized based on these factors. The findings of the studies were synthesized in a narrative manner. Information regarding study design, sample size, participants and settings, type of oral appliance used, strategies or interventions employed to increase adherence, and method of adherence measurement (objective or self-reported) were recorded (**Table 1** and **Table 2**).

Meta-analysis

A meta-analysis was performed using Review Manager (RevMan; Version 5.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) for studies with low and/or unclear risk of bias, similar study design, and comparing 2 types (ready-made vs custom-made) oral appliances prescribed for patients with OSA in regards to patient adherence. Results were analyzed using forest plots with weighted mean differences between ready-made vs custom-made appliances in relation to patient adherence, ie, mean nightly (hours) use of the appliance. The studies were weighted using the inverse variance method and tested for heterogeneity using the Chi square test to assess the significance of heterogeneity and I^2 statistics to measure the diversity between studies. Pooled studies with $I^2 < 25\%$ were regarded as homogenous, and those with $I^2 > 75\%$ were considered to demonstrate high heterogeneity. A fixed-effects model was used and a P value of less than .05 was considered statistically significant, reported along with the 95% confidence interval.

RESULTS

Following the removal of duplicates, 419 articles were considered eligible for screening of the title and abstract. The abstracts were assessed against the selection criteria, with 45 articles considered eligible for full-text screening. Subsequently, fourteen studies were excluded (**Table S2**), with a total of 31 studies included in the review, which consisted of 8 RCTs, 2 controlled clinical trials, 7 prospective cohorts, 11 retrospective cohorts, while the remaining 3 studies were a case-series, case-control, and a mixed-methods study (**Figure 2**). All 31 included studies were subject to qualitative analysis, with 4 studies subject to a meta-analysis. All included studies were undertaken in academic medical centers or sleep centers (**Table S3**).

Figure 2—Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

The majority of the included studies investigated the influence of side effects (45%), disease and patient characteristics (41%), and appliance characteristics (32%) on patient adherence. The efficacy of strategies or interventions to increase patient adherence to OAT in adult patients with OSA was assessed in only a single study.[32] While a self-reported measure of adherence was used in the majority of included studies, objective monitoring of adherence was reported in just 1 study.[33] Studies that considered psychological and social factors (38%) focused on the impact of constructs, such as bed-partner satisfaction levels (improvement reported in the patient's snoring by their partner), self-perceived changes, and type D

personality (a combination personality type of negative affectivity and social inhibition) on oral appliance adherence.

Risk of bias within studies

The risk of bias (**Figure 1**) assessment for random sequence generation, allocation concealment, blinding of outcome assessors, incomplete outcome data, and selective reporting was assessed for the included RCTs (n = 8) and controlled clinical trials (n = 2). The majority of these studies demonstrated a low or unclear risk of bias for the above domains. Only 2 studies[34,35] demonstrated a high risk of bias for random sequence generation, otherwise a low risk of bias was assessed in relation to selective reporting for all included studies. In terms of allocation concealment, 5 studies[20,36–38] demonstrated an unclear risk of bias, 3 studies[32,40,41] indicated a low risk of bias, and a high risk of bias was observed in 2 studies.[34,35] Due to no clear description concerning blinding of outcome assessors, 7 studies[20,32,35–39] exhibited an unclear risk of bias and a low risk of bias was observed in the rest of the 3 studies.[34,40,41] High risk of bias for incomplete outcome data was observed in only 1 study,[34] whereas the remaining 9 studies[20,32,35–41] exhibited a low risk of bias. The findings along with the comments for the judgement are summarized in **Table S4**.

Similarly, observational studies (n = 21) were found to demonstrate a low or moderate risk of bias concerning study participation, study attrition, prognostic factor management, outcome management, study confounding, and statistical analysis and reporting. Four studies[42–45] exhibited a moderate risk of bias for study participation, whereas the remaining studies (n = 17) indicated a low risk of bias. All studies demonstrated a low risk of bias for the domains-outcome measurement and statistical analysis and reporting. In terms of study attrition, 3 studies[43,46,47] exhibited a moderate risk of bias, while a low risk of bias was observed in the remaining studies. Furthermore, 8 studies[33,43–46,48–50] demonstrated a low risk of bias for prognostic factor measurement, and remaining studies exhibited a moderate risk of bias. The majority of the studies indicated a moderate risk of bias for study confounding, while a low risk of bias was observed in 2 studies[33,51] (**Table S5**).

Qualitative study analysis

Patient and disease characteristics

The current review identified 13 studies exploring the influence of patient and disease characteristics, which reported neither supine-dependent OSA, age, obesity, sex, or sleepiness to be related to OAT tolerability.[20,26,33,43–46,48,49,51–54] There were no significant sex differences detected in relation to the cessation of appliance use. Neither disease severity or baseline sleepiness was found to be a predictor of OAT adherence.[26] While the above-reported studies relied upon self-reported adherence, an additional single study found no correlation between objective adherence and anthropometric characteristics, polysomnographic parameters, or excessive daytime sleepiness.[33] Furthermore, among the 13 studies included, 1 study found no significant association between adherence and the following patient anatomical characteristics: upper airway or facial skeletal abnormalities, such as pharyngeal alterations ($P = .62$), retrognathia ($P = .34$), Class II dental occlusion ($P = .64$), craniofacial alterations ($P = .44$), or nasal alterations ($P = .38$)[44]. Although the findings are not statistically significant, these should be viewed carefully as the authors relied upon self-reported adherence, rather than objective adherence.

Appliance fabrication and titration

In terms of appliance factors, 11 studies examined the influence of appliance fabrication and titration on OAT adherence.[20,34–41,54,55] One study compared the modified Herbst appliance (IST) with the Thornton anterior positioner (TAP), which differed in their ability to open the mouth during sleep in a protrusive position.[20] Although the TAP was more effective in treating OSA, its long-term acceptance was less than that of the IST.[20]

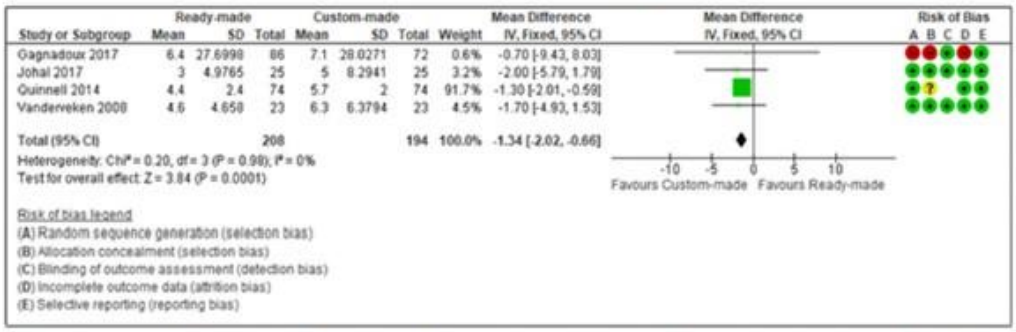
Three studies comparing Mono-Bloc OA with Bi-Bloc OA, with regards to their adherence, have reported rather conflicting results.[35,39,54] Zhou and Lou[37] suggested that monobloc appliance should be considered, as almost half of the patients preferred the appliance to the bibloc device. However, the findings were based on a very small sample size (n = 16). On the contrary, a large prospective single-center study, with a sample size of 153 patients, observed an adherence rate of 83.3% with the Bi-Bloc OA and 68.8% with the Mono-Bloc OA, at 1 year ($P = .04$). The authors concluded that the relatively free mandibular movement may explain the difference in adherence rates.[35] Similarly, Dieltjens et al,[54] while examining the association between Type D personality (a combination personality type of negative affectivity and social inhibition) and OAT adherence, observed a higher discontinuation rate with monobloc OAT in comparison to bi- or duo-bloc appliance (95% confidence interval, 1.77–47.09; $P = .008$) when adjusted for Type D personality, age, sex, and decrease in AHI. However, the findings of the above studies should again be interpreted with caution as they failed to assess adherence using an objective measure and the marked differences in study designs.

Seven studies evaluating the impact of ready-made (nonadjustable/nontitratable) and custom-made OAT observed an overwhelming patient-reported preference for custom-made OAT in comparison to ready-made devices.[34,36–38,40,41,55] The adherence was higher with the custom-made OAT despite more reported dental discomfort ($P = .03$).[34] In an additional RCT with a crossover design, Johal et al reported a response rate of only 24% with a ready-made OAT vs the 64% in the custom-made OAT[39]. It has to be acknowledged that adherence was assessed from self-reports and can be at risk of bias. More recently, the addition of objective adherence monitors has served to confirm the reported levels of self-reported adherence with OAT.[28,29]

Side effects

Side effects, such as dental pain, muscular pain, and excessive salivation associated with OAT may prevent early acceptance of the device and contribute to nonadherence.[56] Moreover, side effects arising from long-term OAT use, such as bite change, may also lead to poor patient adherence.[22,33,52,57] The current review identified 14 studies examining the influence of early and long-term side effects on OAT adherence.[22,26,33,47,49–53,55,56–59]

Figure 3—Forest plot of patient-reported adherence for custom-made oral appliance and ready-made oral appliance.



The forest plot demonstrates 4 studies that indicate increased patient adherence with custom-made appliances in comparison to ready-made appliances. The squares represent the point estimate of the corresponding studies. The area of each square is proportional to the study's weight in the meta-analysis, and the lateral points (horizontal line) indicate the confidence intervals of the respective study. The overall effect or the summary estimate is plotted as a diamond, and the lateral points demonstrate the confidence intervals of the estimate. A mean difference of zero (vertical line) indicates no effect; studies with confidence intervals crossing the vertical line are inconclusive. Powerful studies have narrower confidence intervals. In the graph, the Quinnell study and the overall effect estimate have narrow confidence intervals that do not cross zero, indicating that the meta-analysis could be considered as statistically significant.

The most common self-reported reason for discontinuing the treatment was a lack of treatment effect or discomfort or pain on OAT use, consistent with other reported studies.[22,45,51,56,57] Furthermore, early discontinuation (< 2 years) of treatment was observed due to side effects, discomfort, and inefficacy. In contrast, patients discontinued treatment due to no specific reasons after 2 or more years.[22] Additionally, the higher rates of treatment discontinuation with ready-made OAT was found to be associated with higher reported side effects in comparison to the custom-made OAT.[34,37,40,41]

Psychological and social factors

Among the 31 included studies, 12 studies[22,26,42] examined the influence of the psychological and social factors on OAT adherence. One study reported low rates of perceived effectiveness, self-efficacy, and social support for OAT as a cohort (n = 39) of older patients had low expectation for positive outcomes.[42] However, given that other included studies identified psychological factors, such as a lack of perceived benefits by the patients and their bed partner, and cognitive perceptions such as complete symptom resolution as influential on OAT adherence, the above findings are highly contentious.[22,26,47,51,53,59] Likewise, 2 studies identified that social factors, such as poor marital satisfaction (marital quality and bed sharing frequency) ($P < .04$), support from their partner, and shame caused by the disease symptoms to be associated with continued usage of OAT.[45,51] Nevertheless, the above findings should be viewed carefully due to marked differences in study designs and lack of objective assessment of adherence.

Quantitative analysis

A meta-analysis was undertaken in relation to the use of ready-made OAT vs custom-made OAT with regards to patient adherence (**Figure 3**). Based on these studies,[34,37,40,41] increased adherence was observed with custom-made appliances, with a pooled mean difference of −1.34 (−2.02 to −0.66), with low levels of heterogeneity ($I^2 = 0\%$).

DISCUSSION

Given that oral appliances are removable and have to be used indefinitely, adherence to treatment is of utmost importance for achieving successful therapy.[6] However, adherence to OAT for OSA is highly variable.[14] The current review observed that the relationship between OAT adherence and patient and disease characteristics such as age, sex, obesity, AHI, and daytime sleepiness is relatively weak. Furthermore, no association was observed between objective adherence and anthropometric characteristics, polysomnographic parameters, and excessive daytime sleepiness. It also appears that disease severity and sleepiness may not be associated with OAT adherence. The majority of the included studies exploring the impact of patient and disease characteristics, were retrospective in nature and highly heterogeneous in terms of study participants.

Dieltjens et al conducted a prospective clinical trial to identify the determinants of objective adherence to OAT in patients with OSA[32]. Previous studies on OAT adherence have relied upon patient-reported adherence, which is subject to overestimation.[26,60] Moreover, objective compliance monitors with OAT have only been introduced recently.[28] The trial (n = 51) observed no correlation between objective adherence and anthropometric characteristics, polysomnographic parameters, and excessive daytime sleepiness. Nevertheless, the authors did emphasize the influence of socially disturbing snoring, reporting objective adherence correlated significantly with a decrease in socially disturbing snoring, as reported by

the partner compared with baseline visual analog scale scores for snoring without the appliance.[35] Nerfeldt and Friberg[43] investigated the difference between "arousers" (patients with respiratory arousals) and "desaturaters" (patients with oxygen desaturations) in terms of adherence rates. The authors observed that patients with greater numbers of arousal showed higher adherence (85%) than among the "desaturaters" (55%; P = .034). It was reasoned that the above difference in adherence rate was due to a significant improvement in the Epworth Sleepiness Score among the arousers (Epworth Sleepiness Score ≥ 10), which was not seen among the desaturaters. Furthermore, OAT as a first-line treatment was reported to be a strong predictor (odds ratio 1.77, 95% confidence interval 1.03–3.03; P = .0375) for treatment continuation.[22] Similarly, complete symptom resolution (odd ratio 1.78, 95% confidence interval 1.03–3.03, P = .0384) was also a strong predictor for OAT adherence.[22] These findings support an important role for disease chronicity in terms of patient adherence, which was similar to those reported for other chronic diseases.[61] They also reinforce the link between disease chronicity and long-term treatment persistence, while indicating that patients intolerant of or nonadherent with CPAP are more likely to discontinue OAT.[22] However, Izci et al[51] in a large sample (n = 144) of patients with OSA demonstrated that usage of OAT was not significantly affected by whether a patient was CPAP nonadherent or a refuser (P > .3). Nonetheless, the findings of the above studies should be interpreted with caution, as the studies failed to provide an objective measure of adherence and also due to the marked differences in study design and participant settings with regards to race and ethnicity. However, Johal et al demonstrated excellent long-term objective adherence with OAT in a sample of 42 patients with OSA, who were CPAP intolerant[28].

