Validation of a Novel Screening Tool for Obstructive Sleep Apnoea in Bariatric Surgery Candidates

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Validation of a novel screening tool for obstructive sleep apnoea in bariatric surgery candidates

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Statement of involvement

I confirm that the contents and ideas expressed in this thesis are my own and I have not previously submitted any of the work contained within it for any other award. I carried out all aspects of the research including the application for ethical approvals, recruitment, data collection and analysis. I received advice on the statistical analysis strategy from Mr Joseph Eliahoo of Statistical Advisory Service, Imperial College London. Mr Eliahoo also performed the sample size calculation for the pilot study described in chapter 4.

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Background information on HSST and the Doctor of Clinical Science

Higher Specialist Scientist Training (HSST) is a 5-year programme of professional development in leadership, expert clinical and scientific practice and research in the healthcare science setting. Development on the program consists of a blend of work-based professional training in a chosen speciality (respiratory and sleep physiology) culminating in a peer-assessed professional discussion (IAPS) to determine achievement of the standards of proficiency for Higher Specialist Scientists set by the National School for Healthcare Sciences and an underpinning professional doctorate, of which this thesis is a constituent part.

This thesis is submitted in partial fulfilment of the requirements for the award of Doctor of Clinical Science. 270 credits have already been examined and awarded through taught elements of the programme. 120 Credits at level 7 were obtained completion of Section A (Leadership and Professional Development) and 150 credits at level 8 were obtained from Section B (Specialist Scientific Clinical Program, Respiratory and Sleep Physiology). Section C consists of two parts which together make up the remaining 270 credits for the award. Section C1 has been examined and a report is included in Appendix 1. Details of the modules completed, credits obtained and academic level are shown in Table 1 below.

Although not a constituent part of the academic qualification, the IAPS is an integral part of HSST and demonstration of development to Consultant Clinical Scientist level. A copy of my feedback from the IAPS

assessment is included in Appendix 3 for the interested reader.

Table 1: Modules undertaken as part of the D.Clin.Sci

Module	Module title	Credits
Section A: Leadership and Professional Development (120 credits at level 7)		
A1	Professionalism and professional development in the healthcare environment	30
A2	Theoretical foundations of leadership	20
A3	Personal and professional development to enhance performance	30
A4	Leadership and quality improvement in the clinical and scientific environment	20
A5	Research and innovation in health and social care	20
Section B: Specialist scientific clinical program: Respiratory and sleep physiology (150 credits at level 8)		
B1	Advanced history taking, clinical and communication skills	15

B2	Clinical presentation and management of respiratory and sleep disorders -1	20
B3	Therapeutics	10
B4	Diagnostics and monitoring in respiratory and sleep physiology	15
B5	Contemporary issues in healthcare science (including bioinformatics, genomics and personalised medicine and patient and public involvement)	20
B6	Clinical presentation and management of respiratory and sleep disorders- 2	15
B7	Teaching, learning and assessment	20
B8	Interventions in respiratory and sleep physiology	15
B9	Adult Sleep Disordered Breathing and Respiratory Muscle Physiology	20

Section C: Doctoral research and innovation in clinical science (270 credits at level 8)

C1	Preparing the proposal	
C2	Research project	270

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List of abbreviations

AASM	American Academy for Sleep Medicine
AHI	Apnoea hypopnoea index
AIE	Adverse intraoperative event
AUC	Area under the curve
BMI	Body mass index
CPAP	Continuous positive airway pressure
CSA	Central sleep apnoea
DVT	Deep vein thrombosis
GORD	Gastro-oesophageal reflux disease
HSST	Higher Specialist Scientist Training
ICHNT	Imperial College Healthcare NHS Trust
MMU	Manchester Metropolitan University
NICE	National Institute for Health and Care Excellence
ODI	Oxygen desaturation index
OSA	Obstructive sleep apnoea
OSAHS	Obstructive
PAT	Peripheral arterial tonometry
P_{crit}	Critical closing pressure
PE	Pulmonary embolism
PLMs	Periodic limb movements
PSG	Polysomnography

RDI	Respiratory disturbance index
REC	Research ethics committee
RERA	Respiratory effort related arousal
RIP	Respiratory inductance plethysmography
RP	Respiratory polygraphy
SAE	Serious adverse event
SaO_2	Arterial oxygen saturation
SD	Standard deviation
SpO_2	Peripheral oxygen saturation
TST	Total sleep time

Abstract

Undiagnosed obstructive sleep apnoea (OSA) is increasingly recognised as a serious post-operative risk with bariatric surgery. Demand for pre-operative screening for OSA in bariatric surgery candidates is rising and there is a need for simple, cost-effective screening methods to mitigate the stain on Sleep Services. WatchPAT is a relatively new device, which uses peripheral arterial tonometry rather than airflow to estimate the apnoea hypopnoea index (AHI). While WatchPAT use is increasing in the general sleep clinic population it has not yet been validated in patients with a BMI >35, i.e. the target population in bariatric surgery. The studies described in this thesis aim to validate WatchPAT against the clinical gold-standard in patients on the bariatric pathway and to assess patient acceptability of WatchPAT. 28 bariatric surgery candidates (22 female/6 male, mean ± SD age 44.1 ± 11.6 years, BMI 45.7 ± 7.5 kg/m^2) wore WatchPAT 300 and Embletta MPR simultaneously for one night and the outcome measure, AHI was compared in the two devices. AHI was higher in WatchPAT than Embletta (Median (range) 23.5 (3.9-70.6) versus 11.7 (0.7-46.5) events per hour; z=-4.623, p=0.000). There was a strong positive correlation between WatchPAT and Embletta AHI measurements (r=0.849; p=0.000). Bland Altman plots revealed a systematic bias; differences diverging at higher AHI values. ROC plots were constructed for a range of AHI cut-offs; AUC was highest for an AHI ≥20 (0.986), ≥15 (0.947) and AHI ≥30 (0.979), while for AHI ≥5 the AUC was 0.850. 97% of respondents reported that WatchPAT would be acceptable to them if introduced into the bariatric surgery pathway. These results are similar to those in the non-bariatric sleep clinic population and suggest that

WatchPAT may suitable for use in bariatric surgery patients requiring screening for OSA though further larger scale studies are needed to confirm these findings before incorporating into clinical guidelines.

Thesis overview

This thesis will describe the validation of a novel diagnostic device (WatchPAT 300®, hereafter abbreviated to WatchPAT® for screening of obstructive sleep apnoea (OSA) in morbidly obese (BMI ≥35 kg/m^2) patients being screened prior to bariatric surgery. Chapter 1 is a general introduction to OSA and the relevance of screening in the bariatric surgery population. Chapter 2 is a critical review of the current literature validating WatchPAT® for the diagnosis of OSA. Chapter 3 is a general methods chapter, which describes principles and practical application of the devices and sensors used in subsequent chapters. The results are covered in chapters 4-6: Chapter 4 aims to assess inter-rater reliability of respiratory polygraphy scoring in the bariatric surgery candidates using a sample of data from the main study. Chapters 5 describes a small pilot study which lead to the main validation study described in chapter 6. Finally chapter 7 is a general discussion of the findings and implications for clinical practice.

Chapter 1: General Introduction

Chapter overview

This chapter will introduce the area of interest in this thesis and aims to provide some context on which the subsequent chapters will build. The chapter starts with a general introduction to obstructive sleep apnoea (OSA) including prevalence and symptoms. Normal anatomy and physiology of the upper airway from wake through to sleep are reviewed next, setting the context for a review of the pathophysiology of OSA and the role of chemo-receptors in the control of breathing. The next section briefly reviews the diagnostic methods and criteria to demonstrate the validity of respiratory polygraphy (RP) as a gold standard in this thesis. The review then covers the main risk factors for OSA, focussing more specifically on the role of obesity before moving onto a discussion around bariatric surgery, the risks and rationale for pre-operative screening in patients undergoing bariatric surgery, the clinical pathway and the challenges that arise in practice. Finally, the aims of the thesis are set out.

Obstructive sleep apnoea

OSA is a common condition with a variable symptom burden meaning that it is possible to have the condition without being aware. Data from the Wisconsin Sleep Cohort Study, a longitudinal study of the natural history of sleep-related breathing disorders in the general population, estimated the prevalence of OSA in middle aged adults to be 24% of males and 9% of females (Young et al., 1993). It is characterised by transient occlusion of

the pharyngeal airway during sleep, causing pauses in breathing (apnoeas and hypopnoeas) and loud snoring. A smaller proportion of patients (estimated 4% of men and 2% of women) experience symptoms sufficient to affect their quality of life (Young et al., 1993); referred to clinically as obstructive sleep apnoea hypopnoea syndrome (OSAHS).

The cardinal symptoms of OSAHS include unrefreshing sleep and excessive daytime somnolence (Schlosshan and Elliott, 2004). In addition, patients may suffer sleep disturbance caused by frequent nocturia (Romero et al., 2010), drenching night sweats (Arnardottir et al., 2013) and gastrointestinal reflux (Shepherd et al., 2011). Other commonly reported symptoms include impaired concentration, lethargy, reduced libido and depression (Douglas et al., 2013). The National Institute for Health and Care Excellence (NICE) recommends that continuous positive airway pressure treatment (CPAP) is offered to patients with moderate-severe OSAHS and to those with mild OSAHS where there are symptoms affecting their quality of life and when lifestyle inventions alone are not considered appropriate (NICE, 2021).

Normal anatomy and physiology of respiration

The anatomy of the respiratory system consists of a number of structures through which air passes as it moves from atmosphere to the alveoli of the lungs where gas exchange occurs. The lungs are situated within the thoracic cage, an enclosed system, bounded by the diaphragm and the lung pleura (Kumar and Clark, 2002). During inspiration, air is drawn in through the nares to the nasal vestibule which takes up the anterior third of the nose

(Kumar and Clark, 2002) and past the nasal turbinates which filter, warm and humidify the air (Sahin-Yilmaz and Naclerio, 2011). Air then travels through the pharyngeal airway, a flexible tube like structure which communicates with the nose (nasopharynx) and mouth (oropharynx) and is bounded inferiorly by the larynx, which contains the vocal cords (Kumar and Clark, 2002). Below the larynx is the trachea which splits at the level of the carina into the left and right main bronchi, with each bronchus dividing further into smaller and smaller bronchiole, with the smallest, termed respiratory bronchioles, containing the alveolar ducts which house the alveoli and take part in gas exchange (Widmaier et al., 2006).

The lungs are situated within the thorax, a closed compartment bounded by the diaphragm which separates it from the abdomen and connective tissues and muscles of the neck (Widmaier et al., 2006). During inspiration, the diaphragm descends and flattens and at the same time anterior and superior movement of the rib cage increases the volume of the thorax to generate a negative intrathoracic pressure relative to atmosphere (Wade, 1954). The pressure gradient that ensues allows air to flow into the lungs. The pharyngeal airway is a collapsible tube and therefore susceptible to changes in the transmural pressure during the respiratory cycle (Kubin and Davies, 2012). Upper airway dilator muscles including the genioglossus and sternohyoid help to stabilise the upper and prevent collapse during the respiratory cycle (Schäfer, 2006). The critical closing pressure (p_{crit}) describes the transmural pressure at which the pharyngeal airway will collapse. To maintain airway patency throughout the respiratory cycle, the P_{crit} must be lower than the transmural pressure exerted on the airway during

inspiration (Smith et al., 2012). Schwartz et al. (1988) measured the P_{crit} of healthy individuals and reported a mean ± SD of -13.3 ± 3.2 cm H_2O. By contrast OSA patients have a P_{crit} which is above atmospheric pressure and can be as high as 10 cm H_20 (Smith et al., 2012). The positive P_{crit} in OSA patients means that in its passive state airway patency is compromised during normal respiration (Gleadhill et al., 1991).

Pathophysiology of OSA

OSA is the result of a complex interplay of abnormal neuromuscular response, anatomical abnormalities and modifiable risk factors. The key pathophysiology is illustrated in figure 1.

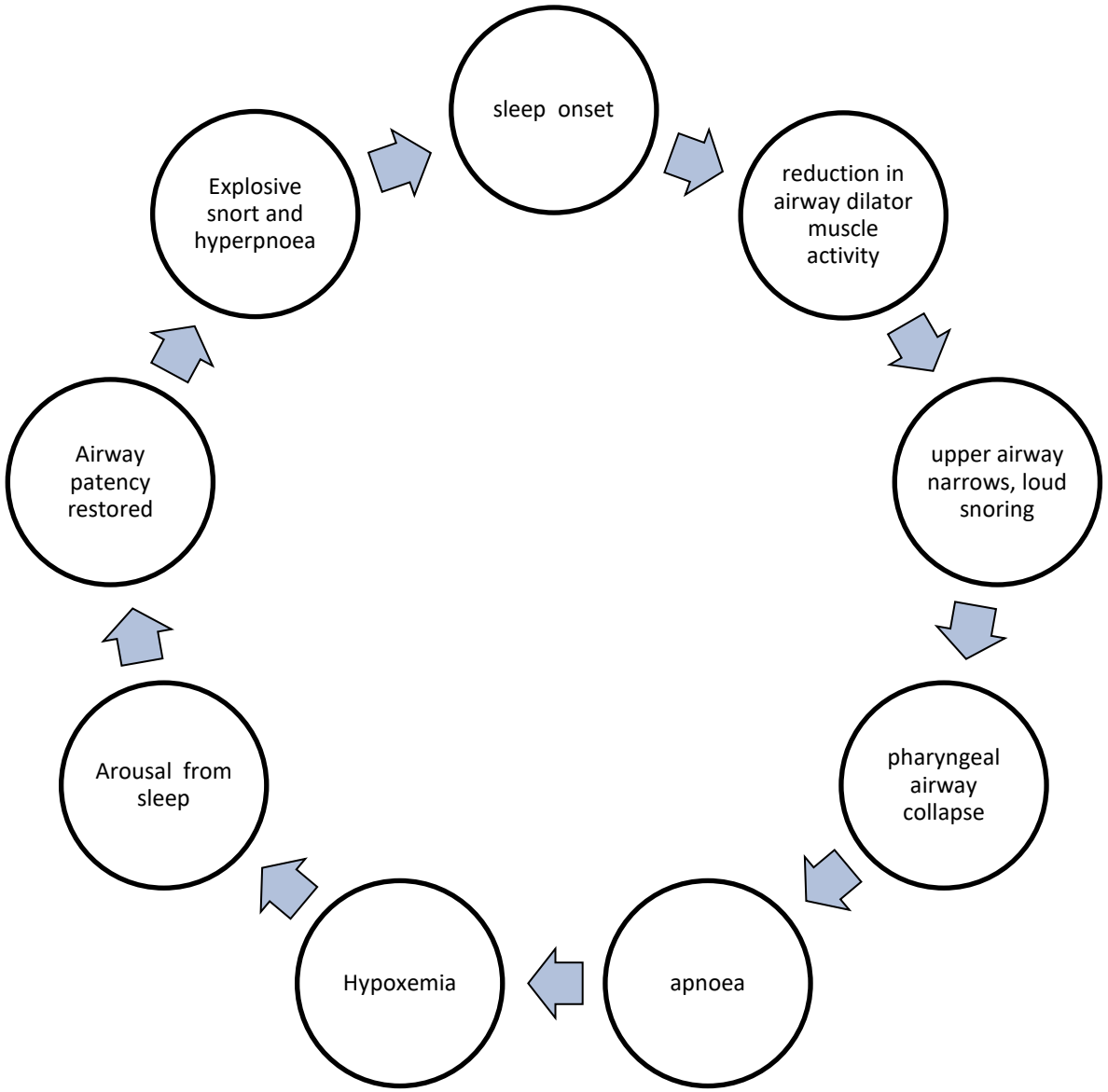

Figure 1: Schematic showing the pathogenesis and consequences of OSA

The figure shows how the sleep onset is associated with a reduction in neuromuscular activity, which leads to pharyngeal airway occlusion, apnoea and hypoxemia in vulnerable patients. Arousal from sleep triggered by resulting hypercapnia restores neuromuscular drive and results in airway re-opening, usually associated with an explosive snort and hyperpnoea followed by resumption of tidal breathing.

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Mezzanotte et al. (1992) showed that the upper airway dilator muscle activity is increased during wake in patients with OSA. Furthermore, Brown et al. (2013) imaged the pharyngeal airway of awake participants with and without OSA and found a negative correlation between apnoea hypopnea index (AHI; the standard measure of OSA severity) and lateral movement of the pharyngeal airway walls during inspiration in wake, suggesting that patients with OSA have an abnormal neuromuscular response to the transmural pressure changes during relaxed breathing. In additional to neuromuscular abnormalities, patients with OSA have an increased volume of soft tissues in the upper airway, which presents an increased mechanical load (Schwab et al., 2003).

Compensatory mechanisms such as increased upper airway dilator activity during wake (Mezzanotte et al., 1992) maintain adequate airway patency through the respiratory cycle while the patient is awake but onset of sleep with the associated global reduction in neuromuscular activity and increased mechanical load exceeds the threshold for P_{crit} and promotes airway narrowing and collapse (Deegan and McNicholas, 1995). The occluded airway prevents normal passage of air causing a transient pause (apnoea) or partial reduction (hypopnoea) in airflow. Respiratory efforts are usually maintained during the event (DeBacker, 2006). Apnoeic events are frequently associated with a drop in the blood oxygen saturation and terminated by an arousal from sleep, causing an abrupt re-opening of the pharyngeal airway (DeBacker, 2006). In OSA, this cycle repeats throughout the night leading to fragmented sleep and intermittent hypoxia (figure 1).

The role of chemoreceptor sensitivity in the pathophysiology of OSA in morbid obesity

Chemoreceptors play a vital role in sustaining blood gas tensions within a narrow physiological range. Peripheral chemoreceptors are located in the carotid body and arortic body. A drop in partial pressure of oxygen in the blood flowing past the peripheral chemoreceptors triggers an outflow of sympathetic activation (Bock, 2018) causing an increase in tidal volume and respiratory rate, peripheral vasoconstriction to divert blood flow to essential organs and increased cardiac output. Central chemoreceptors are located in the medulla oblongata in the brainstem and respond to changes in the arterial partial pressure of CO_2 ($paCO_2$). Increased $paCO_2$ results in increased ventilation while decreases trigger a decrease in ventilation.

In individuals with obesity hypoventilation syndrome, the ventilatory response to hypercapnia is blunted with the slope of the response being about 1/3 of that of the normal response (Zwillich et al., 1975). Compared with normal weight Individuals, obese patients also have an increased rate of oxygen consumption and carbon dioxide production which is usually compensated with an increased respiratory drive at baseline (Shetty and Parthasarathy, 2015). Morgan et al. (1995) found that combined hypercapnia and hypoxia resulted in long-lasting activation of the sympathetic nervous system which persisted even after eucapnia had been restored. Thus abnormalities in the chemoreceptor sensitivity is likely to be an important factor in the development of sleep disordered breathing in patients with morbid obesity and sustained activation of the sympathetic nervous system in this patent group may reduce the signal to noise ratio when measuring

sympathetic nervous system-mediated changes in the peripheral arterial tone as a measure of OSA.

Diagnosis

Diagnosis of OSA is made by analysing changes in physiological signals measured during sleep. The gold standard sleep study is polysomnography (PSG) (Kapur et al., 2017); a comprehensive test usually carried out on an in-patient basis and involving multiple channels including EEG, EOG, submental and tibialis anterior EMG, ECG, body positon and measures of respiration (typically a measure of air flow and/ or temperature at the nose, snoring, respiratory effort, pulse and oxygen saturation). However, in clinical practice, access to PSG is limited and so respiratory polygraphy (RP) is widely accepted as an alternative and has recently been incorporated into guidelines (Collop et al., 2007). RP has fewer channels than PSG and the equipment is portable and relatively simple to use so the test can be carried out at home. The channels are limited to those related to respiration (airflow, snoring, respiratory effort, pulse, oxygen saturation) and body position.

The scoring criteria for minor respiratory events such as hypopneas is altered slightly when using RP to reflect the fact that EEG is not measured: In RP, a hypopnoea can only be scored if it is associated with an oxygen desaturation from baseline of ≥3% (Berry et al., 2018) while if PSG is used, an event may be scored if it results in arousal from sleep (defined as a discernible change in EEG lasting ≥3 seconds) even if the event does not meet the desaturation criteria (Brown et al., 2013). Due to the differences in scoring criteria and potential for events not

associated with an oxygen desaturation to be missed with RP, it is important to understand the impact on the final AHI. A brief discussion of the literature pertaining to the relationship between AHI derived from RP and that from PSG will follow.

Masa et al. (2011) conducted a multi-centred randomised controlled trial in which 359 patients underwent in – laboratory PSG with concurrent RP and home RP in a random order. They reported that the AHI was lower for RP compared to PSG when both tests were conducted concurrently in the laboratory and for home RP compared to PSG on a separate night. However, ROC curves for AHI ≥5, ≥10 and ≥15 showed high levels of sensitivity and specificity (0.917, 0.883 and 0.891 for AHI ≥5, ≥10 and ≥15 respectively). Other studies have used correlation to compare RP and PSG and have consistently reported strong positive correlations ranging from r=0.979 to 0.996) (Ng et al., 2010, Tiihonen et al., 2009, Dingli et al., 2003). Taken together, these studies suggest that RP is a valid tool for diagnosis of OSA.

A second question is whether oximetry alone may be sufficient for diagnosis of OSA. One study investigated the correlation between AHI and 4% ODI at different severity levels and reports rather modest correlations, especially at lower severity levels (r-0.411, 0.589, 0.600 and 0.739 for normal, mild, moderate and severe AHIs respectively) (Temirbekov et al., 2018).

Ernst et al. (2016) investigated the relationship between AHI and 3% ODI in obese patients and found a progressive increase in the difference between AHI and ODI with increasing obesity levels; AHI being lower than 3% ODI. This may be partly explained by lowered pH in the blood of

morbidly obese patients due to hypoventilation which reduces the binding affinity for oxygen molecules to haemoglobin. This results in rapid desaturations in relation to small changes in ventilation which would not usually cause a desaturation in normal weight individuals. These data would suggest oximetry alone is not sufficiently accurate for the diagnosis of OSA in morbidly obese patients.

Risk factors

Obesity is one of the most important modifiable risk factors for OSA and will be dealt with in more detail in the section below. Gender is also an important factor. The prevalence in males is more than double that in pre-menopausal females (Bixler et al., 2001). Craniofacial abnormalities also confer a relative risk with a higher prevalence amongst those with acromegaly (Rosenow et al., 1996), retrognathia (Alamoudi, 2006), inferior positioning of the hyoid (Genta et al., 2014), basal tongue hypertrophy (Zucconi et al., 1992), reduced mandible length (Battagel and L'Estrange, 1996) and longer pharyngeal airway length (Neelapu et al., 2017, Malhotra et al., 2002).

Sleep and OSA in morbid obesity

The role of obesity in the pathogenesis of OSA complex. Although excess weight is commonly implicated in the development of OSA, the relationship is complicated; fat distribution appears to be more important than BMI alone. Martinez-Rivera et al. (2008) measured the BMI and waist to hip ratio in sleep clinic referrals with clinically suspected OSA. They found no difference in BMI between the two groups but a 2.6 times increased risk of having OSA when

the waist to hip ratio was >1 in men or >0.85 in women. Imaging studies have demonstrated that fat distribution in the abdominal wall (Cetin et al., 2019), in particular the L2-L3 and L3-L4 regions (Turnbull et al., 2018) and the retro-palatal region of the upper airway (Li et al., 2012) are important risk factors for OSA. Fatty deposits surrounding the upper airway, in particular the volume of the soft palate, tongue and lateral walls of the upper airway also appear to play an important role (Turnbull et al., 2018).

The gut hormone leptin also appears to play an important role in both the regulation of feeding (Friedman, 2019) and the development of OSA (Imayama and Prasad, 2017). It is predominantly produced by white adipose tissue (Havel, 2000) and studies have shown higher concentrations of leptin among obese patients compared to normal weight controls (Considine et al., 1996). Furthermore, Alagna et al. (2003) found that leptin levels reduced post bariatric surgery.

Studies have also shown that leptin is important in OSA. Öztürk et al. (2003) found a positive correlation between AHI and plasma leptin and Phillips et al. (2000) have argued that OSA may pre-dispose patients to weight gain through leptin resistance. Furthermore, Campo et al. (2007) found a reduced hypercapnic ventilatory response in patients with high plasma leptin concentrations irrespective of body fat percentage, suggesting that this could be an important mechanism linking leptin to obesity and OSA.

Bariatric Surgery

Bariatric surgery is indicated in patients with severe obesity (BMI ≥40 kg/m2) or >35 kg/m2 in association with

significant comorbidities such as hypertension or diabetes after non-surgical options including Tier 3 weight loss support have been tried but the patient has not achieved or maintained clinically significant weight loss (NICE, 2014). The patient must also be medically fit for surgery and committed to long-term follow-up (NICE, 2014). Studies have shown a reduction in the incidence of hypertriglyceridemia, diabetes and hyperuricemia at two and ten years post bariatric surgery and a reduction in HDL cholesterol at two years post-surgery compared to matched controls (Sjöström et al., 2004).

There are several different types of bariatric surgery which typically bring about weight loss through either restriction, malabsorption or a combination of the two. The most commonly performed procedures on the patients included in this thesis were laparoscopic sleeve gastrectomy and laparoscopic roux-en-Y and a brief overview of these procedures, along with another common procedure, fitting of a laparoscopic adjustable gastric band will follow.

Sleeve gastrectomy involves surgically removing 80% of the stomach, thus reducing its capacity. In addition, studies have shown a significant reduction in the hunger hormone, ghrelin with further suppression after a meal (Karamanakos et al., 2008) which is likely to play an important role in weight loss with this type of surgery. Studies have shown an increase in prevalence of gastroesophageal reflux disease (GORD) following sleeve gastrectomy (El-Hadi et al., 2014) and so in laparoscopic roux-en-y is often the preferred procedure in patients who are at risk.

Laparoscopic roux-en-Y works by combining restriction and malabsorption: The stomach and small bowel are both

divided, creating a small stomach pouch which is connected to the small bowel further down the digestive tract resulting in reduced capacity for caloric intake and decreased absorption as the first part of the small bowel is bypassed.

Gastric banding involves the placement of a band just below the gastroesophageal junction and inflated to restrict the stomach capacity and therefore bring about weight loss by limiting caloric intake. Although it is considered the safest of the bariatric procedures, adverse events such as pouch enlargement, band slippage, band erosion, port breakage and port-site infection have been reported (Eid et al., 2011).

Perioperative risks in bariatric surgery

Although bariatric surgery has an excellent safety record, owing to advanced laparoscopic techniques (Reoch et al., 2011) there are some risks which will be discussed here.

In a longitudinal study of adverse intraoperative events (AIEs) in 5882 patients undergoing bariatric surgical procedures over a 4- year period, Greenstein et al. (2012) report a AIE rate of 5% across all procedures; the greatest risk of AIE occurred with open Roux-en-Y gastric bypass (7.1%) while laparoscopic Roux-en-Y bypass had a lower AIE rate of 5.5% and the lowest rate of AIEs (3%) was reported with laparoscopic adjusted gastric banding. The incidence of AIE from the LABS cohort (Greenstein et al., 2012) are shown in Table 2.

Table 2: Incidence of adverse and serious adverse intraoperative events during bariatric surgery from 2 databases.

AIE category	**Rate of complication**
All organ injuries	1.6
Bowel injury	0.9
Liver injury	0.4
Spleen injury	0.2
Blood vessel injury	0.1
Anaesthesia events	0.9
Instrument/ equipment failure	0.8
Revision anastomosis/ stricture	0.6
DVT/ PE	0.4
Death	0.3

Patients with an AIE were also found to have an increased relative risk of post-operative complications compared to those without AIE (8.8 versus 3.8%) (Greenstein et al., 2012). 30- day mortality is generally low in bariatric surgery but a history of deep vein thrombosis (DVT), pulmonary embolism (PE), OSA or reduced functional status have all been shown to be independently associated with an increased risk of a major adverse event (Flum et al., 2009).

In a retrospective audit of surgical complications in 711 patients who had a laparoscopic Roux-en-Y gastric bypass Schürner et al. (2018) found that 34% of patients had surgical complications. Of these, 37% were anaesthesia-related. The most common anaesthesia-related adverse event was post-operative nausea and vomiting which affected 34% of patients. Intubation or extubation related complications were the second most common event, effecting 6%. Intubation events included aspiration, bronchospasm, desaturation, epistaxis and misplacement of the tube (all >1% of the overall adverse events). Extubation events included post-operative reintubation due to pulmonary decompensation and bleeding from the surgical anastomosis. 4 patients experienced adverse drug reactions including hypotension, a rash and bronchospasm in one patient. They reported that patients over 35 and those with volatile anaesthetics had a significantly lower incidence of anaesthetic complications.

Peri- and post-operative adverse events with bariatric surgery in patients with comorbid OSA

OSA is highly prevalent in patients undergoing bariatric surgery. For example, Peromaa-Haavisto et al. (2016) carried out a multi-centre study screening bariatric surgery patients and report a prevalence of 71% meeting the criteria for OSA (apnoea-hypopnoea index on cardio-respiratory polygraphy ≥5 events per hour). In line with general population data, the prevalence was higher in males and increased with age.

It is widely cited in the anaesthetics literature that undiagnosed or untreated OSA confers a substantial additional risk of complications during bariatric surgery,

though evidence in the form of randomised controlled trials is limited.

A retrospective analysis of post-operative complications and mortality in 91,028 bariatric surgery patients with and without OSA showed an increased prevalence of post-operative complications such as the need for emergent, endotracheal intubation in patients with OSA (Mokhlesi et al., 2013). However, when the authors compared all patients who experienced this complication, they found that mortality was lower amongst those with OSA compared to those without.

In a retrospective study of 797 adult patients undergoing bariatric surgery who had undergone pre-surgical screening for OSA with PSG, 618 patients met the criteria for OSA (any severity) and 244 had severe OSA (Vasu et al., 2012). Although 32.5% of patients experienced at least one post-operative complication, the authors did not find an association of complications with severity of OSA. However the majority of these patients were treated with CPAP which might have reduced the risk if there is one.

Kong et al. (2016) studied the peri-operative complications in patients with known OSA (AHI>5) who were not treated with CPAP and reported that 14.9% of these patients developed pot-operative pulmonary complications compared to 2.95% of those patients who were treated with CPAP. However the sample size on the two groups was unequal; the non-CPAP group having just 47 patients from a population of 352 patients.

The mechanism behind the increased risk may be related to a compound effect of anaesthesia and physiological differences in patients with OSA. Anaesthesia has been

shown to reduce upper airway dilator activity, thus increasing the p_{CRIT} in a dose-dependent manner (Eastwood et al., 2005) whilst at the same time, reducing the protective arousal response and the ventilatory response to hypoxemia (Knill and Clement, 1984).

Questionnaire based tools, such as STOP-BANG have been used to attempt to assess likelihood of OSA in bariatric surgery patients. However, the sensitivity and specificity of these in the context of the bariatric population has been shown to be rather modest (Glazer et al., 2018). The desire to mitigate any potential risk has led to the recommendation to refer any patient who may be at risk of OSA to a Sleep Clinic for more formal screening (Sareli et al., 2011, de Raaff et al., 2017) and perioperative treatment with CPAP in patients with a positive sleep study (de Raaff et al., 2017). This places a substantial burden on sleep clinic resources and on the patient themselves. A review of data from the sleep service at ICHNT over a 9-month period to March 2020 shows 5.2% of respiratory polygraphy (RP) tests carried out were from patients referred for pre-operative screening prior to bariatric surgery (unpublished data). With increasing levels of obesity globally and almost a third of the global adult population now classified as overweight or obese (Chooi et al., 2019), the burden on sleep service can be expected to increase.

Challenges with screening in bariatric surgery candidates

Unlike a general sleep clinic population who seek help because they have concerns about their sleep or sleep quality, the bariatric surgery population often do not

perceive themselves to have a problem with their sleep, or at least this is not the reason that they have sought help. The diagnostic pathway for bariatric patients referred for OSA screening can be lengthy (figure 2) and may feel like an additional burden for patients who are typically referred to multiple other specialities for screening and investigation as they are prepared for surgery. As such, anecdotal clinical experience would suggest that their motivation to undergo sleep studies is often low.

Furthermore, for patients with a positive sleep study, the mainstay of treatment is CPAP, which works by applying positive air pressure (relative to atmospheric pressure) via a closely fitting mask, which acts as a pneumatic splint and maintains pharyngeal airway patency (Sullivan et al., 1981). This tends to be poorly tolerated by asymptomatic patients (Weaver et al., 2012). Compliance to CPAP treatment in patients diagnosed as part of a pre-operative screen has been reported to be low (Guralnick et al., 2012) and this is also reflected in our own clinical experience with bariatric surgery patients.