Nonetheless, it is interesting to evaluate these findings in the context of CPAP adherence. A weak association between patient and disease characteristics, such as disease severity, AHI, oxygen desaturation, and Epworth Sleepiness Score on CPAP adherence has been observed.[62–64] Although nasal resistance influences initial CPAP acceptance, nasal anatomy, not necessarily patient-reported nasal complaints, may be influential on CPAP adherence.[64–67] Furthermore, initial CPAP adherence appears to be closely associated with higher neighborhood socioeconomic factors, independent of individual demographic and clinical factors.[68] These findings suggest that socioenvironmental factors are important in terms of patient adherence among patients with OSA. Studies have also examined race as influential on CPAP adherence, all of which have reported lower CPAP adherence in African Americans compared with Caucasian users.[69,70] Factors such as race and ethnicity-based differences in OAT adherence were not examined, as no studies have been published exploring such factors. Similarly, a low socioeconomic index is only considered a barrier to accessing OAT, as its influence on treatment adherence is yet to be explored.[71] Thus, additional studies are needed to understand and help characterize the individual considerations needed for initiating and managing OA treatment within diverse patient groups.

In terms of appliance characteristics, both patient-reported adherence and preference favored the use of custom-made appliances. The preference was not only reflected in the higher number of nights per week but also the number of hours per night that the appliance was used.[40,41] The findings are consistent with a recent systematic review and meta-analysis.[72] Moreover, as OAT for OSA is entirely dependent on patient behavior, patient preference or acceptance cannot be disregarded. However, the majority of the studies were limited to self-reported use and lacked an objective adherence measurement. This reflects the relatively recent introduction of objective adherence monitors.[28] Notwithstanding this, a lack of retention with the ready-made OAT was the most frequently cited reason for discomfort and nonadherence.[37,40,41,49,55]

In relation to side effects, nonusers experienced 1 or more adverse effects and tend to discontinue the treatment earlier, ie, within the first 3 months, whereas those who use the device for longer periods experienced milder problems.[52,58] In a questionnaire-based retrospective study, nonusers reported a higher average number of side effects than users.[52] Similarly, Makihara et al[58] reported that one-third of the nonusers discontinued the OAT within the first month and 40% within in the next 3 months. The most common reasons for discontinuation of treatment were discomfort or lack of treatment effects.[26,52,57] Specifically, pain originating from the masticatory muscles or the temporomandibular joints may be one of the main reasons for poor adherence or abandonment.[32] Consequently, Cunali et al[32] randomized 29 OSA adult patients with temporomandibular disorders into 2 groups, the exercise support therapy group and placebo therapy (PT) group, and they were evaluated prior to and 120 days after OAT. The authors observed higher treatment adherence in the support therapy group (P < .05) compared to the placebo therapy group, as there was a significant reduction of pain intensity in the former group (P < .05) but not in the latter. Long-term occlusal changes may occur with OAT,[26] as such, dental follow-up may be useful in encouraging adherence while limiting possible side effects and the risk of cessation of treatment in long-term OAT users. In terms of the influence of sex, in a retrospective study (n = 251), women experienced and reported more side effects and seemed to have a greater tendency to abandon treatment than men, as 46.8% of the women who answered a questionnaire based-survey had discontinued the use of OAT compared to the 32.8% of men.[26] However, given that the study was retrospective, with data collection from patients at different time intervals, the findings should be interpreted with caution.[26]

Psychological and social factors, such as mood and perception of treatment benefits, and bed partner satisfaction levels were significantly correlated with OAT use.[51] Dieltjens et al identified that self-reported adherence to OAT was significantly lower for adults with OSA and Type D personality, a combination personality type of negative affectivity and social inhibition, compared to patients with OSA without the said personality type[53]. These findings are in agreement with similar observations reported by Brostrom et al[73] in regards to lower CPAP adherence with type D personality. Objective adherence was found to be significantly correlated with a more pronounced decrease in socially disturbing snoring.[33] Research shows that adoption of new health behavior, like a

new physical activity routine or adhering to a prescribed medication regimen, is a challenging endeavor, involving a variety of social, emotional, and cognitive factors.[74] However, evidence in terms of psychological and social factors with regards to OAT adherence is highly underrepresented, which contrasts with the volume of literature concerning CPAP adherence. Efforts to enhance patient education ranging from telephone support to home visits, motivational enhancement, or augmented support,[75,76] have been shown to improve CPAP adherence when compared to standard care. It has also been suggested in a recent Cochrane review that educational, supportive, and behavioral interventions may increase CPAP usage to varying degrees.[77] However, no studies evaluating the efficacy of the above-mentioned interventions in relation to OAT adherence were identified in this review. Evidence concerning the impact of psychological factors, such as patient's perceptions, self-efficacy, and social support on OAT adherence is highly underrepresented in the field of sleep medicine in comparison to various sleep apnea treatments. Therefore, further research is imperative for the development of tailor-made interventions to enhance adherence in patients with low mood and/or psychological disorders.

Strengths and limitations

This is the first systematic review to assess the factors influencing adherence or nonadherence in adult patients with OSA on OAT. To limit publication bias, comprehensive search strategies were implemented along with the use of Covidence, a core component of Cochrane's review toolkit. The review followed the PRISMA reporting guidelines, and the Cochrane Handbook of systematic review was used for risk of bias assessment for the included RCTs.

In terms of limitations, the search yield was limited to 8 RCTs demonstrating low or unclear risk of bias. Furthermore, the application of a meta-analysis in nonrandomized controls trials leads to bias arising from methodological issues and marked differences in study designs. Another possible limitation is the limited evidence identified concerning the impact of psychological and social factors and the effect of strategies or interventions to improve OA adherence.

CONCLUSIONS

A weak relationship was observed between objective OAT adherence and patient and disease characteristics such as age, sex, obesity, AHI, and daytime sleepiness. Nonadherent patients reported more side effects than users and tended to discontinue treatment within the first 3 months. Increased patient adherence was identified with custom-made OAT in comparison to ready-made OA. The review identified limited evidence concerning the influence of psychological and social factors on OAT adherence. Given that majority of the studies relied upon patient-reported adherence, the review observed a considerable lack of objective adherence monitoring.

Further research would be beneficial to describe the determinants of adherence, such as risk perception, self-efficacy, and outcome expectancy and to facilitate patient education and development of tailor-made interventions to enhance adherence to OAT. Similarly, the lack of objective adherence monitoring necessitates the need for future studies that assess adherence objectively.

ABBREVIATIONS

AHI, apnea-hypopnea index
CPAP, continuous positive airway pressure
IST, Herbst appliance
OA, oral appliance
OAT, oral appliance therapy
OSA, obstructive sleep apnea
RCT, randomized controlled trial
TAP, Thornton anterior positioner

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SUBMISSION & CORRESPONDENCE INFORMATION

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DISCLOSURE STATEMENT

All authors have seen and approved the manuscript. Work for this study was performed at the Department of Oral Bioengineering, Institute of Dentistry, Queen Mary University of London, London, UK. The systematic review is part of a PhD program that is university-sponsored. The authors Prof. Ama Johal and Prof. Padhraig S. Fleming are salaried employees of the Centre for Oral Bioengineering, Queen Mary University of London, and Prof Tim Newton of the Department of Population and Patient Health, King's College London. The authors report no conflicts of interest.

Appendix 3 Ethical approval

NHS
Health Research Authority
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19 August 2019

Professor Ama Johal
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Dear Professor Johal

Study title:	**Intervention to enhance adherence to Mandibular advancement appliance in Patients with Obstructive Sleep Apnoea: A Randomized Control Trial**
REC reference:	**19/NW/0391**
Protocol number:	**[##IfProtocolRef##]**
IRAS project ID:	**262092**

Thank you for your submission, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

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 will audit these as part of the annual progress reporting process.

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 listed in the application subject to confirmation of Capacity and Capability (in England, Northern Ireland and Wales) or 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 final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		27 July 2018
IRAS Application Form [IRAS_Form_28052019]		28 May 2019
IRAS Application Form XML file [IRAS_Form_28052019]		28 May 2019
IRAS Checklist XML [Checklist_28052019]		28 May 2019
Letter from sponsor		09 May 2019
Other [Daily Sleep log]	2	22 July 2019
Other [Topic Guide]	2	22 July 2019
Other [Health Pamphlet]	2	22 July 2019
Other [Response to REC, HRA and HCRW assessments]		
Participant consent form [Consent form]	2	22 July 2019
Participant consent form [Consent form for Partner]	01	04 February 2019
Participant consent form [Participant Consent form for One-to-one Interview]	1	22 July 2019
Participant information sheet (PIS) [PIS]	2	22 July 2019
Participant information sheet (PIS) [PIS for One-to-One interview]	1	22 July 2019
Participant information sheet (PIS) [Information sheet for Partner]	1.0	04 February 2019
Referee's report or other scientific critique report		19 February 2019
Research protocol or project proposal [Study protocol]	2	22 July 2019
Summary CV for Chief Investigator (CI) [CI's CV]	1	04 February 2019
Summary CV for student [Research Student CV]	1	04 February 2019
Validated questionnaire [SEMA]		
Validated questionnaire [EQ-5D]		
Validated questionnaire [SES]		
Validated questionnaire [SSQ]		
Validated questionnaire [ESS]	2	22 July 2019

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.

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/

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11 February 2020

Dr. Harishri Tallamraju
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Dear Dr. Tallamraju

Study title:	**Intervention to enhance adherence to Mandibular advancement appliance in Patients with Obstructive Sleep Apnoea: A Randomized Control Trial**
REC reference:	**19/NW/0391**
Amendment number:	**Amendment no. 1**
Amendment date:	**04 December 2019**
IRAS project ID:	**262092**

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*
Covering letter on headed paper		06 January 2020
Notice of Substantial Amendment (non-CTIMP)	Amendment no. 1	04 December 2019
Participant information sheet (PIS) [Patient Information Leaflet]	V3	04 December 2019
Research protocol or project proposal [Study Protocol]	V4	31 January 2020

Appendix 4 Published protocol of the randomised clinical trial

Tallamraju et al. Trials (2021) 22:699
https://doi.org/10.1186/s13063-021-05582-1

Trials

STUDY PROTOCOL Open Access

Intervention to enhance adherence to mandibular advancement appliance in patients with obstructive sleep apnoea: study protocol for a randomised clinical trial

Harishri Tallamraju[1*], J. Tim Newton[2], Padhraig S. Fleming[1] and Ama Johal[1]

Abstract

Background: Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder characterised by the repeated episodic collapse of the upper airway during sleep, resulting in sleep deprivation, giving rise to apnoeas and hypopnoeas. Based on the severity of OSA, there are two primary treatment modalities, continuous positive airway pressure (CPAP) and mandibular advancement appliances (MAA); both are adherence-dependent. MAA is offered to those with mild to moderate OSA and is prescribed as an alternative to patients intolerable to CPAP. However, adherence to MAA treatment is variable and declines over time. Hence, the current study aims to assess the effectiveness of the stage-matched intervention, the Health Action Process Approach (HAPA), on adherence to MAA in patients with OSA.

Methods: A single-centre randomised clinical trial will be undertaken at Bart's Health NHS Trust. Fifty-six participants with newly diagnosed OSA are planned to be enrolled in the study and randomised to intervention care (IC) and standardised care (SC) groups. Participants in the SC group will receive routine care whilst participants in the IC group will receive the stage-matched intervention, developed using the HAPA model. Data indicating MAA adherence will be collected both objectively and subjectively, from micro-sensors embedded in the MAA design and sleep diaries, respectively at 3, 6, 18 and 36 months. In addition, a range of questionnaires designed to assess risk perception, outcome expectancy, and self-efficacy (SEMSA) and quality of sleep (PSQI and ESS) and life (EQ-5DL), socio-economic and social support scales will be used.

Discussion: The currently available treatments for obstructive sleep apnoea depend entirely on the patient's acceptance and use. There are several factors that affect cooperation and wear for example patients' awareness of their condition, social support and psychological behaviour. In addition, mood, such as anxiety, stress, and depression, may affect wear. At the same time, we know that interventions involving more education and behaviour approaches can help patients adapt more easily to some treatments. As a result, the present trial aims to explore the potential role of these factors to maximise treatment success and minimise side effects.

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Trial registration: ClinicalTrials.gov NCT04092660. Registered on September 6, 2019

Keywords: Obstructive sleep apnoea, Mandibular advancement appliance, Patient adherence, Health Action Process Approach, Staged-matched intervention

Administrative information

The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

Title {1}	Intervention to enhance adherence to mandibular advancement appliance in patients with obstructive sleep apnoea: study protocol for a randomised clinical trial (IPOSAT)
Trial registration {2a and 2b}.	ClinicalTrials.gov ID NCT04092660 (9/13/2019)
Protocol version {3}	Version 04, 31.01.2020
Funding {4}	Self-funded
Author details {5a}	Harishri Tallamraju (HT): Research student Prof J Tim Newton (JTN): Research supervisor Prof Padhraig S. Fleming (PSF): Research supervisor Prof Ama Johal (AJ): Chief Investigator and Research supervisor
Name and contact information for the trial sponsor {5b}	Queen Mary, University of London Contact person: Dr. Mays Jawad Research & Development Governance Operations Manager Joint Research Management Office 5 Walden Street London E1 2EF Phone: 020 7882 7275/6574 Email: research.governance@qmul.ac.uk
Role of sponsor {5c}	Data management Record retention and Archiving Monitoring and Auditing Insurance and Indemnity

Introduction

Background and rationale {6a}

Obstructive sleep apnoea (OSA) is a sleep-related breathing disorder characterised by the repeated episodic collapse of the upper airway during sleep, resulting in sleep deprivation, giving rise to apnoeas and hypopnoeas [1].