Undergoing a diagnostic sleep study requires the patient to wear a number of sensors on their body overnight while they sleep. A number of respiratory polygraphy (RP) monitors are on the market to serve this purpose and most involve having a monitor strapped to the body along with bands around the thorax and abdomen to measure respiratory efforts, an oximeter probe on the finger and one or more sensors in or around the nose and mouth to measure breathing. The device used at ICHNT and in this study is the Embletta MPR® (hereafter abbreviated to Embletta® and shown in figure 3). This can feel uncomfortable and restrictive for some patients and is

particularly burdensome for bariatric patients who often complain of insomnia and disturbed sleep (anecdotal observations). Although the test can be carried out at home, it requires cooperation from the patient to obtain a good quality recording and anecdotal evidence suggests that failure rates tend to be relatively high in this population.

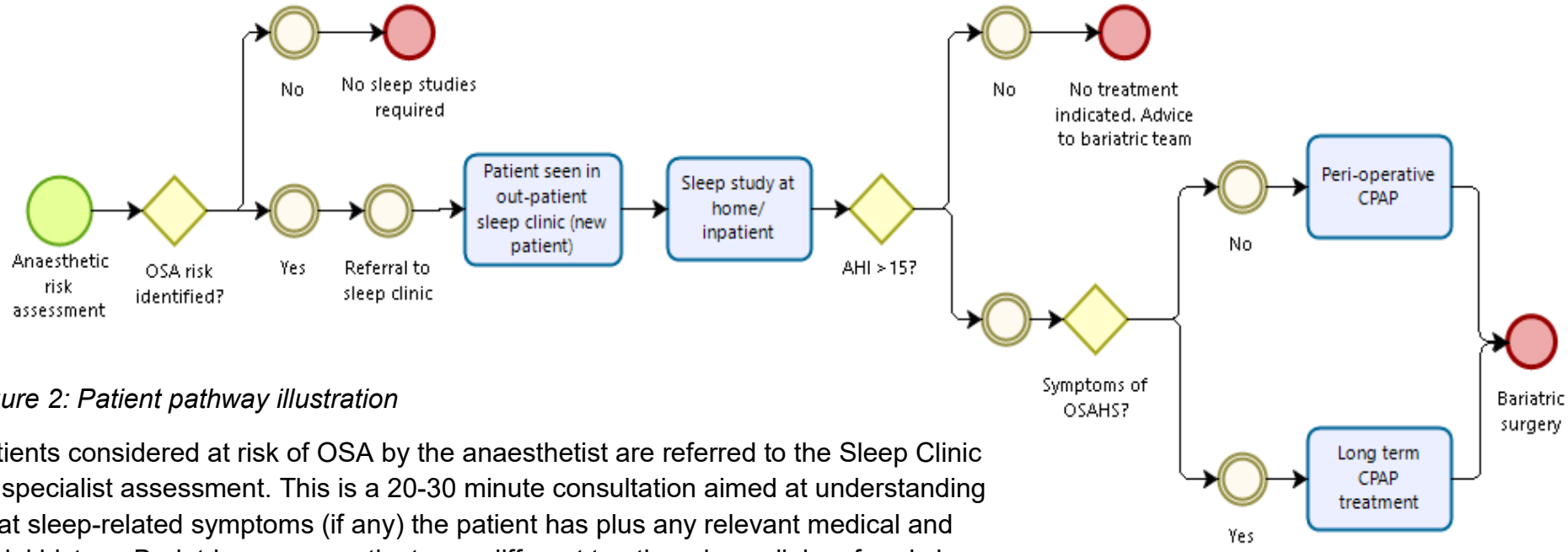

Figure 2: Patient pathway illustration

Patients considered at risk of OSA by the anaesthetist are referred to the Sleep Clinic for specialist assessment. This is a 20-30 minute consultation aimed at understanding what sleep-related symptoms (if any) the patient has plus any relevant medical and social history. Bariatric surgery patients are different to other sleep clinic referrals in that CPAP will usually be prescribed if moderate to severe OSA (AHI≥15 if found) is found but the clinic appointment allows us to assess whether the patient would benefit from long-term CPAP or peri-operative CPAP only. All patients have a sleep study at home which requires visits to collect and return the equipment and those with a positive sleep study a attend to be started on CPAP and have monthly follow-up as they become established on treatment (long-term patients progress to annual follow-up once established).

Historically, consensus guidelines stipulated that where home sleep study devices are used, these should be limited to uncomplicated patients with a high pre-test probability of OSA and the device must measure airflow, respiratory effort and blood oxygen saturation (Collop et al., 2007). However, the latest guideline recognises peripheral arterial tonometry (PAT) as an alternative to traditional flow devices in uncomplicated patients with a high pre-test probability of OSA (Kapur et al., 2017).

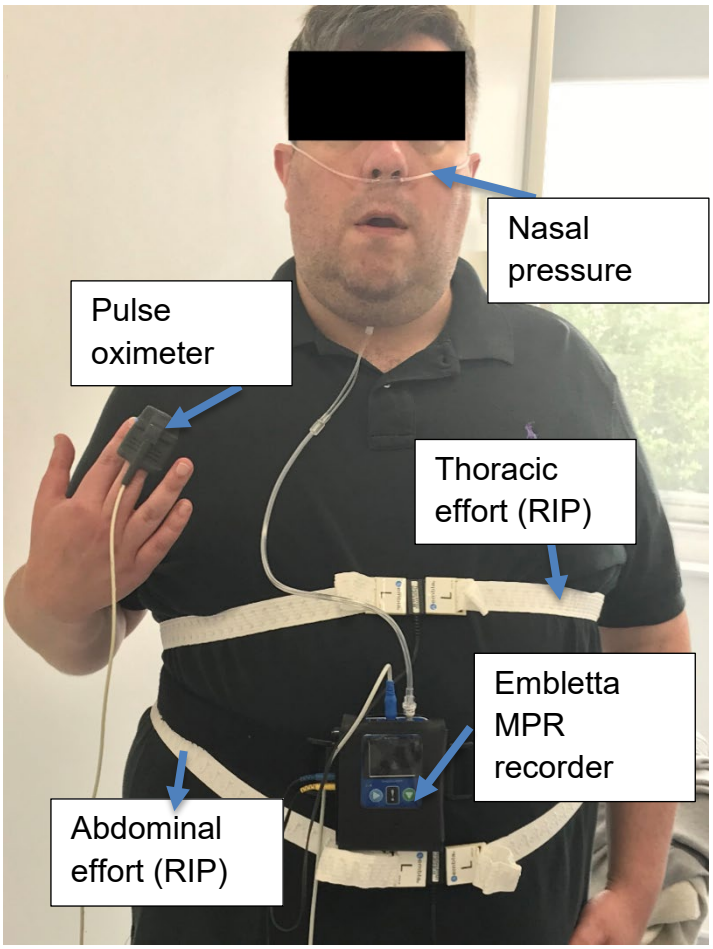

Figure 3: A volunteer wearing the Embletta® MPR

The volunteer is wearing a nasal cannula measuring pressure at the nose (airflow and snoring are derived from this signal and allow the identification of apnoeas and hypopneas), flexible RIP bands around the thorax and abdomen which measure breathing efforts used to distinguish obstructive and central apnoeas, and a pulse oximeter on the finger which makes continuous measures of the oxygen saturation and pulse. All signals are integrated in the recording monitor which is strapped to the patient's chest.

WatchPAT® is a comparatively simple device which uses PAT, body movements and snoring to diagnose OSA. With just 3 sensors (see figure 4) and a low failure rate, it is potentially an attractive option for rapid screening in the bariatric population. However, despite extensive validation of the technology, it has not previously been systematically studied in patients with high BMI (>35 kg/m^2) which is typical of the bariatric surgery population (see chapter 2 for further details).

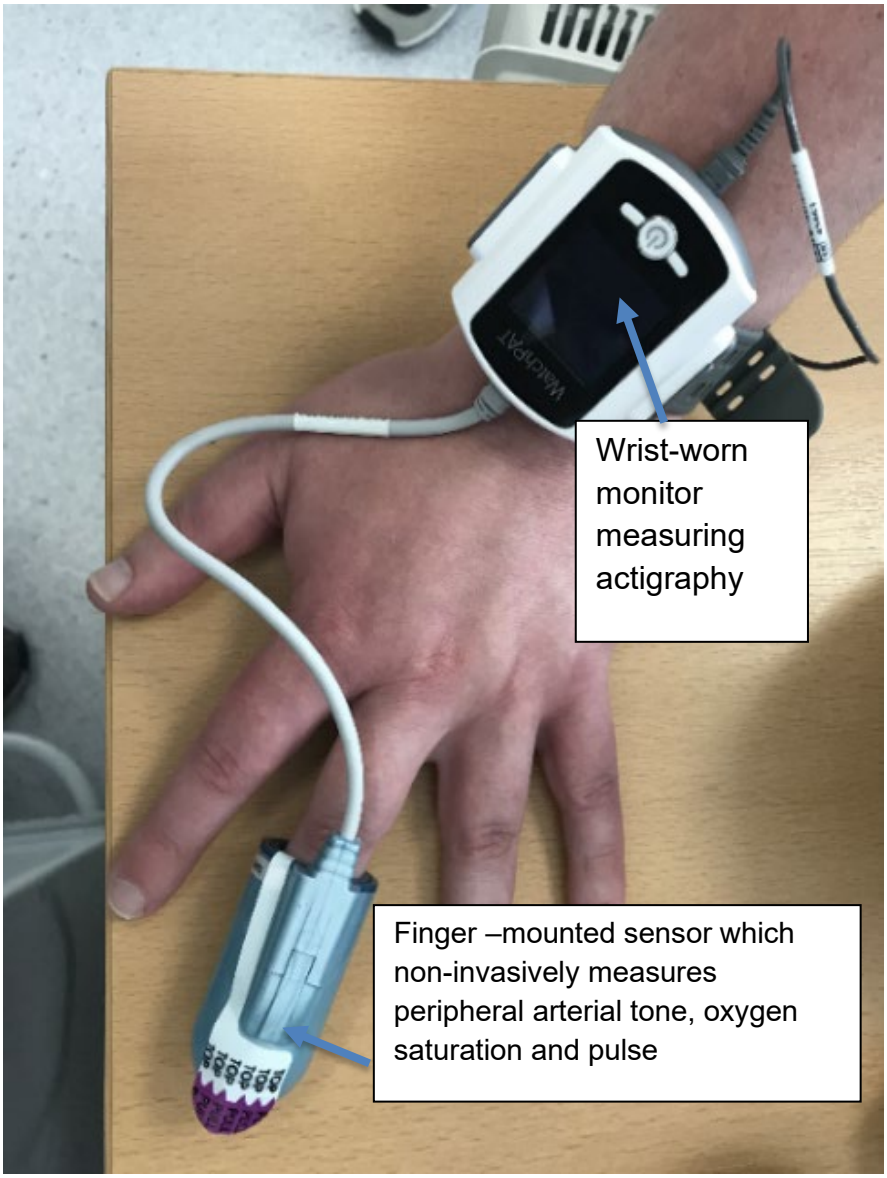

Figure 4: A volunteer wearing WatchPAT 300®

WatchPAT® consists of a finger-mounted sensor which non-invasively measures arterial tone, oxygen saturation and pulse, a wrist-watch style device measuring movement (actigraphy) and a small sensor on the chest which measures snoring and body position (not shown). The device is less restrictive with fewer sensors and may be better tolerated than the Embletta®.

Aims of the thesis

Referrals for OSA screening prior to bariatric surgery represent a unique patient group which is distinctly different from those referred via their GP due to sleep-related symptoms. Clinical experience has shown that they are less likely to present with typical symptoms of OSA and they often complain of discomfort with the Embletta®. Furthermore, the Embletta® has multiple sensors are requires engagement from the patient to set the equipment up correctly and obtain a technically acceptable recording.

WatchPAT® is a relatedly new device which uses changes in peripheral arterial tone to identify arousals from sleep that are associated with the termination of apnoeas and hypopnoeas rather than measuring the airflow directly. Its simplicity and automated scoring algorithm make it a potentially attractive alternative to the current clinical standard for screening in the bariatric surgery population with the potential to save time and improve outcomes for this hard to reach population. However as chapter 2 will discuss, whilst there is a growing body of literature validating the WatchPAT® in patients with a high clinical suspicion of OSA, the device hasn't yet been validated in the bariatric surgery population. Furthermore, the majority of studies carried out to date have used PSG as the gold standard comparator. Whilst PSG remains the usual choice of test in a research context, the more commonly used test in a clinical setting is RP (Embletta®).

The aims of this thesis are to:

1. Test the validity of a device based on PAT technology (WatchPAT®) for the diagnosis of OSA in a previously un-validated group; patients being worked up for bariatric surgery, using the clinical standard test, RP (Embletta®) as the gold standard comparator.
2. Assess the acceptability of WatchPAT® to patients on the bariatric surgery pathway.

Chapter 2 – A Critical review of the WatchPAT® validation literature

Introduction

Diagnosis of OSA has until recently required some direct measurement of airflow along with oxygen saturation (SpO_2) as a minimum (Berry et al., 2018). However, in the most recent edition of the American Academy for Sleep Medicine (AASM) manual, home sleep apnoea tests using level 4 devices (peripheral arterial tonometry (PAT), SpO_2 and actigraphy) have been approved for use for the diagnosis of OSA in uncomplicated patients (Berry et al., 2018), paving the way for cheaper and simpler screening.

This chapter will critically review the validation literature pertaining to the use of PAT technology in the form of the WatchPAT® device (Itamar Medical, Israel) in the diagnosis of OSA. The main question of interest for this review is how well measures of OSA (AHI or respiratory disturbance index, RDI) made by WatchPAT® agree with the more traditional gold standard, PSG or an acceptable flow-based device (respiratory polygraphy, RP).

Methods

A search using PubMed was conducted using search terms [WatchPAT] and [peripheral arterial tonometry AND sleep] followed by hand searching of studies cited in the literature generated from these two searches. Peer-reviewed original articles available in full text and written in English were included in the review. Any model of WatchPAT® was considered for inclusion provided all other criteria were met. Studies were limited to those including

adult patients or healthy volunteers. Studies comparing only sleep staging or non-respiratory parameters were not included in this focussed review.

The initial search revealed 80 results. The results were scanned for duplicates using the built-in duplication detector within Endnote (Version X9) which identified five duplicates. Two further duplicates where the same data had been reported twice were identified on manual review. After exclusion of studies that did not meet the criteria, 34 studies were selected for critical review (Figure 5). Table 3 summaries the studies where AHI has been compared between WatchPAT® and PSG or RP.

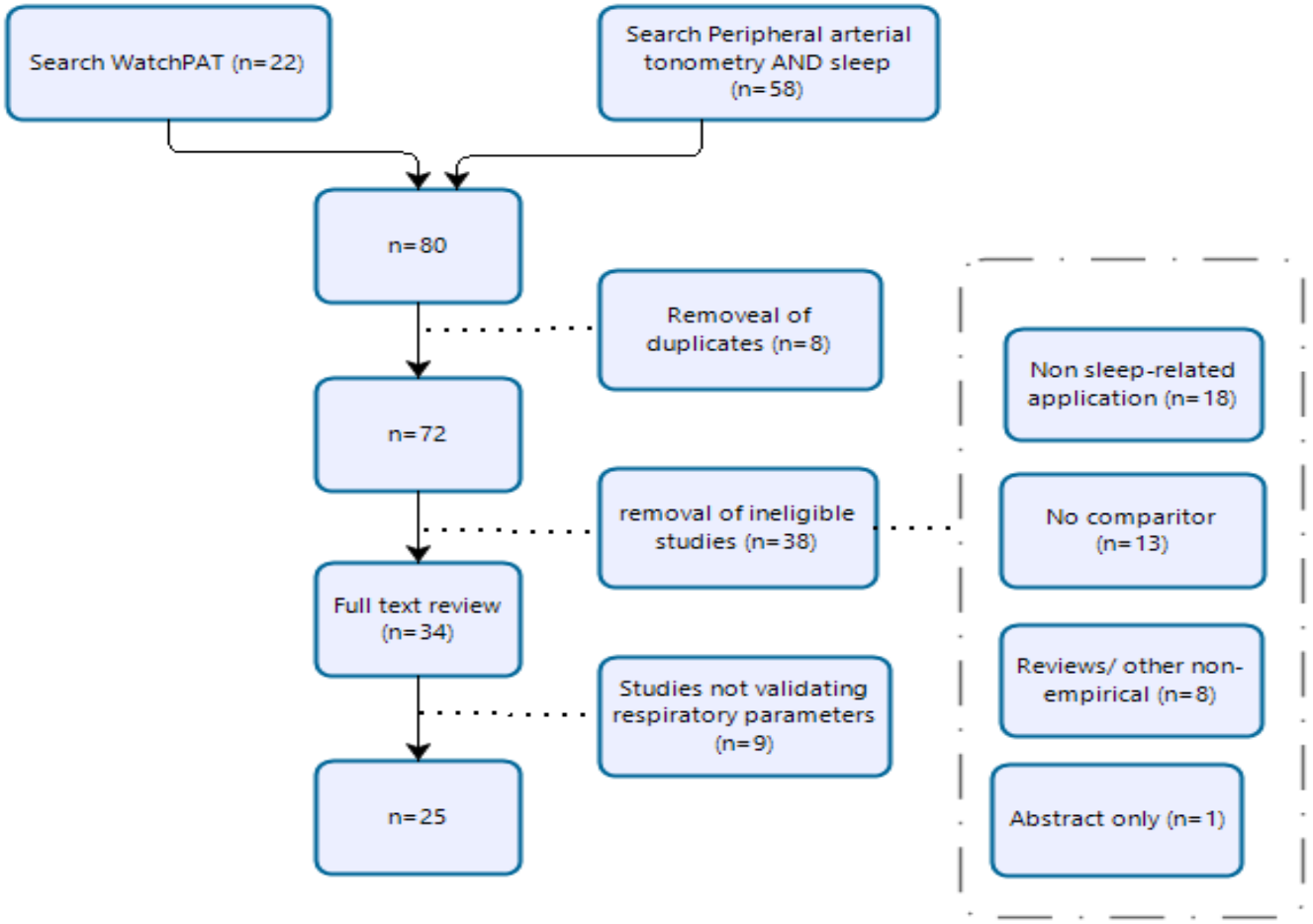

Figure 5: Literature search strategy

A semi-systematic approach was used to try to capture relevant literature. The purpose of the search was to establish whether any prior work had been done to validate WatchPAT in bariatric surgery patients. PAT technology is used in a wide range of applications outside of sleep and therefore in order to focus the search on relevant articles, word “sleep” was added. WatchPAT was also used as a separate search term as the WatchPAT device is the only device of this nature currently being marketed and many of the validation papers use the name of the device in the title

Table 3: Summary of evidence

Reference	N	BMI	Correlation for AHI	AUC for AHI 15/ hr*
Ayas et al. (2003)	30	31.0 ± 7.6	0.87	0.86ǂ
Bar et al. (2003)	135	26.8 ± 5.5	0.88	0.87ǂ
Boyd et al. (2016)	28	36.1 ±7	0.871	-
Ceylan et al. (2012)	51	29.4 ± 4.0	0.941	-
Choi et al. (2010)	25	26.2 ± 2.6	0.94	-
Gan et al. (2017)	20	27.2 ± 5.5	0.94	-
Ioachimescu et al. (2020)	500	31.6 (IQR:28.0-35.9	0.80	-
Jen et al. (2020)	33	28± 7	0.85	0.885
Kinoshita et al. (2018)	61	26.5 ± 4.4	0.69	0.84 □
O'Brien et al. (2012)	31	31.9 ± 8.1	0.76	0.96 Ł

Onder et al. (2012)	56	30.27 ± 5.8 (young) and 30.81 ± 3.22 (old)	0.92	-
Pang et al. (2007)	37	34.6 (21.2-46.8)	0.9288	-
Penzel et al. (2004)	21	-	0.89	-
Pillar et al. (2020)	84	29.8 ± 5.7	0.873 (central AHI 0.799)	0.866
Pinto et al. (2015)	30	-	0.762	0.861ǂ
Pittman et al. (2004)	29	33.9 ± 7.1	0.89	0.89
Pittman et al. (2006)	70	32.6 ± 6.4	0.79	0.95
Schnall et al. (1999)	42	-	0.92	-
Schöbel et al. (2018)	49	30.5 ± 5.3	0.47 (with Embletta)	-
Tauman et al. (2020b)	46 with AF	32±5.5	0.8	0.81
Tondo et al. 2021	47	26±5.67	0.86	-

Weimin et al. (2013)	28	29.99 ± 5.74	0.92	0.930
Yuceege et al. (2013)	85	-	0.909	0.91
Zou et al. (2006)	98	28 ± 4	0.90	0.92

The table summarises the peer-reviewed literature identified as relevant in the semi-systematic literature search. The BMI of the population is particularly important here as the intention was to identify whether any validation studies had been done in patients with a similar BMI to the patient group of interest in this thesis. The reported mean BMIs in the studies identified are typically in the overweight or obese range and are similar to those seen in a general sleep clinic population but lower than those seen in bariatric surgery patients, where the edibility criteria is BMI≥35 kg/m^2 and it is common for patients to have BMIs well in excess of this. The majority of studies report correlation between WatchPAT and PSG AHI and several constructed ROC plots for various AHI cut-offs. The results are included here for quick reference and further detail and critical appraisal is included in the main text.

*Area under the curve (AUC) at an AHI of 15 events per hour unless otherwise noted. Ł AUC for AHI >5; ǂ AUC for AHI> 20/ hour; AUC for AHI >30/ hour.

Correlation studies in WatchPAT®

Several studies have reported a positive correlation between the AHI measured by WatchPAT® versus PSG in patients with clinically suspected OSA (Ayas et al., 2003, Gan et al., 2017, Ioachimescu et al., 2020, Jen et al., 2020, Onder et al., 2012, Penzel et al., 2004, Pillar et al., 2020, Yuceege et al., 2013, Boyd et al., 2016, Choi et al., 2010, Bar et al., 2003, Weimin et al., 2013, Pang et al., 2007, Ceylan et al., 2012, Kinoshita et al., 2018, Pinto et al., 2015, Pittman et al., 2004, Pittman et al., 2006, Schöbel et al., 2018, Zou et al., 2006), those with low probability of having OSA (Tondo et al., 2021) and in patients on CPAP (Penzel et al., 2004). Yalamanchali et al. (2013a) conducted a meta-analysis including 919 from 14 studies and found that both PAT AHI and RDI correlated positively with that measured with PSG (combined correlation of studies measuring RDI r=0.879 (95% CI, 0.849-0.904; P <0.001) and AHI, r=0.893 (0.857-0.920; P <0.001).

In an early study investigating the concept of using PAT to detect OSA, Schnall et al. (1999) found a strong correlation between the total AHI and the transient vasoconstriction and tachycardia measured with PAT technology. Choi et al. (2010) also found a high correlation in a small study involving 25 patients but there are some limitations to this study. Specifically, the majority of participants were male and had a relative low BMI (26.2 kg/ m^2) compared to a typical sleep clinic population.

Respiratory disturbance index

OSA severity is usually described by the AHI, an index calculated by the sum of apnoeas plus hypopnoeas divided by the total sleep time. However, an alternative measure which incorporates all forms of breathing events including snoring and flow limitation not otherwise meeting the criteria for hypopnoea is the respiratory disturbance index (RDI). As a result, RDI would typically be higher than AHI in the same individual. Penzel et al. (2004) looked at the relationship between RDI from WatchPAT 100 and AHI from PSG. Despite measuring slightly different parameters they found a strong and significant correlation ($r=0.89$; $p<0.01$). Another relevant methodological consideration in this study was that they used an oronasal thermistor instead of a measure if airflow to measure AHI. Thermisters are generally less reliable at detecting hypopnoeas (Berg et al., 1997) and therefore the AHI on PSG may be under-estimated.

Clinical implications of bias

The majority of studies in the WatchPAT® validation show the AHI measured by WatchPAT® and PSG are positively correlated. However, few studies provide details on individual data points or discuss the clinical significance of outliers. Ayas et al. (2003) compared an early edition of WatchPAT®, (WatchPAT 100®) to PSG recorded on the same night in 30 patients and found a strong and significant correlation between AHI derived from PSG (the gold-standard) and from WatchPAT® ($r=0.87$). However, detailed examination of the data revealed a number of outliers in whom the difference in AHI would potentially change the management if WatchPAT® had been used

clinically for that patient. For example, in one patient, the AHI on PSG was 5 (on the boundary of normal- mild OSA and below treatment threshold if being assessed clinically) whereas the PAT AHI in this patient was 15 (moderate OSA and a potential candidate for CPAP treatment depending on clinical symptoms). The authors suggest that the presence of periodic limb movements (PLMs) might have contributed to this difference as the WatchPAT® may be picking up arousals caused by PLMs and incorrectly attributing them to respiratory events. However this is not the case in another patient with significant PLMs in whom the AHI was accurate within 2 events per hour.

In a large study of 500 patients from a sleep clinic population (80% male), Ioachimescu et al. (2020) argue that whilst the +4.2 events/ hour bias in AHI on WatchPAT® (using a 3% desaturation criteria for scoring hypopneas) compared to PSG might appear small it can be clinically important when it results in a change in severity classification. This study found that concordance between AHI classifications using WatchPAT® versus PSG was as low as 69.4%. However, examining their data in detail, the authors appear to have included all patients whose severity classification would change with WatchPAT®, even if that change would not be considered clinically significant as the management would not be different (for example reclassification in either direction between moderate and severe OSA). They also report percentage misclassified by severity category rather than as a percentage of the whole sample. Their data shows that a total of 16 patients (3.2% of the total study population) were classified by WatchPAT® as having moderate or severe OSA but did not have OSA on PSG and 3 patients

(0.4% of the total study population) were classified as normal by WatchPAT® but had moderate OSA on PSG. The authors do offer any explanation as to why a small subset of patients are misclassified to such an extent with WatchPAT®.

Tondo et al. (2021) also looked at differences in severity classification using the WatchPAT® versus PSG or RP. They reported that the AHI was under-estimated by WatchPAT® in 9 participants and over-estimated in 9 participants. However, they argue that only 3.3% would have been undertreated based on the profile of mis-classification.

Sensitivity and specificity

In clinical practice, a test is generally considered more useful if it can reliably discriminate those with the disease of interest from those without. A test with high levels of sensitivity and specificity is most desirable. Several studies have calculated the optimal sensitivity and specificity at various AHI thresholds. Zou et al. (2006) found good sensitivity and specificity for detecting an AHI at various thresholds (area under the curve (AUC) were 0.93, 0.92, and 0.93 for AHI >10, 15, and 20 respectively).

Gan et al. (2017) validated WatchPAT® 200 in a population of 20 Asian patients with clinically suspected OSA and report excellent sensitivity (100%) in detecting an AHI >5 events per hour, which the authors suggest makes the test useful as a screening test for undiagnosed OSA in the general population. However, at this level of AHI, specificity is just 75% and the study data suggests a tendency for WatchPAT® to over-estimate the AHI at lower severity levels. Sensitivity at AHI >30 events per hour

(severe) is 80% and specificity is 100%, which the authors argue makes WatchPAT® a good diagnostic tool for patients with a high degree of clinical suspicion for OSA. However when the mean AHI derived from WatchPAT® and PSG respectively was compared statistically, the difference between the two values was found to be statistically significant, a fact that the authors do not comment on further.

A similar bias towards declining specificity at lower AHIs was found in a study by Pinto et al. (2015) who examined sensitivity and specificity at AHI thresholds of 5, 10, 15, 20 and 30 events per hour and found that the accuracy of WatchPAT® was greatest at AHI cut-offs above 20 events/ hour. The authors suggest that this discrepancy could be due to WatchPAT® being more sensitive to respiratory effort related arousals (RERAs) associated with slow and almost imperceptible oxygen desaturations. However, this does raise the question of whether such events are of clinical significance.

Yuceege et al. (2013) looked at the sensitivity and specificity of WatchPAT 200® to detect an AHI >15 events per hour in bus drivers above and below 45 years of age. They found that sensitivity and specificity in those above 45 years of age was good, but they concluded that the device might not be sufficiently sensitive in those below 45 years of age, where prevalence of OSA is lower. This study was done exclusively in male patients who were tested following a night shift and may therefore not be generalizable to other patient groups. Furthermore, the numbers of patients in each age group was relatively small and the study may not have been sufficiently powered for this analysis.

Re-test repeatability

Whilst many studies discussed so far have looked at agreement between WatchPAT® and PSG or RP, Bar et al. (2003) looked at reproducibility of WatchPAT® AHI when measured on two nights in a sub-set of 14 patients taken from a larger validation study. They found a strong positive correlation between the AHI recorded by WatchPAT® on two different nights ($r=0.89$; $p<0.001$). Tschopp et al. (2021) investigated night to night variability in PAT AHI in 51 patients over 3 consecutive nights and found a clinically significant variability on AHI (>10 events per hour) between nights in 35% of patients.

Methodological considerations

A challenge faced by the field and which makes interpretation of these validation studies more difficult is the lack of a universally agreed definition of a hypopnoea. Currently there are two options recommended by the American Academy for sleep medicine which are in routine use (AASM, 2020) and these changes, although subtle, are likely to influence the overall AHI (Ruehland et al., 2009). Ioachimescu et al. (2020) assessed the impact of using either a 3 or 4% desaturation threshold for scoring hypopneas on the level of agreement between WatchPAT® and PSG. They found that the difference between WatchPAT® PSG AHIs showed a mean bias of +4.2 events/ hour when a 3% desaturation criteria was applied but the bias went in the opposite direction (mean bias -6 events per hour) when the more stringent 4% desaturation threshold is used to define hypopnoeas.

Pittman et al. (2004) addressed this issue by applying two different criteria for scoring hypopnoeas in their validation study comparing WatchPAT 100® to PSG. Although the authors report good sensitivity and specify for the sample overall at multiple different RDI cut-offs, it is of relevance that concordance between the data derived from WatchPAT® and PSG was not universal and differences were found in the results of 5 subjects. They report a single significant outlier in whom the RDI goes from 10.8 in the polysomnography to 40.6 in WatchPAT®; a difference which would place the patient in a mild category on the PSG and severe on WatchPAT® and would be highly clinically significant for this patient. There are also differences that would be clinically significant on a number of other patients.

Pittman et al. (2004) also attempted to demonstrate the validity of a WatchPAT® as a home test by comparing the RDI from a WatchPAT® study with that obtained through PSG on a separate night. This method would appear flawed, since total sleep time (TST), an important factor in the RDI calculation, is likely to vary between the two nights. It would have been more useful to demonstrate night-to-night variability between the WatchPAT® on two consecutive nights but this data is not reported. The authors cite the reasons for night-to-night variability as being variability between the home and hospital environment, rather than inaccuracy of the WatchPAT® device, but they do not support this assertion with any data. Of note in this particular study, the first and last authors are employees of the company who market the WatchPAT® device and the study was also funded by the company.

The use of WatchPAT® in population sub-types

As PAT, one of the core signals used by WatchPAT® to detect respiratory events measures changes in the arterial tone, is has been hypothesised that the device might be less accurate in those with atherosclerosis. Kinoshita et al. (2018) assessed the impact of arterial stiffness using brachial ankle pulse wave velocity and found variability in the correlation of WatchPAT® and PSG derived AHIs according to arterial stiffness, with impaired performance of the WatchPAT® in assessing the AHI in the context of increased arterial stiffness (pulse wave velocity > 500 cm/sec). However, there was also a significant difference in TST measured by the WatchPAT® and PSG and the devices were worn on different nights and under different conditions (PSG in hospital and WatchPAT® at home) which might have influenced the overall level of agreement between the two tests, though these factors would presumably apply to all patients regardless of arteriosclerosis.

Onder et al. (2012) hypothesised that age-related changes in the peripheral vasculature might reduce the accuracy of WatchPAT® as a diagnostic tool. They compared the difference in AHI measured by WatchPAT® and PSG in a group of young and older patients and found no significant difference between the two groups. They also found good agreement between WatchPAT® and PSG on AHI across the whole group. The Bland-Altman plot showed one notable outlier where the AHI on WatchPAT® and PSG was substantially different. The authors do not comment on this. However, this particular patient had an AHI of 100 events per hour, much higher than the typical population.

Hypertension is a common comorbidity among patients with OSA (Carlson et al., 1994), Zou et al. (2006)

compared WatchPAT® to home PSG in 98 hypertensive patients and normotensive matched controls. They found a strong positive correlation between WatchPAT® and PSG RDI (r=0.88) and AHI (r=0.90).