OSA is the third most common respiratory disorder in the UK, affecting up to 10% of middle-aged adults [2, 3]. Severe long-term effects of this disease include excessive daytime sleepiness, cognitive dysfunction, hypertension, impaired quality of life, and increased cardiovascular morbidity and mortality [4].

An overnight sleep study is required to establish a diagnosis of OSA and provides the apnoea-hypopnoea index (AHI), which is the sum of the average number of apnoea (complete airflow cessation) and hypopnoea (partial airflow cessation) events per hour of sleep. The AHI has been classified into the following severity grades: mild (5–15), moderate (16–30) and severe (> 30) [5].

Based on the severity of OSA, there are two primary treatment modalities- continuous positive airway pressure (CPAP) and Mandibular advancement appliance (MAA) [6, 7]. CPAP is prescribed to those suffering from moderate to severe OSA. MAA is offered to those with mild to moderate OSA and is the alternative option for patients who cannot tolerate CPAP therapy [8]. It was noted that MAA reduces daytime sleepiness and improves the AHI by protruding the mandible and thereby maintaining an open pharyngeal airway [9]. However, studies have consistently demonstrated that CPAP is more effective than MAA at reducing sleep-disordered breathing and achieving complete control of OSA (AHI < 5) [10]. Despite the greater effect of CPAP on objective polysomnographic parameter (AHI), it does not appear to be more effective at achieving better health outcomes. It seems that the higher efficacy of CPAP is offset by greater MAA adherence. Phillips et al. (2013) showed that CPAP and MAA achieved similar improvements in excessive daytime sleepiness and quality of life. Average MAA adherence was 6.5 h/night compared to 5.2 for CPAP ($p < 0.0001$). These findings are consistent with the results of a recent systematic review and meta-analysis [11]. The meta-analysis presented that adherence was significantly lower with CPAP than MAA by 1.1 h per night ($p = 0.004$).

Although initial subjective treatment adherence to MAA therapy is relatively high, it is declining over time. A phone-based survey of 69 patients with mild to moderate OSA prescribed MAA, reported a 32% adherence rate after 4 years of therapy, indicating a high level of non-adherence [12]. The study also suggested the prevention of barriers, associated with MAA therapy adherence, to improve the efficiency of the appliance and disease outcome. In a systematic review, Hoffstein et al. (2007) reported a wide range of (4–76%) adherence rates in the first year of appliance use and further studies have highlighted that adherence decreases with time [13]: 83% after 1 year [14] and 62–64% after 4–6 year [15, 16].

MAA adherence might differ depending on the type of the appliance, custom-made or ready-made, disease severity, and perhaps patient management [17]. In a recent

systematic review, patient-reported adherence (6.4–7 nights per week and 5–6.3 h per night) and preference ($p \leq 0.001$) were strongly associated to custom-made MAA in comparison to ready-made MAA [18]. Subjective side effects such as dry mouth, excessive salivation, tooth discomfort, muscle tenderness, and jaw stiffness, have never lead to treatment discontinuation [19–22]. In addition, tooth movement and occlusal changes have been seen in objective measurements after 1 to 4 years of follow-up, but these changes have not been reported as being related to treatment withdrawal [23–27].

Dieltjens et al. (2013) were the first to investigate the impact of type D personality disorder on adherence to MAA therapy. Individuals with Type-D personality often possess a negative outlook towards life and are overwhelmed with emotions such as stress, anxiety, and anger. The study assessed 113 patients using two questionnaires: type D scale 14 and a postal questionnaire addressing side effects and adherence to MAA. The study included 83 patients with a baseline type D personality and reported a 45% non-adherence rate amongst them [14]. Patients with a type D personality had a higher discontinuation rate and lower adherence. These findings are in agreement with similar observations reported by Brostrom et al. (2007) in regards to lower CPAP adherence with type D personality [28]. Nevertheless, the study has some limitations. The first limitation of the study is the relatively small sample size (sample bias) and the non-meaningful comparison groups, which may reduce the generalisability of the findings. The second limitation is the subjective assessment of adherence and perceived side-effects rather than employing objective means of adherence measurements. A further limitation is that the characteristic negative reporting trait of the type D patients may cause them to overestimate their non-adherence [14].

Research shows that adoption of a new health behaviour, like a new physical activity routine or adhering to a prescribed medication regimen, is a challenging endeavour involving a variety of social, emotional, and cognitive factors [29]. A multicentre study examined perceived effectiveness, self-efficacy and social support among 122 adult patients with OSA aged ≥ 65 years prescribed for MAA therapy [30]. With a 30% response rate ($n = 39$), the study reported low rates of perceived effectiveness, self-efficacy and social support highlighting the lack of self-efficacy, expectations for positive outcomes and social support experienced by the older patients in the sample. These findings are debatable as literature has identified psychological and social factors and cognitive perceptions as determinants of CPAP adherence, including patients' risk perceptions, treatment outcome expectations, locus of control, and self-efficacy [31–33]. Another possible limitation of the study is that the questionnaires were mailed to the participants, who were only contacted once by the authors explaining the poor response rate. As a result, further research involving larger samples of men and women incorporating modes, which increase the response rate, is necessary to gain a better understanding of the patient's perception of MAA therapy. In turn, this understanding could be implemented for the development of interventions enhancing patient's adherence and experience to MAA treatment.

Interestingly, previous studies in the field of Sleep Medicine have featured an aspect of enhanced patient education ranging from telephone support to home visits, motivational enhancement, or augmented support [34, 35], which have been proven to effectively improve CPAP adherence when compared to usual care. Bakker et al. (2016) conducted a randomised controlled trial of CPAP use, with motivational enhancement (ME) or CPAP only in 83 participants, with moderate to severe OSA. The trial demonstrated a clinically significant increase in CPAP adherence in the intervention arm (CPAP with ME), supporting the use of a motivational enhancement approach to optimise the management of OSA [36].

A recent Cochrane review has also emphasised the efficiency of interventions in enhancing adherence to CPAP by stating that educational, supportive and behavioural interventions increase CPAP usage to varying degrees [37]. Stage theories such as the Health Action Process Approach (HAPA), a social cognition model for behaviour change, can be used to identify factors to target in an intervention and their interrelationships. The model-based approach often uses a quantitative, questionnaire-based approach to assess a small set of factors linked within a model specifying how the factors are related to behaviour and to one another. It includes self-efficacy, outcome expectancies, and risk-perception as distal predictors, intention as a middle-level mediator, and volitional factors (such as action planning) as the most proximal predictors of behaviour. All are considered as determinants of adherence in CPAP therapy [38, 39].

A number of randomised controlled trials within medicine have examined the concept of stage-matched interventions based on HAPA, for example in the context of dietary behaviours [40], physical activity [41] and dental hygiene [42]. In order to investigate the efficiency of interventions on CPAP adherence, 110 OSA (AHI ≥ 15 events/h) patients were randomly assigned into staged-match intervention care (SMC) and standardised care (SC) groups [4]. The staged-match intervention care design, following the principles of HAPA, significantly improved CPAP adherence whilst facilitating intention formation and enhancing treatment self-efficacy. Although

the evidence for stage theories is somewhat inconsistent, a meta-analysis [43] suggests that tailoring interventions to behavioural stages is more effective than a generic, non-staged-tailored approach.

The above stage theory advocates that behaviour intervention takes account of the stages of change. Individuals are presumed to progress through an ordered set of stages whilst contemplating, initiating, and maintaining health behaviour change [44]. Risk perception is an antecedent, that forms an intention to adopt a precautionary action or treatment [4]. After a treatment intention develops, it transforms into detailed action plans and these plans may promote moving further into action and/or a maintenance stage [45] implies that understanding behaviour change over time, on dynamic variables instead of static variables, would achieve maximum intervention effectiveness [4]. This feature differentiates stage theories from social cognition theories, such as the theory of planned behaviour (TPB), which interpret behaviour change as a continuous process.

The approach also recommends a distinction between pre-intentional motivational processes and post-intentional volitional processes [42]. The motivational phase comprises of growing risk perception and outcome expectancies, leading to the development of an intention. Although risk perception is the initial step for developing an intention, it alone is deficient and outcome expectancies, characterised by the advantages and disadvantages of the health behaviour in context are essential to promote intention formation. For example, the more a patient feels vulnerable to the possible health threats of long-term untreated OSA (hypertension, cardiovascular diseases), the more he or she will expect from the MAA therapy.

In the volitional phase, Intention and behaviour implementation (adherence to MAA) would be mediated through action planning [46]. Action planning consists of specifying when, where and how to perform the behaviour [47]. Self-efficacy is an important construct to consider for behaviour change [48] and facilitates maintenance of action [46]. For example, after a patient is provided MAA treatment, he or she would make concrete plans concerning the commencement and continuation of the treatment whilst overcoming the difficulties. Highly self-efficacious individuals are more confident in coping with setbacks and easily tackle unanticipated difficulties, as opposed to individuals with low self-efficacy (Bandura, 1997). Since patients with OSA experience different mindsets from initiation to long-term adherence, it is imperative to frame interventions to optimise adherence, tailor-made to the patients' specific psychological variables at different stages of therapy [4].

In summary, research on increasing adherence to mandibular advancement appliances in obstructive sleep apnoea patients in underrepresented, which is in sharp contrast to the literature regarding CPAP adherence. Thus, we aim to address this shortfall by identifying the factors influencing adherence to MAA in patients with OSA and simultaneously assess the effectiveness of stage theories/stage-matched intervention on subjective and objective adherence, using the HAPA model.

Objectives {7}

Primary objective

Aims and research questions The aim and primary outcome of this study is as follows:

- To assess the effectiveness of stage-matched intervention on adherence to mandibular advancement appliances (MAA) in patients with obstructive sleep apnoea (OSA).

Secondary objectives The secondary outcomes are as follows:

- To identify the psychosocial and socio-economic indicators enhancing adherence of MAA in patients with OSA.
- Use of the indicators to develop a psychological and socio-economic predictor model.

Null hypothesis Stage-matched intervention does not enhance adherence to MAA in patients with OSA compared to standardised care.

Primary endpoint

Adherence i.e. the number of the hours the patient uses the appliance every night will be measured both objectively and subjectively at 3, 6, 18 and 36 months to assess the effectiveness of the interventions in enhancing adherence to MAA.

Secondary endpoint

Self-efficacy, risk perception, outcome expectancy, socio-economic status and social support will be measured to assess the ability of these variables in predicting adherence.

Trial design {8}

This study is a single-centre, superiority, two-arm, parallel-group, individually randomised clinical trial, with 1:1 allocation, designed to test the effectiveness of stage-matched intervention in enhancing patient adherence to MAA therapy in patients with OSA. In addition, we plan to recruit patients with a confirmed OSA

diagnosis, specifically referred for MAA therapy from secondary care.

Ethical approval was obtained from the Greater Manchester West Research ethics committee (REC ref: 19/LO/0972 and 19/NW/0391). Patients meeting the eligibility criteria will be provided with a patient information leaflet explaining the whole study. Interested patients will be asked to sign the informed consent, after which they will be randomly assigned into two groups- intervention care (IC) and standardised care (SC). Only the investigator and chief investigator (CI) will be aware of the participant's allocation.

Participants will be provided with a sleep diary (Additional file 1) to record their hours of sleep and MAA wear-time, which will give a subjective record of the adherence (duration of usage of MAA). The TheraMon®, a micro-sensor included in the MAA design, will be used for the objective documentation of MAA adherence. TheraMon® calculates the actual wear time by measuring temperature every 15 min and then transforms this information into wear time when the temperature ranges between two specific values. In the present study, this range is defined as 28 °C to 38 °C, which includes the vast majority of intraoral temperature values observed in an individual under normal conditions.

At baseline (T0), part of the routine clinical subject demographics to be collected will include age, gender, body mass index (BMI), and neck circumference. The AHI will also be recorded during the initial screening. Following an oral examination, upper and lower alginate impressions will be taken along with the participant's bite. In addition, participants will be asked to complete the following questionnaires at T (0):

- Epworth Sleepiness Scale (ESS)
- Self-efficacy measure for sleep apnoea (SEMSA) modified for oral appliance
- Pittsburgh Sleep Quality Index (PSQI)
- EuroQol-5 Dimension (EQ-5D)
- Socio-economic position questionnaire
- Social support scale

The above questionnaires will provide information concerning the participant's daytime sleepiness, personality, quality of sleep, health-related quality of life, socio-economic status and social support, respectively.

At pre-treatment T(1), participants will undergo the initial fitting of the MAA and be provided instruction on use and care.

Both IC and SC groups will be called for follow-up at 3 (T2), 6 (T3), 18 (T4) and 36 (T5) months. Any problems that the patients might be experiencing regarding MAA use will be attended to at these appointments. In addition, data indicating adherence will be collected and evaluated at the appointments both subjectively and objectively by downloading the data from the sensor using dedicated software.

Furthermore, at T(2), participants will be asked to complete the SEMSA questionnaire, whilst at T(3), participants will need to complete the ESS, SEMSA, PSQI and EQ-5D questionnaires.

One-to-one interviews will be conducted 6 months into treatment with both (n = 5–10) compliant and non-compliant patients. It will comprise of questions, which will address the following topics:

- Patient's awareness of risks and benefits of OSA
- Barriers and facilitators of MAA therapy
- The interviews will be conducted face-to-face, recorded, and transcribed by a third-party service (Essential secretary Ltd., UK). However, due to the COVID-19 pandemic, the interviews will take place online (Microsoft® Teams or Zoom cloud meetings) to ensure the participant's safety. Although, if the participant is comfortable travelling, the interview can be carried out in a private seminar room. Inductive content analysis will be employed to describe the experiences of OSA and MAA therapy of compliant and non-compliant patients without imposing preconceived categories and names of categories to evolve from the data [49].