Early validation studies in WatchPAT excluded patients with arterial fibrillation (AF) as it was assumed that the presence of AF would disrupt the PAT signal. Tauman et al. (2020b) addressed this issue in a multi-centre trial including 101 patients (46 with episodes of AF). They found a strong positive correlation between WatchPAT® and PSG AHI both in the group as a whole and the sub-group with AF. There was a slight reduction in specificity for an AHI ≥15 in the patients with episodes of AF on the night of the study compared to the group as a whole (whole group sensitivity 0.88, specificity 0.63; AF group sensitivity 0.84, specificity 0.5) which the authors do no comment on. The AUC was similar in both groups and they suggest that WatchPAT® is suitable for use in patients with AF.

O'Brien et al. (2012) validated WatchPAT® against home PSG in pregnant women and found a moderate correlation between the AHI measured by WatchPAT® and PSG. However the incidence of OSA in the sample was generally low and just 8 women from the sample of 31 had an AHI> 5 events per hour and only one had a central apnoea index above 5 events/ hour.

In a multi-centre validation study, (Pillar et al., 2020) evaluated the ability of WatchPAT® to discriminate central sleep apnoea (CSA) and OSA The patient population was selectively recruited to include patients with heart failure and a high chance of having CSA. Nevertheless, the numbers of patients having clinically significant CSA appear relatively low (mean ± standard deviation (SD)

central apnoea index 5.9 ± 11.8). They found a strong and significant correlation between the central AHI determined via PSG and WatchPAT® and strong sensitivity and specificity for a central AHI over 10 and 15 respectively. However, the authors do not comment on the power of the study in respect of low numbers with CSA relative to the overall population or the fact that the population studied was highly selective for patients likely to have CSA, which is not typical of a general clinic population.

Conclusion

This review has critically evaluated the WatchPAT® validation literature in patients with suspected OSA in the hospital and home setting. The studies to date suggest that WatchPAT® derived AHI is well correlated with PSG and respiratory polygraphy data. A number of studies have performed ROC analysis and show high levels of sensitivity and specificity at a range of clinically useful AHI cut-offs. Some studies have found small numbers of outliers where the AHI is clinically significant and as yet unexplained. WatchPAT® has been validated for use in a number of clinical phenotypes including those with hypertension and arteriosclerosis, conditions which are relevant to the general OSA population.

As discussed in chapter 1, pre-operative screening for patients undergoing bariatric surgery (by definition with a BMI >35 kg/m^2) forms a significant proportion of the clinical workload undertaken in Sleep Clinics yet the mean BMI of the majority of the studies reviewed is considerably less that seen in a typical bariatric surgery cohort. As described in Chapter 1, bariatric surgery candidates are at high risk of OSA and differ physiologically from the general sleep

clinic population, meaning that it is important to validate WatchPAT® specifically for use in this population.

Chapter 3: General Methods

This chapter will describe the general methods and principles of use of equipment in the studies included in this thesis. It is not intended to provide a detailed overview of the protocols used in the studies, which will be included separately in the chapters focussing on the individual studies.

Diagnostic devices

The device being validated in the studies described in this thesis is the WatchPAT 300® (Itamar Medical, Israel). The clinical gold standard used for comparison is Embetta MPR® (Natus Medical Inc., USA). Both devices are described first in general terms including a list of the applicable sensors, followed by a more detailed discussion of principles and practical application of the individual sensors used in the devices.

WatchPAT®

WatchPAT® (Itamar Medical, Israel) is a multi-channel device designed to be used at home for diagnosis of OSA. It consists of a finger-mounted sensor measuring PAT and SpO_2, a wrist-worn sensor measuring actigraphy and a chest sensor measuring snoring, body position and chest movement. The device is pictured in figure 6.

Figure 6: A picture of the WatchPAT 300® howing all sensors

The picture shows the wrist-worn recording device with integrated actigraphy sensor, the uPAT probe, which also houses the pulse oximeter and PSAT sensors, the RESBP sensor which measures snoring and body position

Physiological data recorded by the system is stored on the device and uploaded to CloudPAT® software (version 2.7.1) and automatically analysed using an algorithm within the software.

Embletta MPR®

The Embletta® (Natus Medical Inc., USA) is a multi-channel portable monitoring device. The device is pictured in figure 7. It is capable of measuring up to 7 channels of data. The measurements routinely used in clinical practice and in this study are nasal pressure (from which airflow is derived), snoring (derived from nasal pressure), respiratory effort, pulse, SpO_2 and body positon. Physiological data is stored on the device and uploaded to specialist software (Remlogic-E, version 3.4.1: Embla Systems, Canada) where the raw signals can be viewed and manipulated.

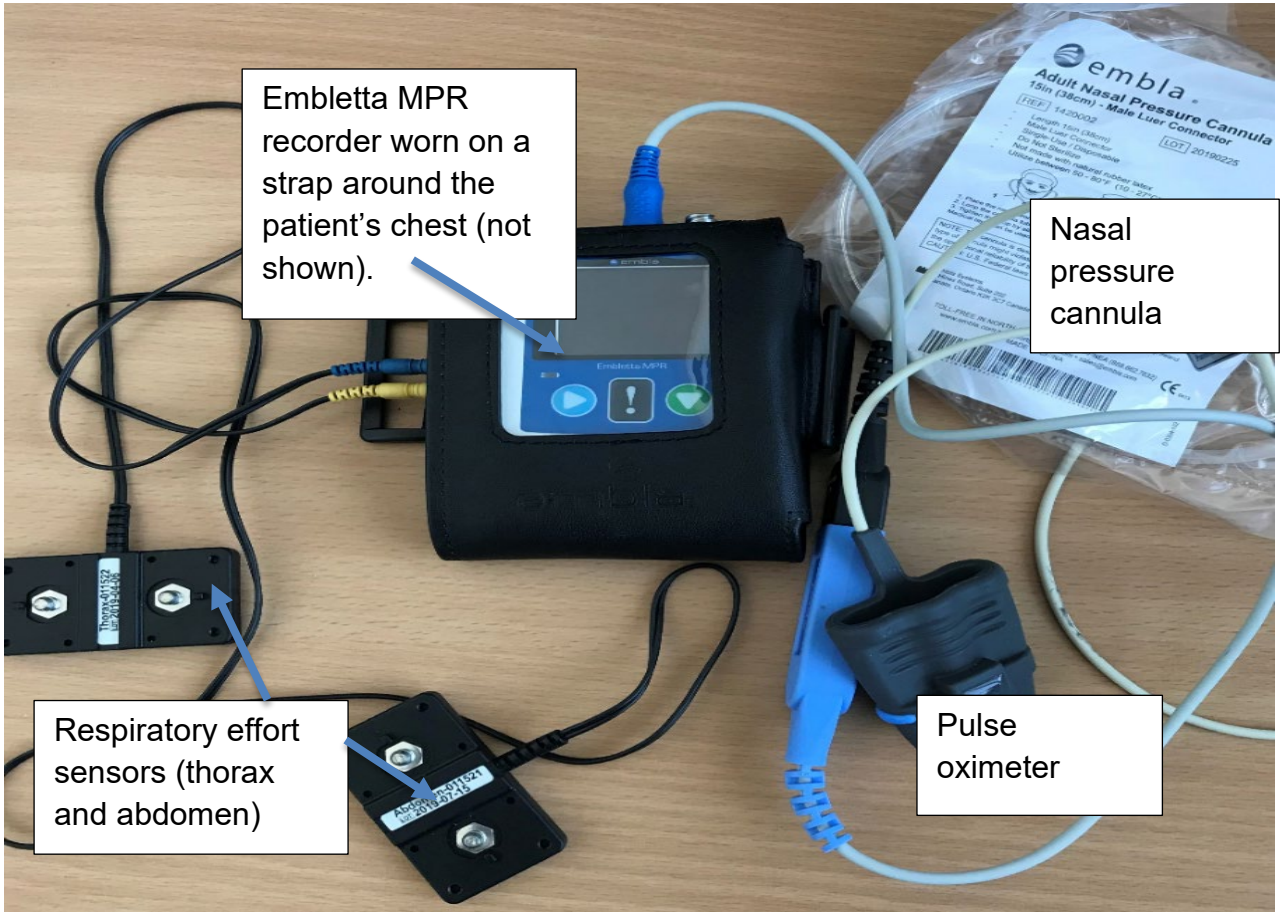

Figure 7: Embletta® MPR device

The component parts of the device are shown. The Embletta MPR recorder (shown in the centre of the picture) is attached to a Velcro® strap and is worn centrally around the patient's chest. It has an integrated position sensor and an LCD screen for viewing signal quality. The respiratory effort sensors to the left of the picture are attached to flexible pre-cut bands which form a continuous loop around the patient's chest and abdomen, connecting at each end to the metal pins on the sensor. The pulse oximeter is worn on a finger of the non-dominant hand. The nasal pressure cannula is worn in the nares and connected to a pressure transducer on the Embletta MPR recorder

Sensors

This section will describe the general principles of measurement for each of the sensors and the device-specific practical application where applicable.

Airflow (Embletta® only)

Measurement of respiration during sleep typically involves some measure of airflow. A number of options exist with each having its own merits and limitations. Available options include measurement of temperature (thermistor) and pressure changes during the respiratory cycle. Thermistors have been shown to have a better specificity for apnoeic events, having the relative advantage that they are able to detect temperature changes associated with respiration at both the nose and mouth, whilst nasal pressure measurement alone may incorrectly detect apnoeic events during mouth breathing (Sabil et al., 2019a). However, temperature change is not sufficiently sensitive a measure to determine the degree of attenuation in airflow and is therefore not suitable for detection of hypopnoeas (Series and Marc, 1999).

To avoid this problem, the AASM (Berry et al., 2018) recommends that both a thermistor and a nasal pressure cannula are used in diagnostic sleep studies, the former being used in the scoring of apnoeic events and the latter for hypopnoeas. However, in a clinical setting, patients tend to be intolerant of sensors, particularly those in and around the nose and mouth. Therefore a pragmatic approach is taken, balancing accuracy with comfort for the

patient. In fact Teichtahl et al. (2003) found that when the AHI is greater than 50 events per hour, either nasal pressure cannula or thermistor alone are similarly accurate in detecting respiratory events. If only one sensor is used, the authors recommend that the nasal pressure cannula should be used rather than thermistor alone (Teichtahl et al., 2003). In the studies described in this thesis, the nasal pressure cannula alone is used in line with routine clinical practice. However, for completeness the commonly used techniques for detecting and quantifying airflow during respiration in sleep studies are described below.

Oro-nasal thermistors

The thermistor is a temperature transducer where resistance decreases with an increase in temperature (Ramanathan and Danielsson, 2001). Expired air is warmer than that of the surrounding atmosphere, thus when the thermistor is placed close to the nose and mouth, the expired air warms the sensor and resistance is decreased as the patient breathes out, while during inspiration, the sensor returns to the temperature of the surrounding atmosphere and resistance increases. The signal produced therefore reflects the respiratory pattern, detecting the presence and absence of respiratory airflow with a high degree of accuracy (Sabil et al., 2019b).

Nasal Pressure Measurement

An alternative way to measure airflow is through measurement of pressure change during the respiratory cycle. As discussed in chapter 1, flow of air into the lungs during inspiration is generated by negative intrathoracic pressure relative to atmospheric pressure as the thoracic

volume increases at the start of inspiration. When airflow is laminar, changes in pressure and flow are related in a linear manner. However, as resistance to flow increases, pressure in the upper airway drops disproportionally to the intrathoracic pressure. Thus, airflow can be calculated by measuring pressure changes at the nares. Flow limitation is defined as decreasing intrathoracic pressure without a corresponding increase in flow rate (Remmers et al., 1978).

The gold standard for measuring airflow during respiration is the pneumotach (Clark et al., 1998), a differential pressure sensor consisting of a closely fitting facemask containing a resistive mesh through which air passes, causing a drop in pressure. As the airway begins to narrow, resistance increases, causing the air flowing through it to become turbulent and this in turn influences the pressure differential across the resistive mesh; a greater pressure differential occurring with increased airway resistance and reduced airflow. Although this method of measuring airflow is highly sensitive and specific (Sabil et al., 2019b) it requires the patient to wear a closely fitting mask which can be poorly tolerated by patients, particularly in the clinical setting and may disturb the patient's sleep.

A more commonly used and acceptable alternative for use in clinical sleep studies is the coupling of a nasal pressure cannula and pressure transducer as a measure of respiration. This has been validated and shown to produce excellent agreement with the pneumotachograph (Heitman et al., 2002). The nasal cannula consists of a column of air which can change pressure and thus transmit pressure changes at the nares to a pressure transducer. The pressure transducer consists of a chamber connected to the cannula and thus subject to the same pressure

changes. The walls of the chamber contain a wheat-stone bridge circuit with variable resisters. A voltage is applied to the circuit. Pressure changes in the chamber cause the walls under the resistors to deform, causing them to produce an electrical signal from the pressure changes.

The studies described in this thesis use a nasal pressure cannula for measurement of airflow. The Embletta® uses a standard 38 cm flexible nasal pressure cannula (Embla systems, Canada). The nasal prongs are positioned about 5 mm into the nares and with the curvature pointing dorsally and the sensor is held in place by hooking over the patient's ears. An adjustable toggle secures the cannula in place under the chin as shown in figure 8. It is common for patients to remove or dislodge the cannula in their sleep and therefore to reduce this risk, a small (approximately 1.5 cm) length of medical tape (Transpore®, 3M, USA) is placed on each cheek secure the cannula in place. The nasal pressure cannula is attached to the pressure transducer within the Embletta® device with a luer lock.

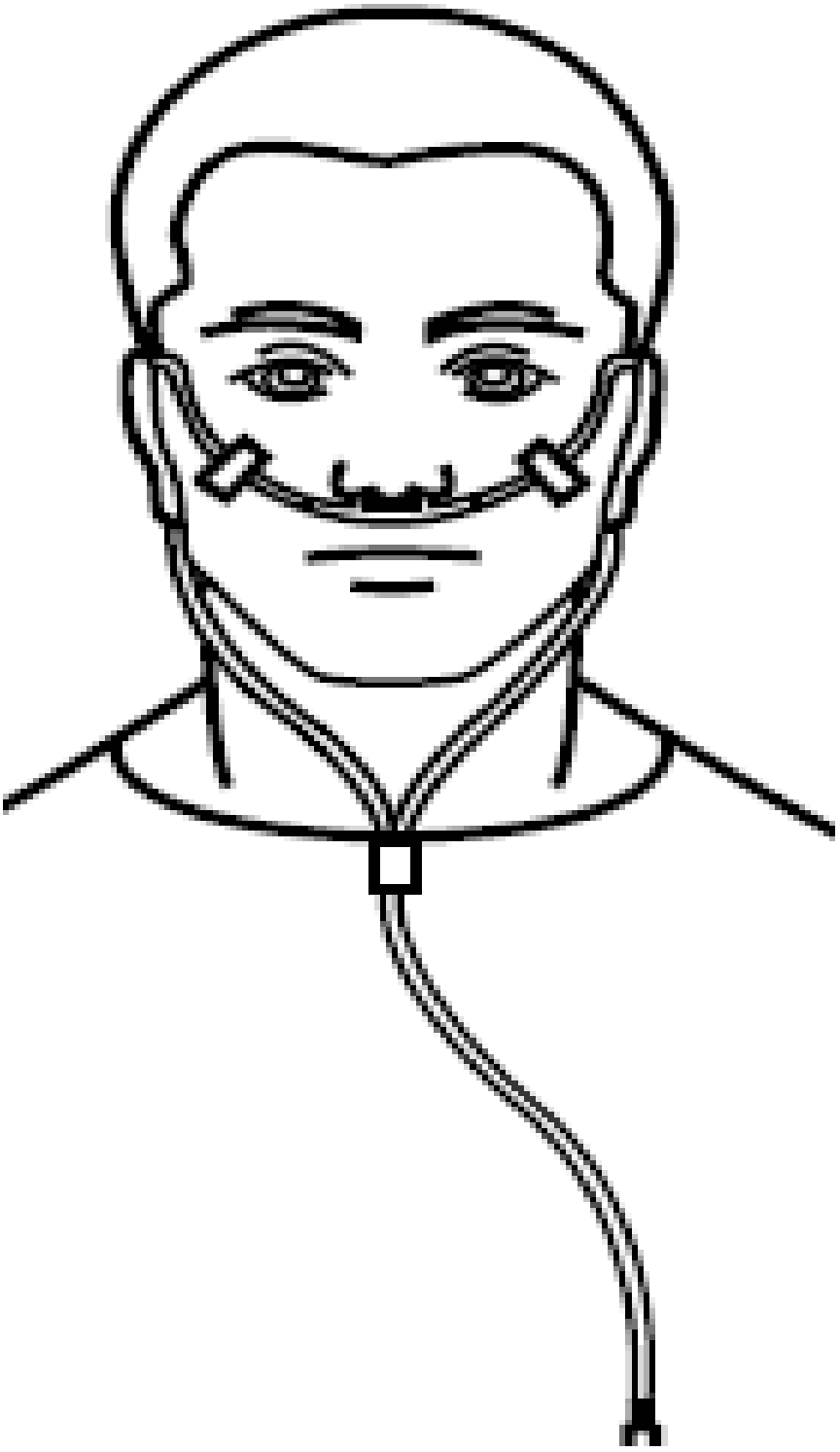

Figure 8: Schematic showing the positioning of the nasal cannula

Source: Embla (2016). Embletta MPR hook-up card. Natus Manufacturing Ltd

The recommended technical specifications for measurement of nasal pressure are listed in the AASM guidelines (Berry et al., 2018). The nasal pressure signal is sampled at a rate of 250 Hz. The raw data is then filtered to exclude non-physiological waveforms caused by interference from other signals. Specifically, a low filter setting of 0.01 Hz is applied and a high frequency filter setting of 90 Hz (maximum available within the software) removes signals of higher frequencies from the data prior to analysis.