Methods: Participants, interventions and outcomes

Study setting (9)

The study will be undertaken at the Royal London Dental Hospital, Bart's Health NHS Trust in line with the CONSORT guidelines.

Eligibility criteria (10)

Inclusion criteria

- Adult (≥ 40 years old)
- Confirmed diagnosis of OSA (AHI ≥ 5)
- Referred for MAA therapy
- Must be able to understand, read and write English; with the assistance of a translator

Exclusion criteria

- Insufficient teeth for MAA fabrication
- Poor dental or periodontal health
- Symptomatic temporomandibular disorder (TMD)
- Previously used an MAA
- Patients with uncontrolled epilepsy

Who will take informed consent? (26a)
In line with standard care, patients will be provided information regarding the study via a Participant Information sheet and what will happen to them if they agree to participate. Once the patients have agreed to participate, the research student (HT) will take written informed consent from the participants.

Additional consent provisions for collection and use of participant data and biological specimens (26b)
Not applicable

Interventions

Explanation for the choice of comparators (6b)
Participants in the SC group will receive the MAA and the routine care except for the staged-matched intervention.

Intervention description (11a)
Participants in the IC group will receive additional support in the form of behaviour change intervention. The behaviour change intervention based on the HAPA model entails delivering interventions in a staged manner. The interventions that will be provided are described in Table 1, along with the time point (Table 2).

Criteria for discontinuing or modifying allocated interventions (11b)
As we are comparing the benefits of supportive information on participant's use of a standard treatment undertaken by NHS, we do not see any specific criteria for discontinuing or modifying allocated interventions.

Strategies to improve adherence to interventions (11c)
The study specifically aims to enhance MAA therapy adherence in patients with OSA. The strategies employed to improve adherence to the intervention i.e. the MAA therapy have been designed on the principles on the behaviour change model, HAPA. These strategies are described in detailed in Table 1.

Relevant concomitant care permitted or prohibited during the trial (11d)
No relevant concomitant care is prohibited during the trial.

Provisions for post-trial care (30)
Mandibular advancement therapy will continue for all patients post the trial.

Outcomes (12)
Primary outcome
Adherence i.e. the number of hours the patient uses their appliance every night will be measured both objectively and subjectively at 3, 6, 18 and 36 months to assess the effectiveness of the interventions in enhancing adherence to MAA.

Secondary outcome
Self-efficacy, risk perception, outcome expectancy, socio-economic status and social support will be measured to assess the ability of these variables in predicting adherence

Participant timeline (13)
The participant timeline is found in Table 3.

Study scheme diagram
The study scheme diagram is found in Fig. 1.

Sample size (14)
A minimum sample size of 56 patients distributed in two groups is proposed for given α (0.01) and power (0.9), for 2 randomly assigned groups, intervention care (n = 28), standard care group (n = 28). Finally, assuming a maximum of 15% dropout, a total number of 64 patients is required.

Recruitment (15)
As part of the routine care for patients presenting with sleep disordered breathing, they are all diagnosed with OSA, on the basis of an overnight sleep study, performed in sleep clinics. Patients requiring mandibular advancement appliance (MAA) therapy are then referred to specific dental sleep clinics for treatment, as part of a multi-disciplinary approach to care. We plan to recruit potential patients, with a confirmed diagnosis of OSA, that are specifically referred for MAA therapy to Barts' Health NHS Trust.

Assignment of interventions: allocation

Sequence generation (16a)
A simple computer-generated randomisation method will be performed using a restricted (10-number block) random number sequence (www.graphpad.com/quickcalcs/randomn2.cfm) to ensure equivalence of numbers in each group. Participants will be stratified by OSA severity. In every 10-number block from the random table, the sequence will be checked to ensure the even numbers are equal to the odd numbers. Each number in the random table will be given a study number and assigned into one of the study groups.

Concealment mechanism (16b)
A table for the allocation of the participants in the study will be composed and kept in a sealed opaque envelope by the CI.

All the documents related to the randomisation, and allocation sequence generation will be kept in a box in a

Table 1 Intervention care content specified by behaviour change techniques and linked to constructs of the HAPA model

Time Point	Intervention component	Behaviour change technique	HAPA construct targeted	Content
T(1)	Pamphlet	Information about consequences	Risk perception and outcome expectancy	The health pamphlet (Additional file 1), based on HAPA, divided into 6 sections, systematically provides information about the risk, benefits and treatment of OSA. Section 2 and 4 of the pamphlets provides spaces for the participants to discuss about risks and benefits that concern them the most. Section 3 explains the various treatments available and a brief explanation of the mechanism of the treatment.
		Action planning Goal setting Problem-solving Social support (unspecified)	Task self-efficacy	Sections 5 and 6 provide valuable information for participants on how to begin with using the appliance and to continue using it regularly. Patients are advised that is normal to struggle at time when starting a new habit and setting short-term attainable goals will aid them in their struggles to adjust. The section suggests participants to seek feedback from their family, especially their sleeping partner regarding their improvement. This type of support motivates the patient to work more towards achieving their goals.
		Self-reward	Coping and recovery self-efficacy	In section 6, participants are told about the importance of rewarding themselves about the effort they put in to achieve their goals.
		Relapse prevention	Recovery self-efficacy	Section 6 also advises the participants to focus on the positives and think about situations that effect their capability and then about options to avoid/cope with these situations.
T(1)	Video	Credible source Social comparison Information about the negative and positive consequences Demonstration of behaviour Feedback on the behaviour Social support (emotional and practical)	Risk perception, outcome expectancy and task and coping self-efficacy	Patients will be shown a video [50] of an OSA patients who are undergoing treatment, in order for them to relate to someone who is going through the same condition as him/her. The video consists of patients talking about how OSA effected their life and its negative consequences. The patients will also talk about what motivated them to start the treatment, how has it changed their life and what does they do to use the appliance regularly. It will also consist of a specialist in the field of OSA, briefly talking about the ill effects of untreated OSA and the specific oral appliance treatment available.
T(1)	Counselling	Information about health consequences Social Support (unspecified and emotional) Verbal persuasion about capability	Risk perception, outcome expectancy and task self-efficacy	Participants will be given an initial counselling session in person along with their partner if they wish. During the session i.e. structured to fit the participants needs… • Their knowledge regarding OSA will be assessed • The above video will be shown • Using the information provided on the pamphlets the risks of untreated OSA and the benefits of the treatment will be discussed • If the partner is present at the appointment, they will be asked to complete a section of the pre- screening questionnaire which is part of the routine clinical examination. In the questionnaire, the partner will also be asked to indicate their and the participant's quality of sleep. In addition, the partner will also be asked to indicate the severity of the participant's snoring and whether it has an influence on their sleep.
T(2), T(3), T(4) and T(5)	Follow up at sleep clinic	Monitoring the behaviour and the outcome	Coping and recovery self-efficacy	Participants would be required to visit the sleep clinic for follow up at months 3 and 6. Their MAA usage will be assessed both objectively and subjectively by downloading the data from the micro-sensor chip embedded in the appliance and by recording the hours from their daily sleep log respectively.
		Focus on past success and verbal persuasion about capability	Coping and recovery self-efficacy	Feedback would be provided depending on the participant's usage. Their planning sheets would be discussed, and appropriate feedback will be provided whilst encouraging them to set more active goals and plans.

Table 1 Intervention care content specified by behaviour change techniques and linked to constructs of the HAPA model *(Continued)*

Time Point	Intervention component	Behaviour change technique	HAPA construct targeted	Content
		Social comparison	Coping and recovery self-efficacy	To increase their emotional support other patient's feedbacks and successful treatment would be shared.
		Problem-solving	Coping and recovery self-efficacy	Additionally, participants will be prompted to identify common factors that act as barriers for them in using the appliance and will be helped to find solutions to overcome such factors tailored to the participants needs.
3, 6, 18, and 21 weeks	Booster phone calls	Verbal persuasion about capability	Coping and recovery self-efficacy	Participants will receive calls at weeks 3, 6, 18 and 21 approximately 10–15 min in duration, prompting them to keep working towards their goals and stating that they are capable of achieving them.
		Social support unspecified	Coping and recovery self-efficacy	Participant's partner's experience of the treatment will also be discussed by asking them to share their thoughts on the participant's improvement.
		Problem-solving	Coping and recovery self-efficacy	Additionally, participants will be prompted to identify common factors that act as barriers for them in using the appliance and will be helped to find solutions to overcome such factors tailored to the participants needs.

locked cabinet away from the clinical environments in the CI's office.

Implementation (16c)
Research student (Harishri Tallamraju)

Assignment of interventions: Blinding

Who will be blinded (17a)
Only the research student (HT) and CI will have access to the Master file and patient allocation. Patients will be anonymised and allocated a unique study number and the data then blinded to the statistician, for analysis.

Procedure for unblinding if needed (17b)
Not applicable

Data collection and management

Plans for assessment and collection of outcomes (18a)

- Questionnaire responses
- Mandibular advancement appliance with an in-built sensor will be used to collect objectively measured adherence

Plans to promote participant retention and complete follow-up (18b)
Data concerning adherence will be retained.

Data management (19)
The data recorded in this study will be stored securely both physically and electronically. The data will be accessed at the Queen Mary University of London by the CI and research student only and will be password protected. The personal data of the participants will be securely held within the research facilities at the Queen Mary University of London, by the chief investigator. Data transfer for analysis will be undertaken in an anonymised form, using unique ID numbers and password-protected access.

Confidentiality (27)
Information related to participants will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldecott Principles, The Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

Plans for collection, laboratory evaluation and storage of biological specimens for genetic or molecular analysis in this trial/future use (33)
Not applicable

Statistical methods

Statistical methods for primary and secondary outcomes (20a)
Both objective and subjective data of adherence i.e. duration of the usage of the appliance will be collected at 3, 6, 18 and 36 months will be analysed to assess the effectiveness of Intervention care in comparison with standardised care.

Comparison of pre- and post-treatment scores of ESS, SEMSA, PSQI, and EQ-5D, for both the groups, will aid in identifying significant differences in terms of improvement.

Table 2 Intervention care and standardised care components

Time point	Intervention care group	Standardised care group
T0 (Baseline)	• Questionnaires - ESS, SEMSA (Modified for Oral Appliance) PSQI, EQ-5D, Socio-Economic Position and Social Support	• Questionnaires - ESS, SEMSA, PSQI, EQ-5D, Socio-economic position, Social Support scale
T1 (Pre-treatment)	• Providing instruction about how to use the MAA • Health pamphlet based on HAPA theory • Assessment of knowledge of OSA and involvement of the partner in education • A brief education focusing on the benefits associated with MAA • 10-min video education about OSA, emphasising the negative consequences if OSA is untreated • Risk perception communication • Setting Goals and action planning (steps to facilitate the use of MAA)	• Providing instruction about how to use the MAA • Health pamphlet about OSA and MAA
T2 (3 months into treatment)	• Phone calls to be made at 3 and 6 weeks - Problem-solving - Evaluation of the patient and partner perception of treatment - Verbal encouragement - Setting attainable goals and action planning • Follow up at Sleep Clinic -Assessment of MAA use -Problem Solving -Verbal Encouragement -Sharing other Patient's Feedbacks and successful treatment experiences • Questionnaire -SEMSA	• Follow up at Sleep Clinic - Problem-solving - Assessment of MAA use • Questionnaires -SEMSA
T3 (6 months into treatment)	• Phone calls to be made at 18 and 21 weeks - Problem-solving - Partner involvement in treatment and family support - Verbal encouragement - Setting attainable goals and action planning • Follow up at sleep clinic - Assessment of MAA use - Problem-solving - Verbal encouragement - Sharing other patient'sfeedbacks and successful treatment experiences • Questionnaires - ESS, SEMSA, PSQI, EQ-5D • One-to-one interviews	• Follow up at Sleep Clinic - Problem-solving - Assessment of MAA use • Questionnaires - ESS, SEMSA, PSQI, EQ-5D • One-to-one Interviews
T4 (18 months into treatment)	• Assessment of MAA use	• Assessment of MAA use
T5 (36 months into treatment)	• Assessment of MAA use	• Assessment of MAA use

Statistically, evaluate the ability of the variables -self-efficacy, risk perception, outcome expectancy, social support and socio-economic position, to predict patient adherence at 3, 6, 18 and 36 months.

List of statistical procedures

Assuring random assignment to groups, for this purpose, we need to test whether the observations differ in any of the time zero measurements. Indifference means there is no allocation bias.

T-test for each of the variables between SC and IC

1. Risk perception
2. Outcome expectancy
3. Self-efficacy
4. ESS – time zero
5. PSQI – time zero
6. EQ5D – time zero
7. Social support
8. Socio-economic (ordinal) – chi-square test

In case of violation of the t test assumption (normality of the error term), Wilcoxon tests will be implemented.