Figure 9 shows the signal recorded from the nasal flow trace (derived from the pressure signal) during normal quite breathing.

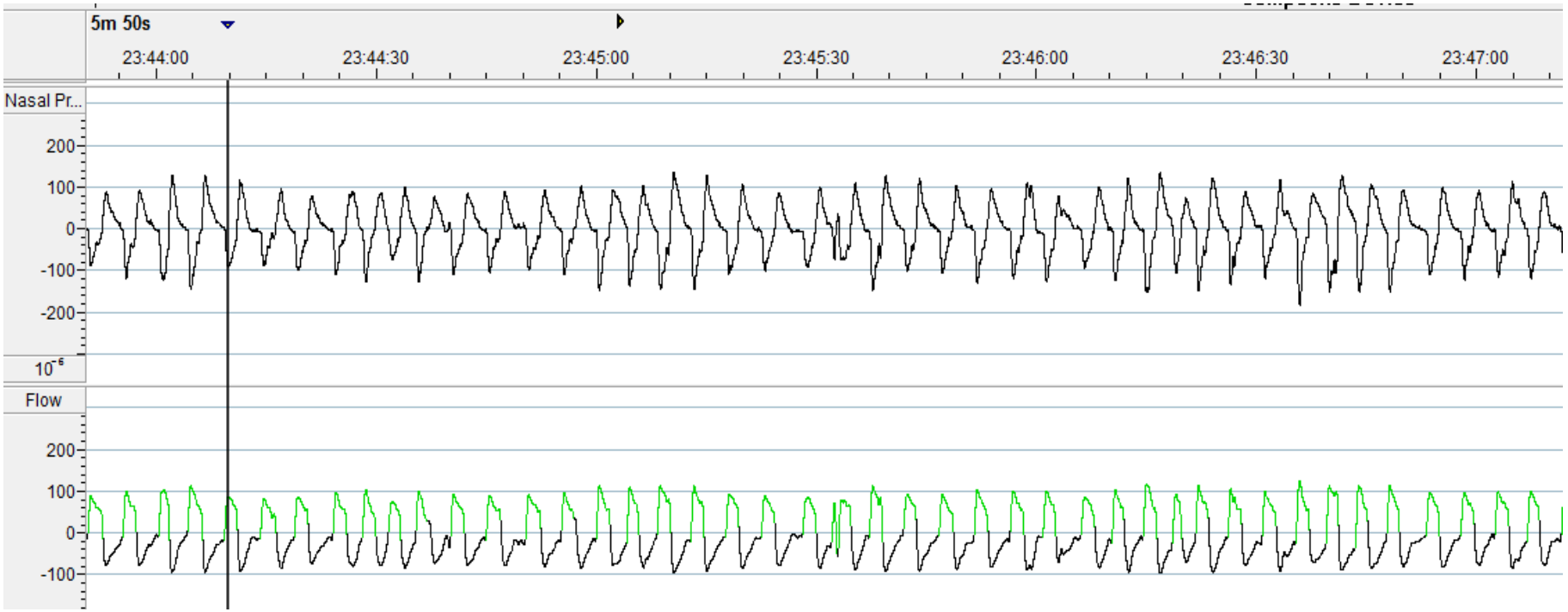

Figure 9: Nasal pressure and flow during relaxed breathing

Nasal pressure is shown in the upper trace and flow in the lower trace. Inspiration is represented by a positive deflection on the trace. Normal tidal breathing is characterised by a regular sinusoidal trace. Nasal pressure is directly measured using the nasal pressure cannula which is attached to a pressure transducer. Airflow is derived from the pressure trace and is routinely used in scoring apnoeas and hypopnoea.

Measurement of respiratory effort

Both the Embletta® and WatchPAT® measure respiratory effort. The sensors used and principles of measurement differ between the two devices and are described below.

Respiratory effort measurement in the Embletta® MPR

Respiratory effort is measured using respiratory inductance plethysmography (RIP). The RIP belt consists of a copper wire arranged in a coiled fashion and mounted onto an elasticated belt (figure 10). The belt is secured in a continuous loop around the patient's body whereby inductance varies with the cross sectional area it surrounds. Changes in cross sectional area in the thorax (or abdomen) during normal respiration will therefore induce a change in inductance of the copper wire. The wire is connected at each end to an oscillator circuit whereby the output frequency of the oscillator varies with inductance (Cohen et al., 1994).

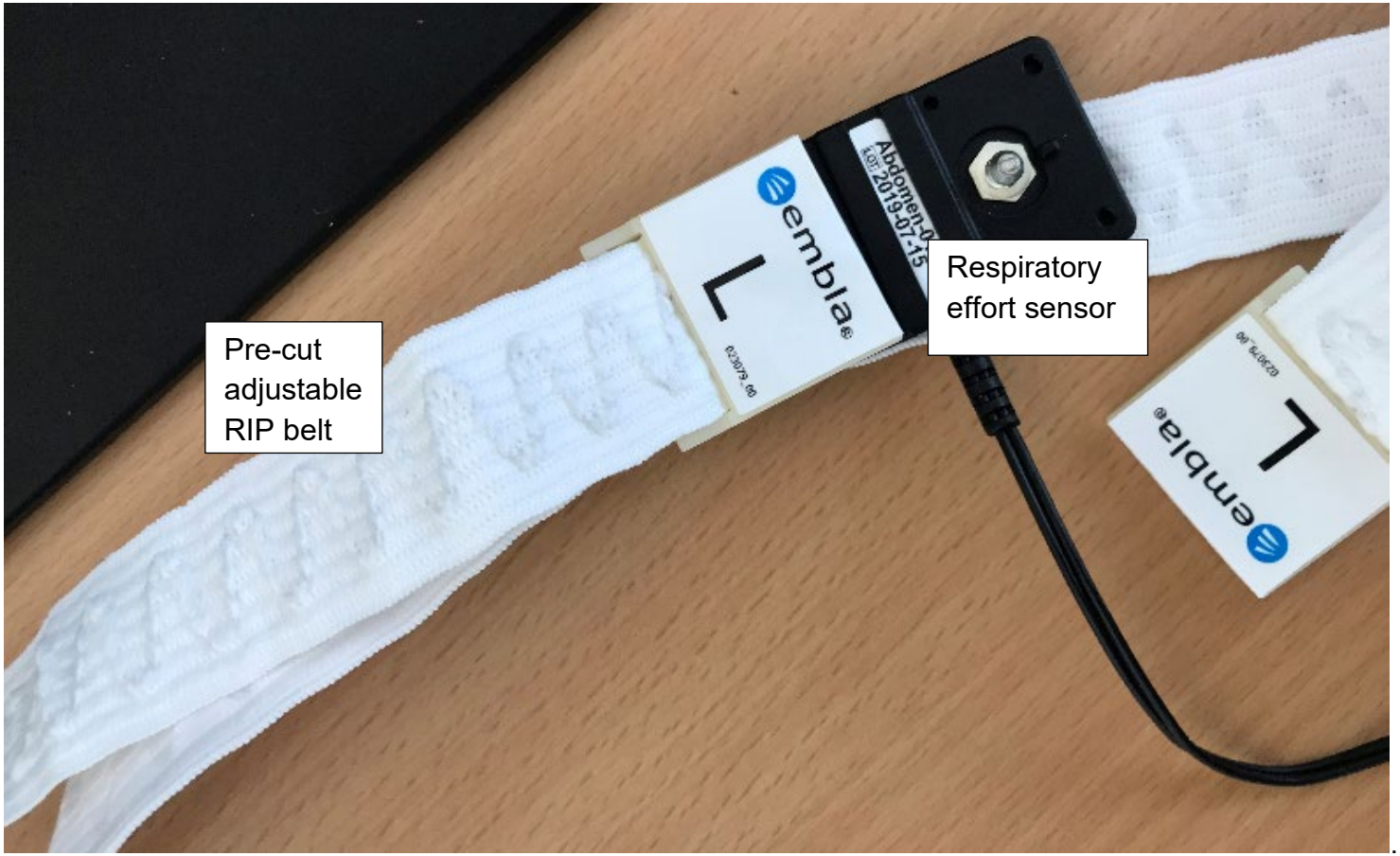

Figure 10: RIP belt and sensor

The pre-cut adjustable RIP belt is shown attached at one end to the sensor. Two RIP belts are worn, one around the thorax and the around the widest part of the abdomen. The belt itself has a copper wire arranged in a sinusoidal pattern and when attached in a continuous loop to the sensor, produces a small current which is transduced to a waveform

If calibrated, RIP technology can be used to measure tidal volume (Clarenbach et al., 2005). For the purpose of measuring respiratory effort during sleep, it is sufficient to use un-calibrated RIP bands as the precise lung volume is not the measure of interest.

In the Embletta®, the respiratory effort signal from the RIP bands is sampled at a rate of 100Hz. High (15 Hz) and low (0.1 Hz) frequency filters are applied to the raw data prior to processing to minimise artefact and non-physiological waveforms.

Patients are instructed to wear the equipment over a light-weight T-shirt. Two disposable pre-cut RIP belts (Natus, USA) of the appropriate size for the patient are used; one placed around the thorax and the other around the abdomen at the level of the naval (figure 11). The belts are attached to the sensors (Natus, USA) by snap on connectors with touch proof connectors connecting the sensors to the Embletta MPR. The belts are tightened to fit snuggly around the body without twisting or excessive strain.

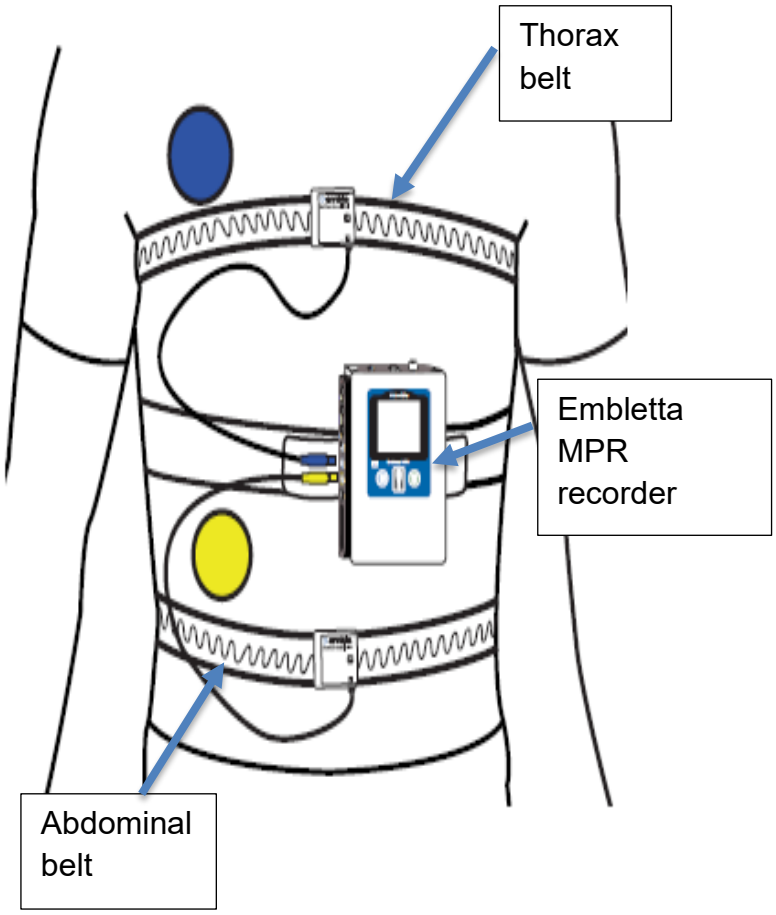

Figure 11: Schematic showing the positioning of the RIP belts on the thorax and abdomen

The RIP belts are shown plugged into the Embletta MPR recorder. Colour coding is used on the sensors to support patients in fitting the bands to the correct anatomical location.

Source: (Embla, 2016). Embletta MPR hook-up card. Natus Manufacturing Ltd

During normal relaxed breathing, the signal from the RIP bands forms a sinusoidal pattern mirroring that of the airflow signal (all signals in phase) (figure 12). In an obstructive apnoea paradoxical signals are seen in the thoracic and abdominal bands (figure 13). Figure 14 shows a central apnoea, where respiratory effort is absent. Sometimes, respiratory effort may resume during the latter half of the event in the event of a mixed apnoea.

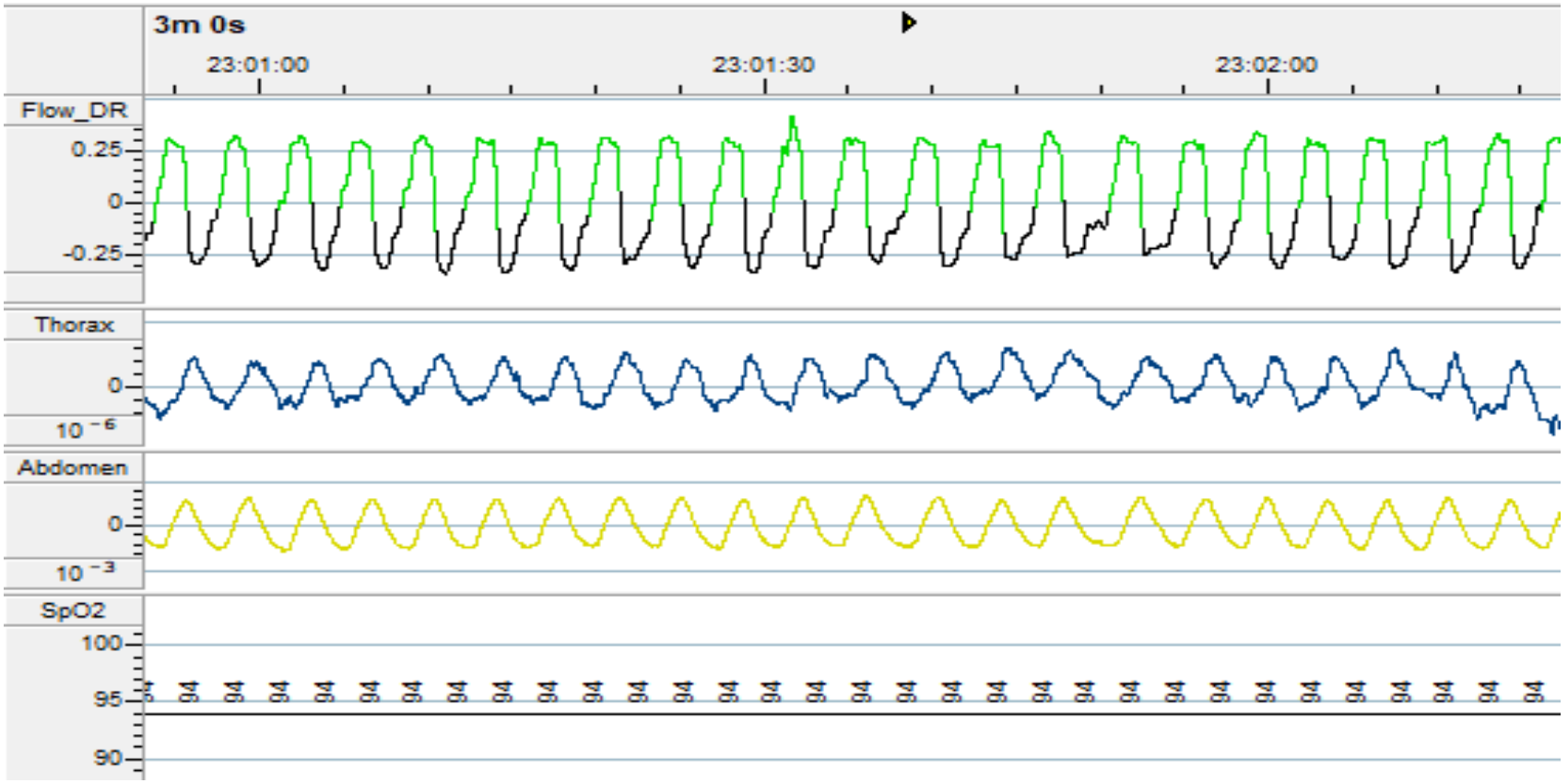

Figure 12: Excerpt from a sleep study showing normal breathing

From top, traces shown are airflow, thoracic and abdominal effort and SpO_2. The airflow, thorax and abdominal traces all follow a synchronous and sinusoidal pattern. SpO_2 is stable and measured at 94%.