Assessing the aims of the study

In order to assess the aims of the study, we will test each of the repeated measures first by themselves

Table 3 Schedule of assessment

Assessment	Baseline T0	Pre-treatment T1	3 months T2	6 months T3	18 months T4	36 months T5
Questionnaires						
Epworth Sleepiness Scale (ESS)	X			X		
Self-Efficacy Measure for Sleep Apnea	X		X	X		
(SEMSA)				X		
Pittsburgh Sleep Quality Index (PSQI)	X			X		
EQ-5D	X					
Socio-Economic Questionnaire	X					
Social Support Questionnaire	X					
Age	X					
Gender	X					
Body mass index (BMI)	X					
Neck circumference	X					
Objective measure of adherence			X	X	X	X
Subjective measure of adherence			X	X	X	X
One-to-one interviews				X		

using a repeated measures ANOVA controlling for groups:

1. Adherence – reported, times 3, 6, 18, 36 difference 3–6, 6–18, 18–36
2. Adherence – objective, times 3, 6, 18, 36 difference 3–6, 6–18, 18–36
3. ESS, time 6, difference 0–6
4. PSQI, time 6, difference 0–6
5. EQ5D, time 6, difference 0–6
6. Risk perception, times 3, 6, difference 0–3, 0–6, 3–6
7. Outcome expectancy, times 3, 6, difference 0–3, 0–6, 3–6
8. Self-efficacy, times 3, 6, difference 0–3, difference 0–6, 3–6

Once we understand the trends in the data, we can construct multiple regressions for Adherence variables. These can be the final measures from time 6 or the differences between them and previous times, 0 or 3. In these models, we will use the Psychosocial variables and socio-economic as predictors, beyond the group classification.

Interim analyses (21b)
The CI will make the final decision to terminate the trial.

Methods for additional analyses (e.g. subgroup analyses) (20b)
Not applicable

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data (20c)
All randomised participants will be included in the main analyses. An intention-to-treat analysis will be carried out relating to any protocol non-adherence or dropouts. However, due to the nature of the trial very few dropouts are anticipated. Nevertheless, sensitivity analysis will be performed for any of the missing data.

Plans to give access to the full protocol, participant level-data and statistical code (31c)
Not applicable

Oversight and monitoring

Composition of the coordinating centre and trial steering committee (5d)
Not applicable

Composition of the data monitoring committee, its role and reporting structure (21a)
The data recorded in this study will be stored securely both physically and electronically. The data will be analyzed in the Queen Mary, University of London by the CI of the research student. The data will be password protected and the only the CI and the research student will have full access. The personal data of the participants will be securely held within the research facilities at the Queen Mary, University of London, by the chief investigator.

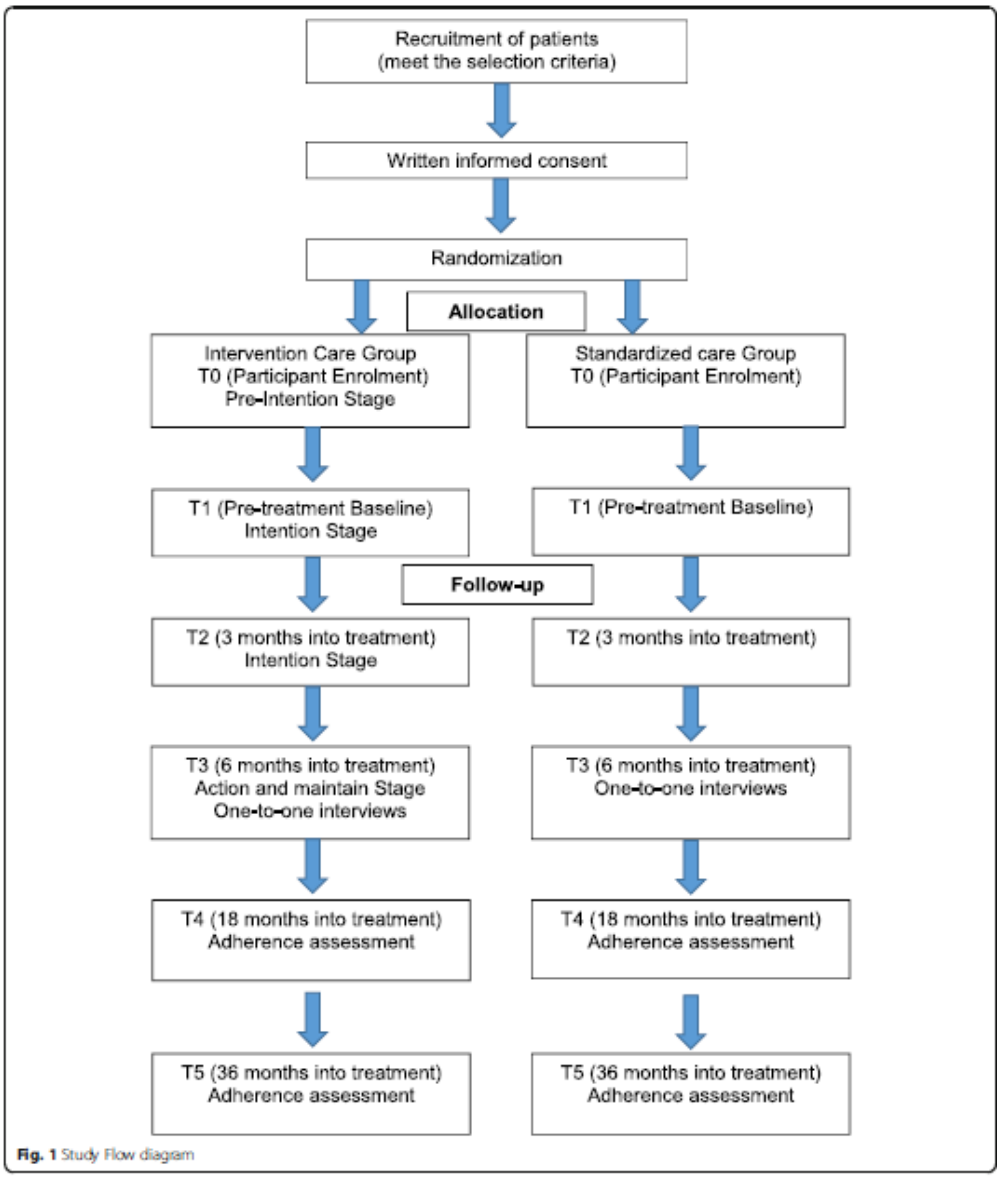

Fig. 1 Study Flow diagram

Adverse event reporting and harms (22)

We expect no adverse events in the study, as it is questionnaire-based and relates to routine clinical care of MAA therapy in relation to OSA management.

Frequency and plans for auditing trial conduct (23)

The sponsor or delegate retains the right to audit any study, study site or central facility. In addition, the funders may audit any part of the study where applicable.

Plans for communicating important protocol amendments to relevant parties (e.g. trial participants, ethical committees) (25)
Any protocol amendments will be communicated to the sponsor (Joint Research Management Office), the relevant research ethics committee and to the study participants.

Dissemination plans (31a)
It is intended that the results of the research would be presented at conferences or organising/attending workshops. In addition, the results will be published in a peer-review journal.

Discussion
Not applicable

Trial status
Protocol version 04, Dated: 31/01/2020
Date recruitment began: December 2019
Approximate date of recruitment completion: September 2021

Abbreviations
AHI: Apnoea/Hypopnoea index; CI: Chief investigator; BMI: Body mass index; CPAP: Continuous positive airway pressure; ESS: Epworth Sleepiness Scale; EQ-5D: EuroQol-5 Dimension; HAPA: Health Action Process Approach; IC: Intervention care; MAA: Mandibular advancement appliance; OSA: Obstructive sleep apnoea; PSQI: Pittsburgh Sleep Quality Index; QUIPS: Quality in prognosis studies; SEMSA: Self-efficacy measure for sleep apnoea; SC: Standardised care; T0: Baseline; T1: Pre-treatment; T2: 3-month follow-up observation; T3: 6-month follow-up observation; T4: 18-month follow-up observation; T5: 36-month follow-up observation

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13063-021-05582-1.

Additional file 1.

Acknowledgements
Not applicable

Authors' contributions
HT and AJ conceived the study, contributed in its design and development of the original protocol. AJ, PSF and JTN are research supervisors for HT. AJ, PSF and TN have reviewed and advised on the final study protocol. HT and AJ will participate in data collection. HT wrote the first draft of the manuscript, with principle edits by AJ. All authors read, edited and approved the final manuscript.

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Availability of data and materials
Not applicable

Declarations

Ethics approval and consent to participate
Ethical approval was obtained from the Greater Manchester West Research ethics committee (REC ref: 19/LO/0972 & 19/NW/0391). Written, informed consent to participate will be obtained from all participants.

Consent for publication
Not applicable

Competing interests
The authors declare that they have no competing interests.

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Publisher's Note

Appendix 5 Participant information leaflet for the randomised clinical trial

PARTICIPANT INFORMATION SHEET

(Version 3.0, 4.12.2019)


Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea: A Randomized control trial

We would like to invite you to take part in our study in which we aim to assess whether additional support approaches will help patients use their anti-snoring (sleep apnoea) mouth guard for more hours as compared to those who receive routine care. We also will try and identify factors that help us to understand why some patients choose to wear their anti- snoring mouth guard more than others.

Please take your time to read through this participant information leaflet and only then sign the informed consent sheet if you would like to take part in this project. The information is very useful to us and the future patients being offered this treatment and very much appreciate your help. If you require any further clarification please feel free to contact the chief or principle investigator [details below].

What is this study about?

The main purpose of this study is to assess whether additional support approaches would help patients wear their anti-snoring (sleep apnoea) mouth guard for longer periods of time, when

compared those who receive routine care. We also aim to explore the reasons behind why some patients choose to wear their anti-snoring mouth guard more than others.

Your participation would involve answering some simple questionnaires regarding your sleep condition, psychological health and about your circumstances. The Questionnaires will take

approximately 15 minutes to complete and will be given to you at your routine sleep clinic appointment.

Why are we doing this study?

Anti-snoring mouth guards are recommended for patients with sleep apnoea and they been shown to be effective. However, they rely entirely on the patient's acceptance and use. There are thought to be a number of factors that can affect cooperation and wear. The decision to use the anti-snoring mouth guard effectively depends on factors, such as the patients' awareness of their condition, social support and psychological behaviour. Mood, such as anxiety, stress and depression may affect wear. At the same time we know that additional support approaches, which involve more education and behaviour approaches can help patients to adapt more easily to some treatments. As a result, we would like to explore the potential role of these factors to help future patients make the most of their treatment.

Why me?

You were invited to help with this study because you are an adult, suffering from obstructive sleep apnoea and recommended to use an anti-snoring/sleep apnoea mouth guard.

Do I have to take part?

No. Taking part in this study is completely optional. If you wish not to participate, your care will continue as normal and will not be affected. If you would like to participate in the study, we will ask you to sign a consent form.

What happens to me if I take part?

You will be asked to complete a set of questionnaires used to assess your general health and personality-type. The questionnaires will take approximately 15 minutes to complete. Information such as age, gender, body mass index (BMI) and neck circumference will be recorded. All participants will then be given an anti-snoring (sleep apnoea) mouth guard and receive either the routine instructions on usage or be offered additional support which includes a video over the planned study period of 6 months. Initially fitting of the anti-snoring (sleep apnoea) mouth guard will take place at the first appointment. A daily sleep diary will be provided to you to keep a record of how many hours you have used the anti-snoring mouth guard.

You will be called for follow-up at 3, 6, 18 and 36 months into treatment which is part of the standard routine care. You either will receive routine instructions or be given additional support and a removable plastic retainer. The plastic retainer is used to keep the teeth in their original position and will need to be worn for one hour during the day. At follow-up appointments, you will also be required to complete questionnaires and the hours of anti-snoring/sleep apnoea mouth guard usage will be assessed.

After 6 months, some of the participants will be invited to take part in interviews to gain a better understanding of their experience of their treatment and their thoughts about what helped or prevented them from using the appliance more.

What happens if I wish to leave the study?

You are free to withdraw from the study at any time without any reason. All the information collected will be stored safely. Once you withdraw from the study no further research

information will be collected and if you specifically request, any previous information collected can be discarded. Alternatively, previous information will be retained and analysed in an anonymous manner with the remaining patient information depending at which time point you choose to withdraw, e.g. after 1-, 3- or 6-months.

Are there any disadvantages in not taking part?

No, your decision not to take part will not affect the care you were to receive.

Are there any benefits in taking part?

By taking part in this study you will help us to better understand what factors are important in helping patients use their anti-snoring (sleep apnoea) mouth guard. This will in turn help us find ways to help future patients get the most out of their treatment.

What are the possible risks of taking part in the study?

There are no risks involved in this study

Will my taking part in this study be kept confidential?

Queen Mary University of London is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake 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. Queen Mary University of London will keep identifiable information about you for 20 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, the information about you that we have already obtained will be retained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at http://www.arcs.qmul.ac.uk/media/arcs/policyzone/Privacy-Notice-for-Research- Participants.pdf

NHS will collect information from you and your medical records for this research study in accordance with our instructions.

NHS will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Queen Mary University of London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. NHS site will pass these details to Queen Mary University of London along with the information collected from you and your medical records. The only people in Queen Mary University of London who will have access to information that identifies you will be people who need to contact you to confirm any missing data and invite you to partake in the qualitative study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

NHS will keep identifiable information about you from this study for 20 years after the study has finished according to Queen Mary University of London/Barts Health NHS Trust policy.

The data will be archived in the Corporate Records Facility at 9 Prescot Street, London, E1 8PR.

What will happen to the results of this study?

In order to share the knowledge gained from the study, the findings will be published in a medical journal and presented at health conferences including voluntary and support sleep apnoea patient groups.

What if there is a problem?

Any problem that occurs during the study will be addressed appropriately. Please contact the chief investigator [contact below] to solve the problem immediately. If you remain unhappy and wish to complain formally, you can do this through the NHS complains procedure. Details can be obtained from:
http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/NHScomplaints.asp x

In the event that something does go wrong and you are harmed during the research due to negligence, then you may have grounds for legal action for compensation against the sponsor of this study, Queen Mary university of London. The sponsor will compensate for injury caused directly by the procedure you received during your participation.

Who has reviewed the study?

This research project has been reviewed by a group of clinical researchers. In addition it will be looked at by an independent group of people, which includes both professionals and lay public, whose purpose is to review all NHS research to protect your interests, called a Research Ethics Committee.

Where can I obtain Alternative means of support?

Independent advice could be obtained from: Patient Advice and Liaison Service (PALS)

For Barts Health NHS Trust hospitals: Integrated for Royal London, patient Advice Liaison Service (PALS). Telephone: 020 3594 2040, e-mail address: pals@bartshealth.nhs.uk. Service is available Monday to Friday, 9.30am-4.30pm by appointment.

Thank you very much for taking the time to read about the research. If you take part, you can help us make a difference to others in the future.

Further information and contact details

To contact the Chief investigator of the study:

Professor Ama Johal, Dental Institute, The Royal London Dental Hospital Phone: 0207 377 7686

Email: a.s.johal@qmul.ac.uk

If you would like to find out more about this study or arrange an appointment, please contact the Researcher: Dr. Harishri Tallamraju, Dental Institute, 4th floor, The Royal London Dental Hospital Email: h.tallamraju@qmul.ac.uk

Appendix 6 Consent from for the randomised clinical trial

IRAS ID: 262092

Centre Number:

Study Number:

Participant Identification Number for this trial:

CONSENT FORM FOR PARTICIPANT

Title of Project: Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea: A Randomized control trial

Name of Researcher:

Please initial box

1. I confirm that I have read the information sheet dated..... (version .....) for the above study. I have had the opportunity to consider the information, ask questions and have had 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 my medical notes and data collected during the study, may be looked at by individuals from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future and may be shared anonymously with other researchers. ☐

5. I understand that the information held and maintained by Queen Mary, University of London may be used to help contact me or provide information about my health status. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature

Name of Person	Date	Signature taking consent

Appendix 7 Sleep diary

DAILY SLEEP LOG

(VERSION 2.0, 22.07.2019)

Participant identification number for the study: _____

Title of the study: Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea: A Randomized control trial

To help us understand your sleep problems, we need a report of the times when you sleep, nap and how often you wake during sleep. In addition, we need to know the times when you drink coffee, tea and alcoholic beverages.

If medication is taken, record the time medication is needed.

IT IS IMPORTANT THAT YOU KEEP THIS RECORD FOR 7 DAYS. Each column begins a new day; the first column is an example for you to study.

Start Date	Example	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Naps: times & length you napped	2:00 pm 45 min 6:30 pm 30 min							
Medication: Amount & Time taken	Zimovane 5mg x 1 10:30 pm							
Coffee & Tea No. of cups/time	C. x 1 7:00 am T. x 2 6:30 pm							
Alcohol: No. of units/time	A. x 2 7:00 pm A. x 1 10:00 pm							
Time in bed before lights out:	30 min							

Lights out:	11:00 pm							
Estimated time to fall asleep	45 min							
Estimated number of awakening in night & duration	2:00 am @20 min 4:30 am @ 1 hour							
Time of awakenings	7:30 am							
Total hours of sleep	@ 7hrs							
Overall sleep quality night: **Poor= 1** **Average= 2** **Good= 3**	3							

If you have any queries, please contact Prof. Ama Johal via his secretary at The Royal London Hospital on 0207 377 7379.

Appendix 8 Self-efficacy measure for sleep apnoea questionnaire

PERCEIVED SELF-EFFICACY MEASURE FOR SLEEP APNOEA

DIRECTIONS: This survey asks you about sleep apnoea and Mandibular Advancement Appliance (MAA) or Anti-snoring mouth guard, a treatment for sleep apnoea. Please put a (✓) in the box under your answer to each question. Pick only one answer for each question. Please try to be as careful as possible. All information will be kept confidential.

1A. My chances of having high blood pressure compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

2A. My chances of falling asleep while driving compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

3A. My chances of having a heart attack compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

4A. My chances of having difficulty concentrating compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

5A. My chances of falling asleep during the day compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

6A. My chances of having an accident because of falling asleep while driving compared to people my own age and sex who do not have sleep apnoea are:

Very low	Low	High	Very high

7A. My chances of being depressed compared to people my own age and sex who do not have sleep apnea are:

Very low	Low	High	Very high

8A. My chances of having problems with sexual desire or sexual performance compared

to people my own age and sex who do not have sleep apnoea are:

Very low	Low	High	Very high

These questions ask you what you think may happen to you if you do or do not use anti- snoring mouth guard nightly to treat sleep apnoea. Please put a (✓) in the box under your answer to each question for how true each statement would be for you.

1B. If I do use the anti-snoring mouth guard, I will decrease my chances of having an accident while driving.

Very low	Low	High	Very high

2B. If I use the anti-snoring mouth guard, then I will not snore.

Very low	Low	High	Very high

3B. If I do not use the anti-snoring mouth guard, I will be less alert during the day.

Very low	Low	High	Very high

4B. If I use anti- snoring mouth guard, then my job performance will improve.

Very low	Low	High	Very high

5B. If I use anti- snoring mouth guard, my relationship with my significant other and friends will improve.

Very low	Low	High	Very high

6B. If I do not use anti-snoring mouth guard, I will increase my chances of having a heart attack.

Very low	Low	High	Very high

7B. If I use anti- snoring mouth guard, my bed partner will sleep better.

Very low	Low	High	Very high

8B. If I use anti-snoring mouth guard, I will feel better.

Very low	Low	High	Very high

9B. If I use anti-snoring mouth guard I will be more active.

Very low	Low	High	Very high

10B. If I use anti-snoring mouth guard my desire and sexual performance will improve.

Very low	Low	High	Very high

These questions ask you about wearing anti-snoring mouth guard, if it should be prescribed for you. Please put a (✓) in the box under your answer to each question that best indicates how true each statement would be for you.

1C. I would use the anti-snoring mouth guard, even if it made me feel claustrophobic.

Very low	**Low**	**High**	**Very high**

2C. I would use the anti-snoring mouth guard, even if it will take me longer to get ready for bed.

Very low	**Low**	**High**	**Very high**

3C. I would use the anti-snoring mouth guard, even when I travelled.

Very low	**Low**	**High**	**Very high**

4C. I would use the anti-snoring mouth guard, even when it is uncomfortable.

Very low	**Low**	**High**	**Very high**

5C. I would use the anti-snoring mouth guard, even if it made my mouth dry.

Very low	**Low**	**High**	**Very high**

6C. I would use the anti-snoring mouth guard, even if it were a bother.

Very low	**Low**	**High**	**Very high**

7C. I would use the anti-snoring mouth guard, even if it disturbed my bed partner's sleep.

Very low	Low	High	Very high

8C. I would use the anti-snoring mouth guard, even if it made me feel embarrassed.

Very low	Low	High	Very high

9C. I would use the anti-snoring mouth guard, even I had to pay for some of the cost.

Very low	Low	High	Very high

Appendix 9 Pittsburgh sleep quality index questionnaire

Sleep Quality Assessment (PSQI)

What is PSQI, and what is it measuring?

The Pittsburgh Sleep Quality Index (PSQI) is an effective instrument used to measure the quality and patterns of sleep in adults. It differentiates “poor” from “good” sleep quality by measuring seven areas (components): subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medications, and daytime dysfunction over the last month.

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.

During the past month,

1. When have you usually gone to bed? _____
2. How long (in minutes) has it taken you to fall asleep each night? _____
3. What time have you usually gotten up in the morning? _____
4. How many hours of actual sleep did you get at night? _____

5. During the past month, how often have you had trouble sleeping because you	**Not during the Past month (0)**	**Less than once a week (1)**	**Once or twice a week (2)**	**Three or more times a week (3)**
A. Cannot get to sleep within 30 minutes				
B. Wake up in the middle of the night or early morning				
C. Have to get up to use the bathroom				
D. Cannot breathe comfortably				
E. Cough or snore loudly				
F. Feel too cold				
G. Feel too hot				
H. Have bad dreams				
I. Have pain				

J. Other reason (s), please describe: _____

_____

How often you have had trouble sleeping because of this reason (s):

( )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 (0	Fairly good (1)	Fairly bad (2)	Very bad (3)

7. During the past month, how often have you taken medicine (prescribed or “over the counter”) to help you sleep?				
8. During the past month, how often have you had trouble staying awake while driving, eating meals, or engaging in Social activity?				
9. During the past month, how much of a problem has it been for you to keep up the enthusiasm to get things done?	Very good (0	Fairly good (1)	Fairly bad (2)	Very bad (3)

Appendix 10 EuroQol – 5 Dimension questionnaire

EQ-5D-5L

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 ❑

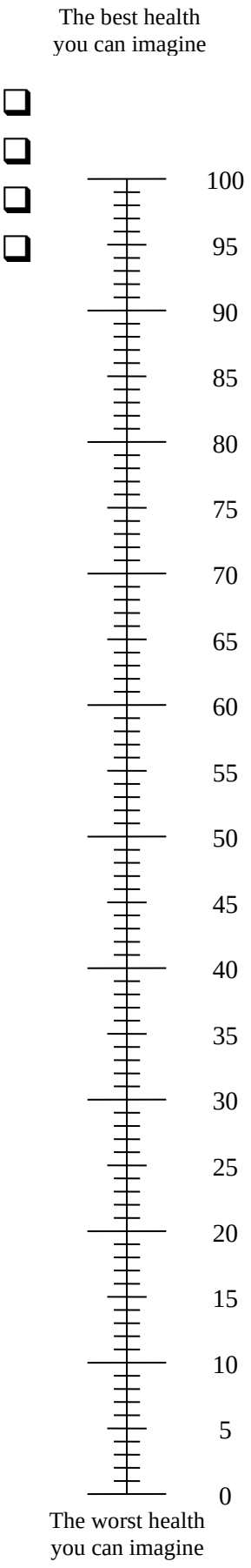
I am moderately anxious or depressed ❑

I am severely anxious or depressed ❑

I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the <u>best</u> health you can imagine.
  0 means the <u>worst</u> 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 = ☐



Appendix 11 Socio-economic position questionnaire

SOCIO-ECONOMIC POSITION QUESTIONNAIRE

(Based on National Statistics Socio-Economic Classification)

1) Did you ever attend school?
   ☐ No ☐YES ☐ No, but I can read and write

2) What was the highest degree or qualification that you obtained?
   ☐Elementary Primary School ☐Secondary school without O level(s)
   ☐Secondary school with O level(s) ☐Technical Education
   ☐A/AS/S levels ☐University
   ☐Postgraduate

3) How old were you then (when you obtained your highest degree or qualification)?
   ☐Please specify: _____years old ☐Don't know

4) Last week, were you any of the following?
   ☐In training/student ☐Casually Employed
   ☐Full-time Employed ☐Retired
   ☐Currently Sick/disable ☐I have never worked
   ☐Part-time employed ☐looking after home/family
   ☐None of the options:
   Specify _____

The following questions are related to your employment status. Please choose one option.

5) Do (did) you work as an employee or are (were) you self-employed?
   ☐Employee ☐Self-employed with employees
   ☐Self-employed/freelance without employees (Go to question no. 8)

6) **For employees**: How many people work (worked) for your employer at the place where you work (worked)?

   For self-employed: How many people do (did) you employ? (Go to question no. 7 when you have completed this question)

☐1 to 24 ☐25 or more

7) Do (did) you supervise any other employees? (A supervisor or foreman is responsible for overseeing the work of other employees on a day-to-day basis)
☐Yes ☐No

8) Tick the box to show which best describes the sort of work you do. If you are not working now, please tick the box to show what you did in your last main job.

☐ Modern professional occupations such as: teacher- nurse- physiotherapist- social worker- welfare officer- artist- musician- police officer (sergeant or above)- software designer

☐ Clerical and intermediate occupations such as: secretary- personal assistant- clerical worker- office clerk- call center agent- nursing auxiliary- nursery nurse

☐ Senior managers or administrators (usually responsible for planning, organizing and coordinating work, and for finance manager- chief executive

☐ Technical and craft occupations such as: motor mechanic- fitter- inspector- plumber- printer- tool maker- electrician- gardener- train driver

☐ Semi-routine manual and service occupations such as: postal worker- machine operative- security guard- caretaker- farm worker- catering assistant- receptionist- sales assistant

☐ Routine manual and service occupations such as: HGV driver- van driver- cleaner- porter- sewing machinist- messenger- laborer- waiter/waitress- bar staff

☐ Middle or junior managers such as: office manager- retail manager- bank manager- restaurant manager- warehouse manager- publican

☐Traditional professional occupations such as: accountant- solicitor- medical practitioner- scientist- civil/mechanical engineer

Appendix 12 Social support questionnaire

Social Support Questionnaire

(Stepnowsky et al., 2002)

Directions: Please indicate how much you agree or disagree

	Disagree Completely	Disagre -e	Neither Agree nor disagree	Agree	Agree Completel y
1. I have people in my life who will support me in using the Anti-Snoring mouth guard regularly.	1	2	3	4	5
2. I have people in my life who will encourage me to use the Anti-Snoring mouth guard even when it causes dry mouth or jaw discomfort.	1	2	3	4	5
3. I have people in my life who will encourage me to keep using the Anti-Snoring mouth guard even when it is uncomfortable.	1	2	3	4	5
4. I have people in my life who will give me ideas for making the Anti-Snoring mouth guard more comfortable.	1	2	3	4	5
5. I have people in my life who will help me adjust to using the Anti-Snoring mouth guard.	1	2	3	4	5
6. I have people in my life who will be upset if I stopped using the Anti-Snoring mouth guard.	1	2	3	4	5
7. I have people in my life who will support me in using the Anti-Snoring mouth guard nightly.	1	2	3	4	5
8. I will get the help I need to use the Anti-Snoring mouth guard nightly.	1	2	3	4	5
9. The healthcare staff will be helpful in helping me to use the Anti-Snoring mouth guard nightly.	1	2	3	4	5

Appendix 13 Health pamphlet

- Long-term wear of an MAA carries a risk of causing small changes in the position of your teeth and how they meet together (your bite). Long-term use can therefore change your bite (or the way in which your front teeth meet).
- You must maintain a high level of tooth cleaning and regular appointments with your dentist.