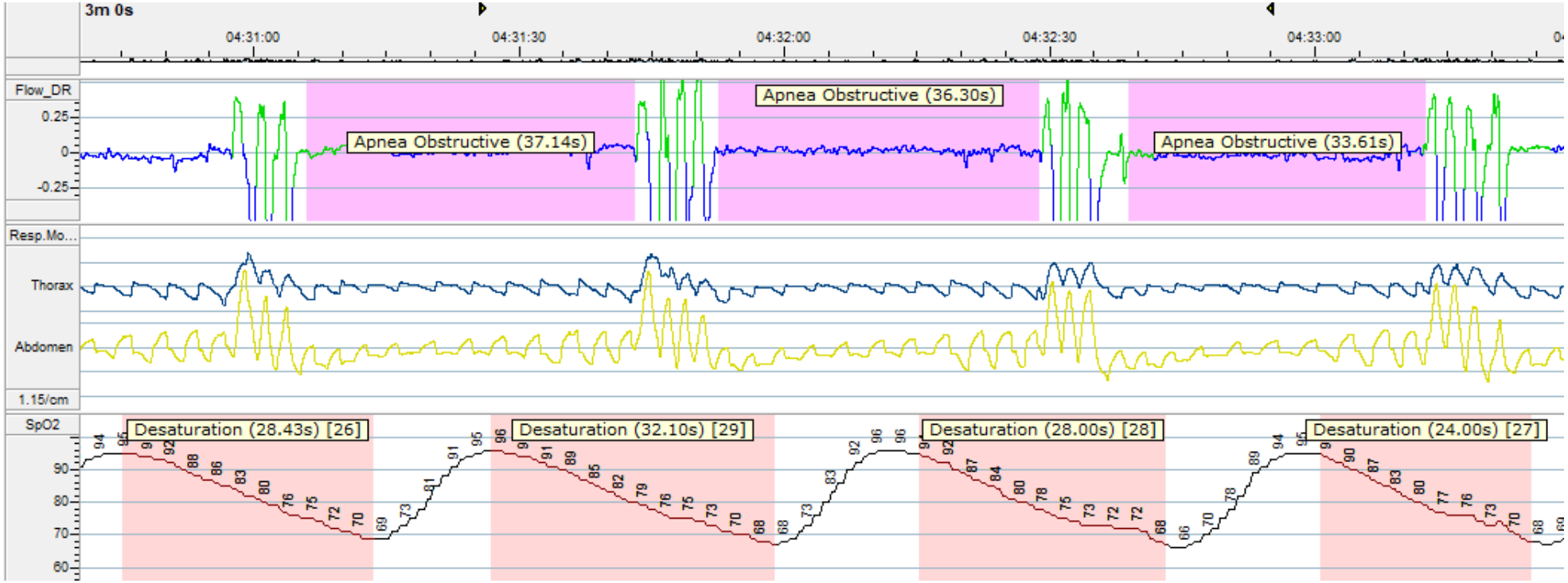

Figure 13: An excerpt of a recording showing obstructive apnoeas

Traces from the top: airflow, thoracic and abdominal efforts and SpO_2. Obstructive apnoeas are highlighted in pink. The signals from the thoracic and abdominal effort move paradoxically during the apnoeas. The events are associated with transient dips in SpO_2. The SpO_2 returns to baseline quickly on resumption of breathing after an obstructive apnoea in direct contrast to the central events in figure 14.

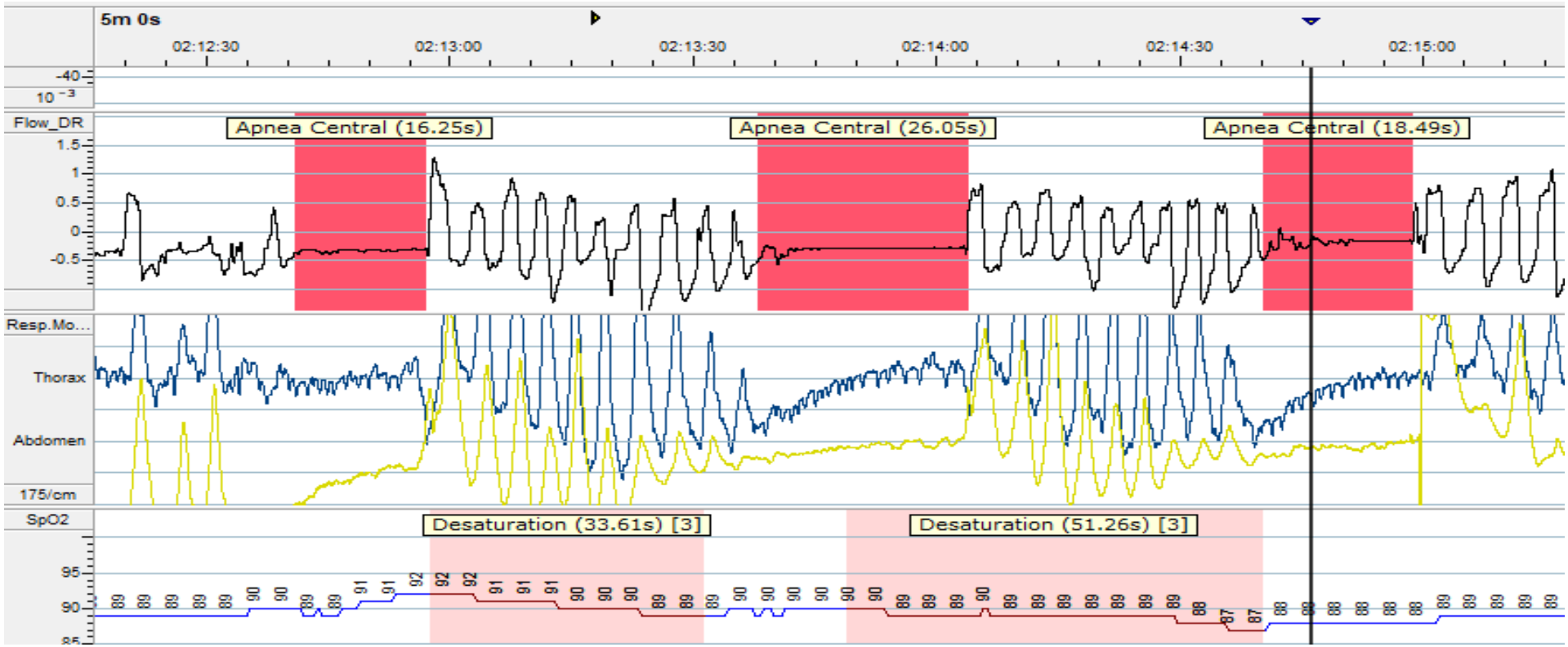

Figure 14: Excerpt of a recording showing central apnoeas

Traces shown from top: airflow, thoracic and abdominal efforts and SpO_2. Central apnoeas are highlighted in red. The respiratory effort signals are absent during apnoeas and effort resumes during periods of normal breathing. Two of the events are associated with oxygen desaturations. SpO2 is slow to return to baseline following resumption of breathing which is characteristic of central sleep apnoea.

Respiratory effort measurement in WatchPAT®

The WatchPAT® measures chest movement with the RESBP sensor. The sensor, placed below the suprasternal notch also measures snoring and body position. It contains a triaxial accelerometer which measures respiratory effort-related chest movement. This is combined with information from the pulse wave signal, specifically the systolic upstroke. Respiratory effort produces pressure fluctuations within the thorax which can dynamically alter the systolic upstroke during the breathing cycle. Upper airway resistance creates large intrathoracic pressure swings which vary throughout the course of the breathing cycle, producing a cyclical pattern of changes in the systolic upstrokes over time. In a central event, the systolic upstroke is not subjected to these pressure swings and the upstroke therefore takes a stereotypical form which does not vary throughout the breathing cycle. These measures are further corroborated by the absence of snoring during central events and a reduction in breathing movements picked up by the wrist-worn actigraphy sensor (Pillar et al., 2020).

Oxygen saturation (SpO_2)

Haemoglobin reversibly binds oxygen, with each molecule containing 4 binding sites which can each carry a molecule of oxygen. SpO_2 is described by the percentage of available haem binding sites within the haemoglobin of the blood that are bound to oxygen at any point in time. A healthy individual with normal lung function and normal perfusion should have a resting oxygen saturation at sea level of 98-99% (Rojas-Camayo et al., 2018).

The oximeter works on the principle of light spectrometry. The sensor consists of two light emitting diodes (LEDs) which emit light sources in the red (660 nanometres) and infrared (940 nanometres) wavelengths and an opposing sensor which measures reflected light from the two diodes. The relative absorption properties of underlying tissues such as bone are known constants and therefore the differential absorption is predominantly explained by the colour of the blood in the underlying vasculature. Haemoglobin with oxygen bound is darker and therefore absorbs a greater amount of the red light than in its unbound form (reduced haemoglobin) (Jubran, 2015) and figure 15 (Nitzan et al., 2014).

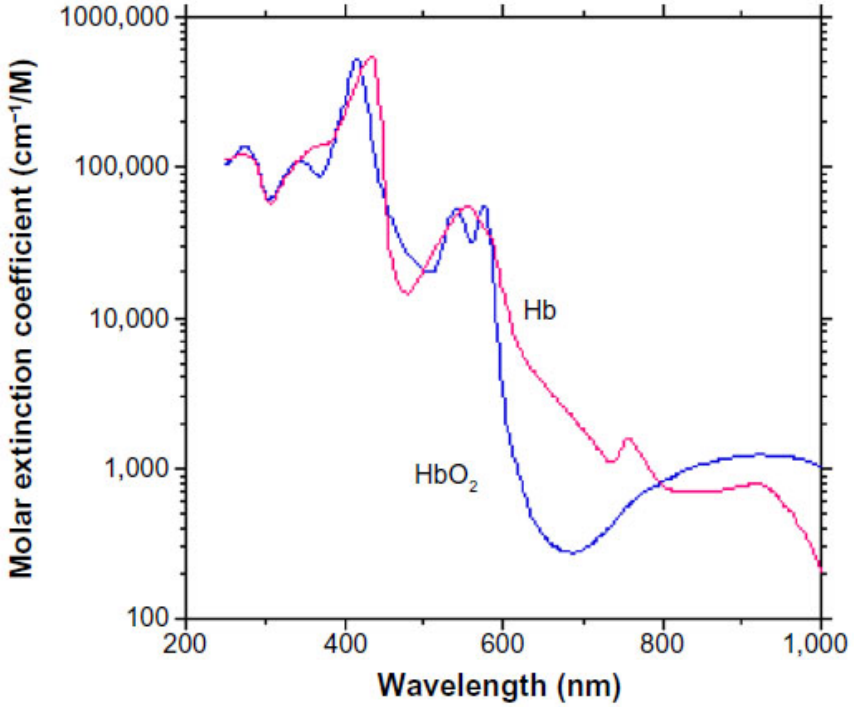

Figure 15: Absorption spectra of oxyhaemoglobin and reduced haemoglobin

The absorption spectra of reduced haemoglobin (Hb) and oxyheamoglobin (HbO_2). The oximeter takes advantage of the different absorption spectra of these two forms of haemoglobin with notable divergence at 660 and 940nm meaning that by measuring absorption at these wavelengths at a given point in time, the % saturation of the blood passing though the underlying vessels can be calculated.

Source: Nitzan, M., Romem, A., and Koppel, R (2014). Pulse oximetry: fundamentals and technology update. Med Devices (Auckl), 7, 231-9

The sensor is factory-calibrated against directly measured arterial blood samples with known oxygen saturations. Using the known relationship between SpO_2 and SaO_2 the oximeter is capable of producing an estimate of SaO_2 which is accurate across a broad range of values down to 75%. At values below 75%, the relationship becomes progressively non-linear resulting in an overestimation of the SpO2 at low SaO_2 values (Chapman et al., 1986). However the oximeter is highly accurate over the range of expected physiological values.

A number of other factors have been shown to reduce the accuracy of pulse oximetry, including hypotension (Mardirossian and Schneider, 1992) hypothermia (Schramm et al., 1997), vasoconstriction (Mardirossian and Schneider, 1992) and dark nail polish (Cote et al., 1988), all of which may results in an inaccurate SpO_2 reading. Skin pigmentation has also been shown to affect accuracy in pulse oximetry at saturations below 80% with increasing with lower levels of oxygen saturation. For saturations between 70-80% the bias was 2.4-3.6% depending on the make of oximeter (Feiner et al., 2007). This may be a relevant consideration in the bariatric surgery population where hypoventilation may be present.

The pulse oximeter used with the Embletta® is a Nonin PureSAT® with soft grip finger probe (Natus, Ireland). The signal is sampled at a rate of 3Hz and in order to smooth out small fluctuations of the signal caused by measurement error and movement, the signal is then digitally displayed as a 4-beat rolling average.

Prior to placement of the pulse oximeter, the patient is asked to remove any nail polish or acrylic nails to reduce impedance to the signal. The first finger on the non-

dominant hand is usually selected for measurement, though some patients find it more comfortable to wear the sensor on a different finger. The chosen finger is inserted into the Nonin® soft grip sensor with the LED over the nail bed. The sensor cable is then fed up through the sleeve of the patient's T-shirt and out through the neck hole before being plugged into Embletta® recorder. Cables are secured with medical tape (Transpore®, 3M, USA) to reduce the likelihood of the oximeter cable becoming tangled in the night and causing dislodgement of the senor.

Body position

Both the Embletta® and WatchPAT® devices measure body positon. In the Embletta®, body positon is measured from a sensor integrated within the main recording device. The signal is derived from data generated by 3 gravity sensors and measuring position of the device relative to gravity in 3 dimensions (X, Y and Z). The recording device is worn centrally on the front of the chest and attached securely with a Velcro® strap so that as the patient changes position, the device remains in place. The sampling rate for body position on the Embletta® is 20 Hz.

The position sensor in the WatchPAT® is contained with the RESBP sensor. This sensor consists of a small disk attached to the sternum which contains a 3 axis accelerometer which measures body position.

Snoring

Snoring is measured differently by two systems. The Embletta® records nasal pressure and it is therefore possible to derive the snoring signal from fluctuations in

pressure during inspiration. As the airway narrows, it becomes increasingly resistant to airflow and the inspiratory portion of the flow signal becomes blunted. Snoring and airflow limitation causes the usually laminar airflow to become turbulent, causing vibrations which are picked up by the pressure transducer and can be seen as a fluctuating inspiratory flow signal (Figure 16).