Do any of these worry you? (Please tick)

1. **Adapting to the anti-snoring device** ☐
2. **Excessive saliva in the mouth** ☐
3. **Changes in your bite** ☐
4. **Visiting the dentist regularly** ☐

*6. How can Self-efficacy help **YOUR** treatment?*

- **Self-efficacy** (or Self-confidence) describes how **YOU**, the patient can help improve the results of your treatment.
- We have found that to help **YOU** adapt to this new treatment seeking **Advice** and **Feedback** from individuals who have undergone the same treatment, helps in personal motivation.
- We will help **YOU** to identify the relative advantages and disadvantages of undergoing this type of treatment.
- As treatment for sleep apnoea is lifelong, it can be very helpful to set short achievable goals such as to "increase one hour of usage every 3 nights" to help achieve the desirable goal of greater than 6 hours use per night.
- If the goal is achieved, praise and treat yourself! **Your sleeping partner and family will certainly notice the improvement!**
- Lifestyle changes such as decreased **alcohol consumption** & **smoking** and **regular physical exercises** for e.g. even a **daily 30-minute walk** will help you achieve your goal and improve your sleep.

- Moods, emotions and stress levels can all influence how you feel and your personality.
- **Confidence** and **low levels of anxiety** and **nervousness** help improve your sense of self- efficacy.
- Always try to approach difficult tasks as challenges and avoid focusing on the negatives.

OBSTRUCTIVE SLEEP APNOEA (OSA)

PATIENT HEALTH PAMPHLET

NAME: _____

AGE: _____

SEX: _____

1. What is Obstructive Sleep Apnoea?

Obstructive Sleep Apnoea (OSA) is a serious breathing problem where the airway at the back of the throat becomes blocked during sleep. It effects men and women. Currently, OSA is a significant health care burden in the UK, for individuals, the NHS and society as a whole. Although awareness of OSA is rising in the population, 42% of people who snore or whose partner snores have not even heard of OSA.

2. Why do I need to have any treatment?

You might have experienced Excessive daytime sleepiness and memory problems, as a consequence of OSA.

Which of the following do you think are most relevant to you?

(Please tick)

- Increased risk of Diabetes ☐
- Increased risk of motor vehicle accidents ☐
- Memory problems ☐
- Shorten life expectancy ☐
- Weight gain ☐
- Depression ☐
- Job Impairment

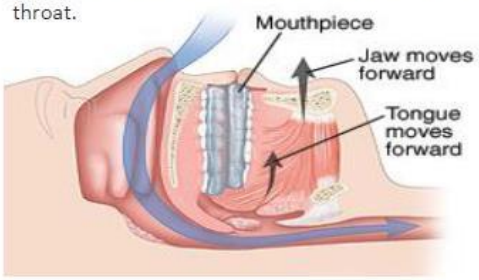
Other (please describe):_____

3. What are my treatment options?

Treatment of OSA depends on the severity of the disease. People with severe OSA should be treated with Nasal Continuous Positive Airway Pressure (CPAP). This acts by pushing air through the nose to keep the airway open during sleep.

Patients with mild-to-moderate sleep apnoea are treated with Mandibular Advancement Appliances [MAA] also known as Anti-snoring mouth guards or Oral appliances.

These are best made to fit and use the teeth to hold them in place during sleep. They work by moving (in a gradual fashion) the bottom jaw forward, opening the airway at the back of the throat.



4. What are the benefits of wearing the appliance regularly?

Most importantly, the appliance prevents the airway at the back of your throat from collapsing and thereby **Improving** the **Quality Of Sleep**, whilst **reducing** the **risks Of Heart Disease**.

Which of the following benefits are most important to you?

- Increased daytime alertness ☐
- Increased concentration in daily activities ☐
- Increased emotional well-being ☐
- Increased life expectancy ☐

Other (Please describe): _____

5. What is it like to wear the appliance?

- The appliance, like all new things, will require a little getting used to. Most patients adapt to their appliance within a week.
- You may also experience more saliva, in the mouth at first but once you are used to the appliance, this improves.

Appendix 14 Pre-screening questionnaire

S4S Dental Laboratory

PRE-SCREENING QUESTIONNAIRE

Snoring and obstructive sleep apnoea (OSA)

Remember:

- All patients can be treated for snoring with a Sleepwell mandibular advancement splint (MAS)
- Even if OSA is suspected, Sleepwell can be provided to help treat the patient's snoring
- OSA referral is simple - complete the tear off part of this questionnaire and give to the patient

Snoring and daytime sleepiness can have a profound impact on quality of life:

- **Daytime sleepiness** - less effectiveness at work and increased risk of accidents
- **Reduced energy** - poor motivation to exercise and weight gain
- **Relationship issues** - sleeping in different bedrooms, reduced sex life and higher stress levels
- **Hypertension** - those who snore or suffer from OSA have an elevated risk of high blood pressure

OSA is a serious condition in which a person stops breathing (or suffers extreme low oxygen levels) whilst asleep. It often occurs in conjunction with snoring.

Patient name: .....

Address: .....

Postcode: .....

Telephone - home: .....

Telephone - mobile: .....

The following questions relate to your lifestyle and general health. Please indicate whether you have suffered with any of the below, providing further details when the answer is yes.

Heart problems Y / N .....

High blood pressure Y / N .....

Diabetes Y / N .....

Thyroid syndrome Y / N .....

Do you take any prescribed medicines? Y / N .....

Please indicate:

Alcohol consumption ..... units/week

Smoking level ..... no/day

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PRE-TREATMENT QUESTIONNAIRE

PLEASE ENSURE THAT THIS FORM IS COMPLETED USING BLACK INK AND IN CAPITALS

PATIENT'S MAIN CONCERNS

Please indicate if you have suffered with any of the conditions below, giving further details when required:

	Circle	Details
Headaches on waking	Y / N	.....
Daytime sleepiness	Y / N	.....
Sleepiness whilst driving	Y / N	.....
Snoring most nights	Y / N	.....
Snorting or gasping during sleep	Y / N	.....

PREVIOUS TREATMENT IN RELATION TO SLEEP DISORDERS

	Circle	Details
Lifestyle change	Y / N	.....
Nasal CPAP	Y / N	.....
Surgery	Y / N	.....
Previous sleep study	Y / N	If yes, note AHI score: .....

SLEEPING PARTNER QUESTIONNAIRE (optional, if the partner is present)

Partner's name: .....

Please indicate **your** quality of sleep:

Good ☐ Average ☐ Poor ☐

Please indicate **your partner's** quality of sleep:

Good ☐ Average ☐ Poor ☐

How would you rate the severity of your partner's snoring? Please tick one box only.

- No snoring ☐
- Mild snoring ☐
- Moderate snoring ☐
- Loud snoring ☐
- Very loud snoring ☐

Does your partner's snoring disturb your sleep? Please tick one box only.

- Never ☐
- Hardly ever ☐
- Sometimes ☐
- Usually ☐
- Always ☐

FLEMONS ADJUSTED NECK CIRCUMFERENCE

Neck size - not collar (cm)			..... cm
Hypertension	Y / N	if YES, add 4	.....
Habitual snorer	Y / N	if YES, add 3	.....
Choke or gasp most nights	Y / N	if YES, add 3	.....
		Total	.....

How likely are you to doze off or fall asleep in the following situations (in contrast to just feeling tired)? Even if you haven't been in some of these situations recently, try to work out how they may affect you. Choose the most appropriate number for each situation:

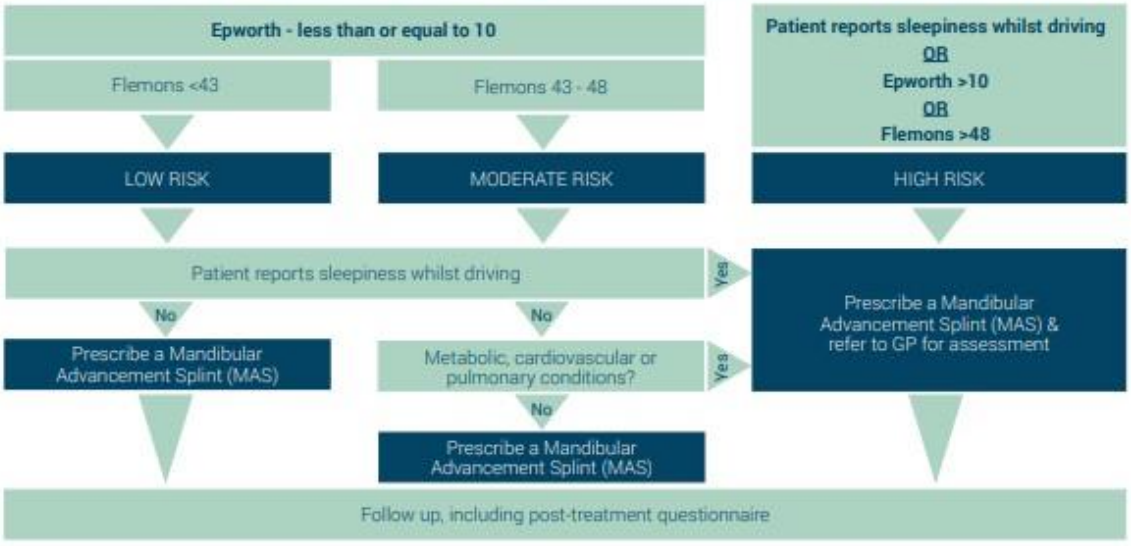
0 - NEVER doze **1** - SLIGHT chance **2** - MODERATE chance **3** - HIGH chance

Sitting and reading	.....
Watching TV	.....
Sitting, inactive in a public place (i.e. theatre, meeting)	.....
As a passenger in a car for an hour, without break	.....
Laying to rest in the afternoon, when circumstances permit	.....
Sitting and talking to someone	.....
Sitting quietly after lunch when NO alcohol has been consumed	.....
In a car, stationary for a few minutes in traffic	.....
Total (0-24)	.....

DENTIST USE ONLY - Oral examination

Incisor relationship	Class 1 Class 2 Div I Class 2 Div II Class 3
Overjet	..... mm
Overbite	..... mm
OH/Periodontal condition	Good Fair Poor
Tonsils - enlarged/inflamed	Y / N
Bruxism/clenching/grinding of teeth	Y / N Severe/Not Severe (please note severity on lab ticket)
TMJ assessment:	
Max lateral movements	L ..... mm R ..... mm
Max opening	..... mm
Max protrusion	..... mm
Tenderness to palpitation	Y / N
Pain on mandibular movement	Y / N
Smooth movement	Y / N
Locking and/or luxation	Y / N

CARE PATHWAY: TO DETERMINE PATIENT'S LEVEL OF OSA RISK



3

GP REFERRAL

To - GP details

.....
.....
.....
.....
.....

From - GDP details

.....
.....
.....
.....
.....

Date: .....

Dear Dr .....

Patient name: .....

I have assessed the above patient in relation to his/her presentation of snoring. I have provided him/her with a Sleepwell mandibular advancement appliance to address their snoring complaint.

Your patient has collective signs and symptoms of obstructive sleep apnoea (see summary below) and I feel that he/she requires further medical assessment.

Daytime sleepiness (Epworth Sleepiness Score .....)

Reports sleepiness whilst driving ☐

Stops breathing during sleep ☐

Flemons Adjusted Neck Circumference Score: .....

a) Snorts or gasps during sleep ☐

b) Habitual snoring ☐

Other Comments: .....

.....

.....

On the reverse of this letter is a summary of the Epworth Sleepiness Scale and Flemons Adjusted Neck Circumference. Further information regarding snoring and OSA can be found on the S4S website: www.s4sdental.com.

I would appreciate any feedback regarding the outcomes of further investigation. If I can be of any further assistance, please do not hesitate to contact me.

Yours sincerely,

.....

4

SNORING & OBSTRUCTIVE SLEEP APNOEA

Snoring and OSA is a serious medical issue. It leads to broken sleep for snorers and their partners, can have a profound impact on quality of life, and can be highly embarrassing.

Daytime sleepiness – Less effectiveness at work and increased risk of accidents

Reduced energy – Poor motivation to exercise, causing weight gain

Relationships – Sleeping in different bedrooms, reduced sex life, and higher stress levels

Hypertension – Patients who snore and have OSA have an elevated risk of high blood pressure

OSA is the term used when a person stops breathing for short periods whilst asleep, before creating a gasp, snort or choking sound. Breathing interruptions, known as 'sleep apnoea', reduce oxygen levels in the blood. During sleep, the brain reacts quickly and releases adrenaline, which causes partial wakening. This cycle can occur many times, interrupting sleep and leading to daytime tiredness.

SCREENING & DIAGNOSIS

The NHS will not treat simple snorers due to financial constraints, and only 50% of sleep centres provide a comprehensive treatment service for OSA.

SNORING TREATMENT

Mandibular advancement splint therapy (MAS therapy) offers effective treatment for simple snoring and mild to moderate OSA. Continuous Positive Air Pressure (CPAP) should be offered to sufferers of severe OSA.

What is a mandibular advancement splint (MAS therapy)? This is a collective name for mouthpieces which are designed to prevent the lower jaw from dropping back during sleep, in turn reducing the risk of airway narrowing. The narrowing of the airway causes the soft tissue to vibrate, causing the sound of snoring. The role of mandibular advancement splints in the management of snoring is widely recognised (SIGN guidelines, 2003). The most clinically proven and effective mandibular advancement splint is Sleepwell - available from S4S trained dentists. Lower cost, self-diagnosis treatments are called Snoresolve and Snoreshield.

EPWORTH SCALE M.JOHNS Sleep, 1991 Dec; 14(06):540-5

A method for measuring daytime sleepiness: the Epworth sleepiness scale.

Johns MW. Sleep Disorders Unit, Epworth Hospital, Melbourne, Victoria, Australia.

The Epworth sleepiness scale (ESS) is a simple, self-administered questionnaire which is shown to provide a measurement of the subject's general level of daytime sleepiness.

180 adults answered the ESS, including 30 normal men and women as controls and 150 patients with a range of sleep disorders. They rated the chances that they would doze off or fall asleep when in eight different situations, commonly encountered in daily life. Total ESS scores significantly distinguished normal subjects from patients in various diagnostic groups, including OSA, narcolepsy and idiopathic hypersomnia.

ESS scores were significantly correlated with sleep latency, measured during the multiple sleep latency test and during overnight polysomnography. In patients with OSA syndrome, ESS scores were significantly correlated with the respiratory disturbance index and the minimum SaO2 recorded overnight. ESS scores showed patients who simply snored did not differ from controls.

ADJUSTED NECK CIRCUMFERENCE (ANC)

W Flemons N Eng J Med Vol 347 No 7 Aug 2003 p.498-504 A Screening Tool for Apnoea Prediction

An adaptation of prediction rule 12, based on neck circumference, can be used to estimate a patient's probability of having a sleep test result that is diagnostic of sleep apnoea. Neck circumference (measured in centimetres) is adjusted if the patient has hypertension (4cm in added), is a habitual snorer (3cm is added), or is reported to choke or gasp most nights (3cm is added).

A low clinical probability corresponds to an adjusted neck circumference of less than 43cm, an intermediate probability (4 to 8 times as probable as a low probability) to a neck circumference of 43 to 48 cm, and a high probability (20 times as probable) to a neck circumference of more than 48cm. Together with the consideration of the severity of symptoms, the clinical probability estimate helps guide management.

12 Flemons WW, Whitelaw WA, Brant R, Remmers JE, Likelihood ratios for a sleep apnoea clinical prediction rule. Am J Respit Crit Care Med 1994; 150:1279-1285 (Abstract).

PATIENT INFORMATION

Snoring results from a partial closure of the airway during sleep, and most commonly occurs in isolation (simple snoring). Less often, it can take place as part of a more serious condition, OSA, which can be potentially life-threatening. This screening questionnaire has been used by your dental practitioner to help identify your risk of OSA. However, only a sleep physician can diagnose OSA after performing an overnight sleep recording that measures your breathing patterns.

Anti-snoring dental appliances have been shown to play an effective role in the management of patients with snoring and/or OSA.The appliance will not cure the disorder, but works by temporarily repositioning the lower jaw and tongue forwards - keeping the airway open. In order to be effective, the appliance must be worn each night. If the use of the appliance is discontinued, the symptoms will recur. There is no guarantee that an appliance will be effective in every patient, due to individual variation in response. A high standard of oral hygiene is important for a successful outcome, as is the care and use of the device as per supplied instructions.

It is important that you return for assessment after the fitting of your appliance. You will be asked to complete a simple questionnaire, designed to assess your response to treatment and gain feedback from your partner. Whilst this provides valuable feedback, for OSA sufferers, a follow-up overnight sleep recording with Sleepwell in the mouth is the only way to know if your breathing has improved sufficiently.

After wearing the appliance, most patients initially report a degree of drooling, or some patients feel that their teeth do not come together (bite) properly. These are short-term effects and lessen with time. If, however, you awaken with a dry mouth sensation, the fit of the appliance may need adjusting to improve its grip on the teeth. There is a risk that long-term wear can result in a degree of movement in your teeth. It is therefore important that you maintain the health of your teeth, and, most importantly, your gums with regular dental care. Very rarely, the jaw joints may become sore. This is most typically seen in patients with a history of jaw discomfort and/or those who self-adjust their appliances too aggressively. In addition, the splint may require replacement as a result of wear or breakage.

PATIENT CONSENT - LOW/MODERATE RISK OF OBSTRUCTIVE SLEEP APNOEA

I have given complete and accurate replies to the questions within this document, have read the information given to me and understand how Sleepwell, made by S4S (UK) Ltd, may help my snoring and/or sleep apnoea. **I understand that I would need to undergo an overnight sleep study in order to diagnose OSA.**

Patient's name: ..... Patient's signature: .....

Date: .....

Clinician's name: ..... Clinician's signature: .....

Date: .....

PATIENT CONSENT - HIGH RISK OF OBSTRUCTIVE SLEEP APNOEA

I have given complete and accurate replies to the questions within this document, have read the information given to me and understand how Sleepwell, made by S4S (UK) Ltd, may help my snoring. **I understand that I would need to undergo an overnight sleep study in order to diagnose OSA. I have also been made aware of the risk of having OSA and have been advised as follows:**

To visit my GP with a letter provided by the dentist ☐

Patient's name: ..... Patient's signature: .....

Date: .....

Clinician's name: ..... Clinician's signature: .....

Date: .....

DISCLAIMER - The questionnaires being described in this handout have been obtained from published scientific literature. However, we do not endorse their sole use to establish a diagnosis of OSA. It is important to emphasise that the subjective responses upon which these questionnaires rely have the potential to be underestimated by some people. Particular care should be taken in interpreting the results for people whose occupations require high alertness, such as transport drivers. An overnight sleep study would be required to diagnose OSA.

Appendix 15 Participant information leaflet for the qualitative study

PARTICIPANT INFORMATION SHEET

(Version 1.0, 22.07.2019)

Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea

We would like to invite you to take part in a one-to-one interview in which we aim to assess your perspective of what helps and/or prevents you from using your anti-snoring mouth guard. We also will try and identify factors that help us to understand why some patients choose to wear their anti-snoring mouth guard more than others do.

Please take your time to read through this participant information leaflet and only then sign the informed consent sheet if you would like to take part in this project. The information is very useful to us and the future patients being offered this treatment and very much appreciate your help. If you require any further clarification please feel free to contact the chief or principle investigator [details below].

What is this study about?

The main purpose of this study is to assess whether additional support approaches would help patients wear their anti-snoring (sleep apnoea) mouth guard for longer periods of time, when compared those who receive routine care. The one-to-one interview will give us a deeper insight of your treatment experience.

Your participation would involve attending one-to-one interviews and answering some simple questions which will help us assess your perspective of what helps and/or prevents you from using your anti-snoring mouth guard.

Why are we doing this study?

Anti-snoring mouth guards are recommended for patients with sleep apnoea and they have been shown to be effective. However, they rely entirely on the patient's acceptance and use. There are thought to be a number of factors that can affect cooperation and wear. The decision to use the anti-snoring mouth guard effectively depends on factors, such as the patients' awareness of their condition, social support and psychological behaviour. Mood, such as anxiety, stress and depression may affect wear. At the same time, we know that additional support approaches, which involve more education and behaviour approaches can help patients to adapt more easily to some treatments. As a result, we would like to explore the potential role of these factors to help future patients make the most of their treatment.

Why me?

You were invited to help with this study because you are an adult, suffering from obstructive sleep apnoea and are using/used the anti-snoring mouth guard.

Do I have to take part?

No. Taking part in this study is completely optional. If you wish not to participate, your care will continue as normal and will not be affected. If you would like to participate in the study, we will ask you to sign a consent form.

What happens to me if I take part?

Once you agree for you to take part in the study, and after the consent form has been signed, you will be asked to attend a one-to-one interview. The interview will approximately take 60 minutes to complete. A one-to-one interview is a conversation between you and the researcher, where you will be asked questions in a meeting room in the hospital, to help us better understand what helped or prevented you from using your anti-snoring mouth guard regularly. The interview is quite flexible so that you can also ask questions for further clarification. Please be reassured that there is no right or wrong answers and we only want to gain a deeper insight of your treatment experience.

The researcher will use an audio-recording device to record the interview. Each participant will be given a unique and unidentifiable code, and recordings will be sent to a third party – Essential Secretary Ltd. - for transcription purposes. Once recordings are transcribed, the audio files will be deleted. All information that you provide will be kept confidential and anonymous.

What happens if I wish to leave the study?

You are free to withdraw from the study at any time without any reason. All the information collected will be stored safely. Once you withdraw from the study no further research information will be collected and if you specifically request, any previous information collected can be discarded.

Are there any disadvantages in not taking part?

No, your decision not to take part will not affect the care you are to receiving.

Are there any benefits in taking part?

By taking part in this study you will help us to better understand what factors are important in helping patients use their anti-snoring (sleep apnoea) mouth guard. This will in turn help us find ways to help future patients get the most out of their treatment.

What are the possible risks of taking part in the study?

There are no risks involved in this study.

Will my taking part in this study be kept confidential?

Queen Mary University of London is the sponsor for this study based in the United Kingdom. We will be using information from you and/or your medical records in order to undertake 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. Queen Mary University of London will keep identifiable information about you for 20 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, the information about you that we have already obtained will be retained. To safeguard your rights, we will use the minimum personally-identifiable information possible.

You can find out more about how we use your information at http://www.arcs.qmul.ac.uk/media/arcs/policyzone/Privacy-Notice-for-Research-Participants.pdf

NHS will collect information from you and your medical records for this research study in accordance with our instructions.

NHS will use your name, NHS number and contact details to contact you about the research study, and make sure that relevant information about the study is recorded for your care, and to oversee the quality of the study. Individuals from Queen Mary University of London and regulatory organisations may look at your medical and research records to check the accuracy of the research study. NHS site will pass these details to Queen Mary University of London along with the information collected from you and your medical records. The only people in Queen Mary University of London who will have access to information that identifies you will be people who need to contact you to confirm any missing data and invite you to partake in the qualitative study or audit the data collection process. The people who analyse the information will not be able to identify you and will not be able to find out your name, NHS number or contact details.

NHS will keep identifiable information about you from this study for 20 years after the study has finished according to Queen Mary University of London/Barts Health NHS Trust policy. The data will be archived in the Corporate Records Facility at 9 Prescot Street, London, E1 8PR.

What will happen to the results of this study?

In order to share the knowledge gained from the study, the findings will be published in a medical journal and presented at health conferences including voluntary and support sleep apnoea patient groups.

What if there is a problem?

Any problem that occurs during the study will be addressed appropriately. Please contact the chief investigator [contact below] to solve the problem immediately. If you remain unhappy and wish to complain formally, you can do this through the NHS complains procedure. Details can be obtained from: http://www.nhs.uk/choiceintheNHS/Rightsandpledges/complaints/Pages/NHScomplaints.aspx

In the event that something does go wrong and you are harmed during the research due to negligence, then you may have grounds for legal action for compensation against the sponsor of this study, Queen Mary university of London. The sponsor will compensate for injury caused directly by the procedure you received during your participation.

Who has reviewed the study?

This research project has been reviewed by a group of clinical researchers. In addition it will be looked at by an independent group of people, which includes both professionals and lay public, whose purpose is to review all NHS research to protect your interests, called a Research Ethics Committee.

Where can I obtain Alternative means of support?

Independent advice could be obtained from: Patient Advice and Liaison Service (PALS)

For Barts Health NHS Trust hospitals: Integrated for Royal London, patient Advice Liaison Service (PALS). Telephone: 020 3594 2040, e-mail address: pals@bartshealth.nhs.uk. Service is available Monday to Friday, 9.30am-4.30pm by appointment.

Thank you very much for taking the time to read about the research. If you take part, you can help us make a difference to others in the future.

Further information and contact details

To contact the Chief investigator of the study:

Professor Ama Johal, Dental Institute, The Royal London Dental Hospital
Phone: 0207 377 7686

Email: a.s.johal@qmul.ac.uk

If you would like to find out more about this study or arrange an appointment, please contact the Researcher:

Dr. Harishri Tallamraju, Dental Institute, 4th floor, The Royal London Dental Hospital

Email: h.tallamraju@qmul.ac.uk

Appendix 16 Consent from for the qualitative study

IRAS ID: 262092

Centre Number:

Study Number:

Participant Identification Number for this trial:

CONSENT FORM

Title of Project: Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea: A Randomized control trial

Name of Researcher:

	Please initial box
1. I confirm that I have read the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had 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 my medical notes and data collected during the study, may be looked at by individuals from NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records.	☐
4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers.	☐
5. I understand that the information held and maintained by-Queen Mary, University of London may be used to help contact me or provide information about my health status.	☐
6. I agree to take part in the above study.	☐

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature

Appendix 17 Topic guide

Topic Guide

Title of the study: Intervention to enhance adherence to mandibular advancement appliance in Patients with Obstructive sleep apnoea: A Randomized control trial

Introduction

- Presenting myself and my role in the study
- Welcome. Thank you for being here today. We would like to know about your perspective of what helps and hinders mandibular Advancement Appliance (MAA) usage, also known as Anti-snoring mouth guard.
- Would you mind reading the consent form and signing it?
- The interviewed will be recorded using a digital recorder, and you will be notified about the start and end of the recording. No personally identifiable information will be collected during the interview. Your participation is voluntary, and you are free to stop me at any time of the conversation.
- It is important to note that there are no right or wrong answers.

Do you have any questions before we start?

[Turn on the recorder]

Topics/Questions

1. Your understanding of Obstructive sleep apnoea
   - Obstructive sleep apnoea
   - Various treatments that the participant is aware of?
   - What experiences had you had with the previously prescribed treatments?
2. Why do you feel the anti-snoring mouth guard would be of use to you?
   - Had you heard of them or see one before?
   - Do you have any understanding of how they work?
3. Planned usage of anti-snoring mouthguard
   - How likely are you to continue the use of the anti-snoring mouthguard?
   - What would help or what can be done to ensure this?
   - Additional support
     - Follow-up Appointments
     - Telephone support
4. Other reasons that might have influenced the usage of the anti-snoring mouthguard
   - Lack of motivation
     - Self-motivation
     - Family & Friends
     - Health care workers
   - Social support
   - I didn't have to pay for the appliance
5. Other experiences concerning the treatment

Thank you for your time!

[Turn off the recorder]