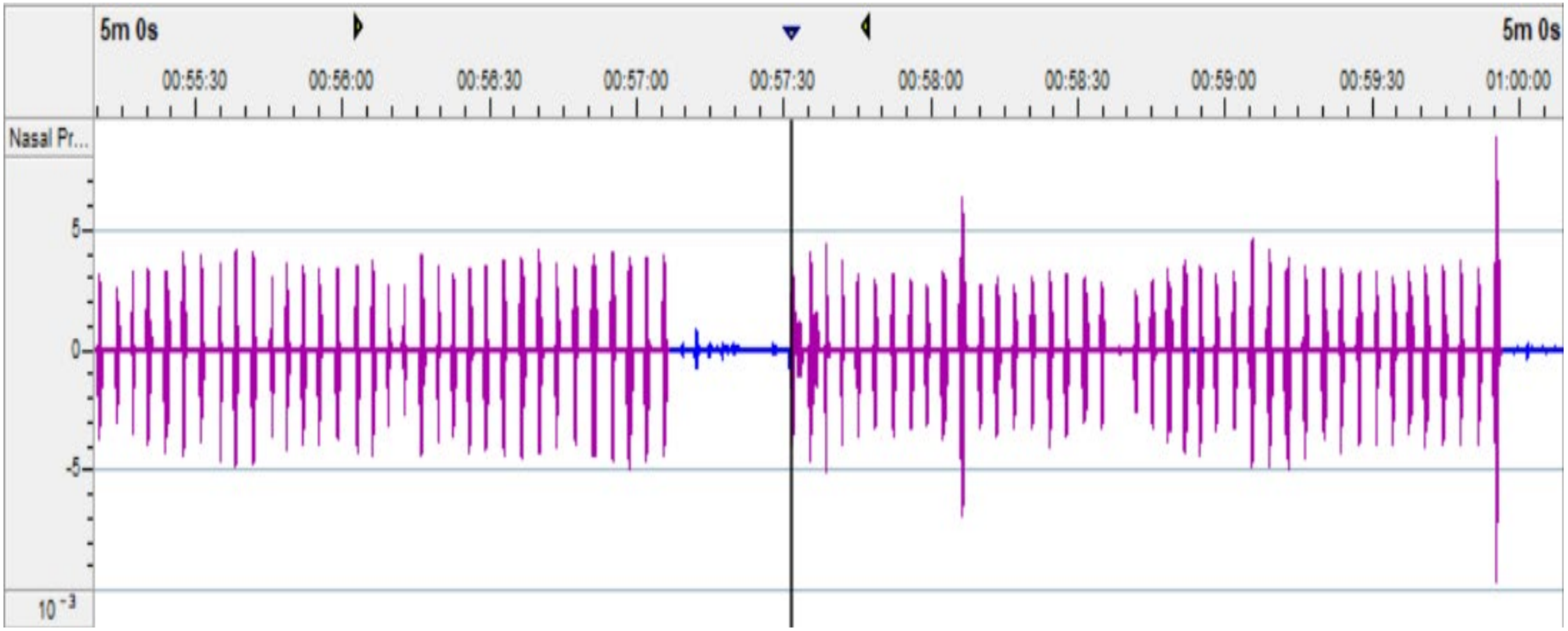

Figure 16: Snoring signal derived from the nasal pressure trace

Snoring signal is derived from the nasal pressure signal which has a 10Hz low cut filter applied. The trace shown is a 5-minute epoch. Snoring is represented by positive and negative deflections relative to baseline and is highlighted in purple. This except shows a short period with no snoring, where the baseline is relatively stable and low amplitude.

The WatchPAT® does not have a direct measure of nasal airflow and therefore uses sound to detect snoring. The RESBP sensor worn on the sternum is a decibel sensor, which contains a highly sensitive microphone capable of detecting sounds and converts them into an analog voltage.

Peripheral arterial tonometry (PAT)

PAT is a technique for non-invasively measuring changes in arterial tone using plethysmography to measure the pulse wave amplitude at a given site. A relative reduction in pulse wave amplitude signals an increased arterial tone and dynamic changes in the pulse wave amplitude are indicative of local vasoconstriction and vasodilation.

Arterial tone is under the influence of the sympathetic nervous system, which causes localised vasoconstriction to divert blood flow towards essential organs during increased oxygen demand (for example, exercise-mediated local hyperaemia to the exercising muscles) or reduced availability (hypoxemia). Thus, measurement of pulse wave amplitude at the periphery has been shown to be an effective measure of sympathetic nervous system activity (Hamunen et al., 2012).

The cardiovascular system and vascular tone are under constant modification through the alpha and beta-adrenergic pathways, with the alpha-1 adrenoceptors being responsible for mediating vasoconstriction in response to stressors including body cooling (Charkoudian, 2010) and acoustic startle (Girard et al., 2001).

The cutaneous vasculature supplying the fingers is unique in that it contains exclusively alpha-1 adrenoceptors. This makes the finger an optimal location from which to measure reflex peripheral vasoconstriction in response to hypoxic insult during obstructive sleep apnoea.

At the start of an apnoea, there is an initial suppression of sympathetic nervous system activity causing a relative dilation of the blood vessels. As stress on the system increases, there is a gradual increase in sympathetic nervous system activity causing an increase in heart rate (via the beta-adrenoceptor pathways) and alpha-adrenoceptor mediated localised peripheral vasoconstriction (Lurie, 2011). This pathway plays an important role in diverting blood away from the less essential organs such as the skin and ensures the continued supply of oxygenated blood to the brain and vital organs.

In OSA, the PAT signal is measuring the sympathetic activation that builds during and peaks at the end of an apnoeic event, rather than the event itself (Grote et al., 2003). Thus when combined with other data (changes in oxygen saturation, snoring and movements), PAT amplitude can be a reliable predictor of apnoeic events during sleep (Zou et al., 2004).

O'Donnell et al. (2002) studied the PAT amplitude changes in response to flow limitation with and without an arousal and demonstrated a reduction in PAT amplitude in response to flow limitation regardless of whether or not there was a discernible EEG arousal.

In addition to being a reliable marker for stressor-induced transient local vasoconstriction, the PAT signal has also been used to differentiate sleep stages. The baseline

sympathetic activity and therefore arterial tone is known to differ from wake to sleep and REM sleep. Sympathetic activity is at its highest level during REM sleep, causing a reduced PAT amplitude which transiently increases during arousal from sleep in healthy volunteers (Somers et al., 1993).

The uPAT® sensor consists of three compartments. Two are arranged in opposition to one another at the tip of the sensor. The third compartment is not directly involved in the measurement but serves to hold the finger in line with the sensor throughout the measurement. Together the three components apply a uniform pressure (70 mmHg) over the distal part of the finger to prevent venous pooling and to ensure the sensor remains in continuous contact with the underlying vasculature. Changes in the underlying arterial tone mediated by sympathetic vasoconstriction can then be detected by pneumatic changes within the measurement compartments. The signal is then electronically transduced, filtered and amplified (Schnall et al., 1999). This local vasoconstriction produces a discernible attenuation of the PAT amplitude signal. When the PAT signal is aligned with pulse, oxygen saturation and movement, it is possible to deduce that the cause of the arousal was indeed an apnoeic event (see figure 17, Schnall *et al.,* 1999; pp.941).

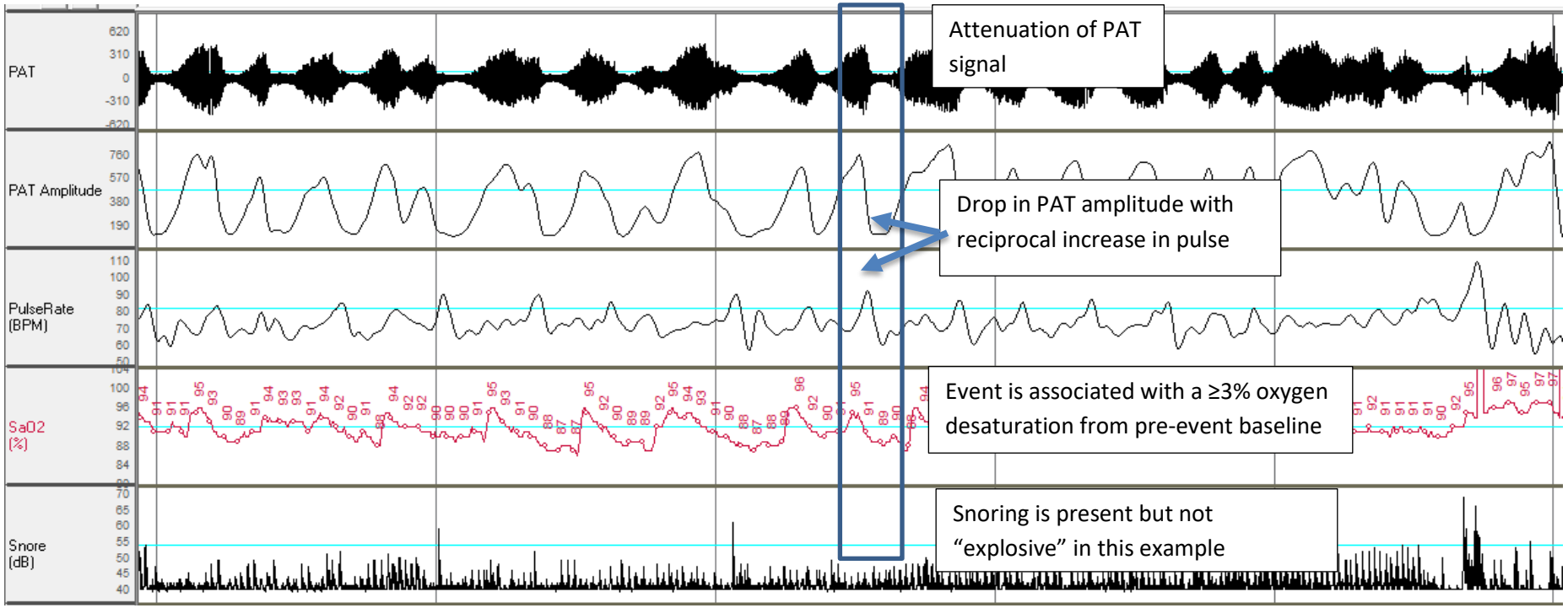

Figure 17: An excerpt from a WatchPAT® recording showing the raw data signals

Signals shown from top are: PAT, PAT amplitude, pulse SpO2, and snoring. The highlighted section is one event. There is a global attenuation in the PAT signal seen in the top trace. Individual respiratory events are characterised by a reciprocal pattern with a sharp drop in the PAT amplitude with a simultaneous increase in pulse rate (representing arousal from sleep). For the event to be classed as an apnoea or hypopnoea, there must be a concurrent oxygen desaturation of ≥3% from baseline or explosive snoring (≥40 dB) and no pre-event change in body position (not shown on this example). The event highlighted does not include explosive snoring but can be scored due to the oxygen desaturation.

Actigraphy

The actigraphy sensor in WatchPAT® consists of an accelerometer mounted in a watch style device worn on the non-dominant wrist. Oscillations are sampled at 100 Hz. Studies validating actigraphy against PSG have shown that it can detect sleep with good sensitivity though specificity is relatively poor (Marino et al., 2013).

WatchPAT® uses a combination of actigraphy data plus the global PAT amplitude and pulse to determine total sleep time (TST) and sleep stages and studies have been done to validate this again PSG. For example, Hedner et al. (2011) validated WatchPAT 100® against PSG and found moderate agreement in the ability to detect light, deep and REM sleep and good agreement for sleep efficiency. Their study included 189 patients with OSA as well as 38 healthy volunteers and they report that the presence of OSA did not affect the sensitivity and specificity of the algorithm.

O'Brien and Gozal (2007) measured arousals from sleep in healthy non-snoring children simultaneously with PSG, PAT and pulse transit time. They report good sensitivity of PAT (0.92) in detecting arousals when movement arousals were included. Specificity was low (0.19) whether or not movement arousals were included. The authors suggest that this might be due to children not having fully formed sleep macro and micro-structure and in fact PAT is picking up arousals that cannot be seen visually on the EEG due to this. This could be a plausible explanation given that PAT has been shown to be highly sensitive and specific in adults (Pillar et al., 2002). However, as shown by O'Donnell et al. (2002) severe upper airway obstruction causes a reduction in PAT amplitude in the absence of an EEG arousal though the magnitude of reduction in PAT

amplitude is greater when an EEG arousal is present. This suggests that in adults at least, PAT may be more sensitive in detecting arousals that would otherwise not be seen when EEG alone is used as the measure of arousal.

Apnoea hypopnoea index (AHI) calculation

The WatchPAT® and Embletta® both have automated scoring algorithms for calculating the AHI. The WatchPAT® does not directly measure flow but rather uses changes in the PAT amplitude along with SpO_2 snoring and actigraphy to detect arousals caused by respiratory events. The Embletta® measures flow and is therefore able to detect apnoeas and hypopnoeas directly. For the studies described in this thesis, manual editing of the Embletta® data was carried out to improve accuracy of the final AHI in accordance with normal clinical protocol. WatchPAT® data was not manually edited in the studies described in this thesis as the test is designed to be used with the automated scoring algorithm and the accuracy of the device in this context was of interest. Nevertheless, guidelines for the manual scoring of PAT events have been developed and for completeness are described below.

Calculation of AHI by WatchPAT®

As the WatchPAT® does not measure airflow, the traditional definitions of apnoeas and hypopnoeas do not apply. Zhang et al. (2020) described a method for manually reviewing the automated scoring produced by the WatchPAT® data. The sleep, wake and REM periods are first adjusted according to pattern recognition of the combined physiological signals. For example, wakefulness is typically associated with relatively increased activity and

heart rate variability; REM is typically associated with increased heart rate variability, relatively little movement and SpO_2 values at their lowest; non-REM would be associated with relatively little movement and lower heart rate compared to wake. In terms of overall PAT amplitude, the baseline PAT amplitude is low during wake, increased during non-REM sleep and low during REM sleep.

Respiratory events are characterised by transient reduction in the PAT amplitude with a reciprocal increase in pulse. For the event to be valid, it must be associated with a 3 or 4% drop in SpO_2 (depending on desired scoring criteria; a 3% threshold was chosen for studies in this thesis to match that used with the Embletta®) or explosive snoring (>50 dB).

Calculation of the AHI by Embletta®

The definitions used for the scoring of apnoeas and hypopnoeas are in line with the AASM guidelines, which are routinely accepted as the standard for scoring sleep (Berry et al., 2018). Specifically, an apnoea is defined as a reduction in nasal airflow of greater than 70% from baseline and lasting for more than 10 seconds in duration. Apnoeic events are further classified into obstructive, central and mixed events based on the presence or absence of continued thoraco-abdominal effort. Obstructive apnoeas are typically associated with paradoxical throaco-abdominal effort traces (see figures 12-14).

The alternative definition for hypopnoea is used in this study (Berry et al., 2018). Specifically a hypopnoea is defined as a reduction in nasal airflow of greater than 30% from baseline for a duration of ≥10 seconds coupled with

an oxygen desaturation of greater than 3% from pre-event baseline.

Conclusion

In summary, this chapter has provided an overview of the methods used to evaluate patients for OSA in the clinical setting. It has introduced the two devices that will be compared in the studies described in this thesis and described the principles of measurement and practical application of the relevant sensors.

Chapter 4: Inter and Intra-rater reliability in respiratory polygraphy scoring

Background

Interpretation of physiological signals collected during an RP study is based on pattern recognition which is inherently subjective. In a study by Bridevaux et al. (2007) 8 raters independently scored 88 studies and measured agreement using intra-class correlation coefficient. They reported significant variability between raters with an ICC of 0.73 for AHI and 0.98 for ODI. Variability within the same scorer reviewing the data on different days is also well known. The studies that will be described in this thesis will use RP as the gold standard against which performance of the WatchPAT will be compared. It is therefore important to ensure that any bias introduced by manual scoring is understood and reduced as far as possible. This chapter will describe an inter- and intra-rater reliability study using a subset of data from the studies included in this thesis.

Methods

In order to assess inter-rater reliability, 10 RP studies from the dataset described in Chapter Six were re-analysed by an experienced colleague (Rater B) who had not been part of the original study and the ratings were compared to those of rater A (A^1-B). Intra-rater reliability was assessed by the author (Rater A) re-scoring the same studies at least six months after first scoring (A^1-A^2).

The strategy for selecting studies to re-score was designed to cover the range of severity levels from the original

dataset. The data was first ranked in order of AHI (lowest to highest) and every third study in rank order selected for re-scoring. Prior to re-scoring, the studies were sorted alphabetically to reduce any possible bias or pre-conceptions of AHI severity. Both raters scored the studies without reference to the previously scored report or the WatchPAT data. Start and stop times for the RP study were manually adjusted to match those on the WatchPAT after all studies had been rescored to prevent un-blinding during re-scoring.

An intra-class correlation co-efficient (ICC) was calculated to assess the agreement between the author (rater A) scoring the same data at two time points at least 6 months apart for both AHI and 3% ODI. ICC was also used to assess inter-rater reliability between scorer A and scorer B in the same dataset.

Results

Inter-rater reliability: The mean ± SD bias between the author (rater A) and an independent scorer (rater B) was as follows: AHI 2.94 ± 2.88 events/ hr (Intra-class correlation coefficient (ICC) 0.982) and 3% ODI 2.28 ± 1.70 events/ hr (ICC 0.982).

Intra-rater reliability: The mean ± SD bias between the two time-points was as follows: AHI 3.9 ± 4.9 events/ hr (Intra-class correlation coefficient (ICC) 0.90) and 3% ODI 0.55 ± 1.59 events/ hr (ICC 0.99).

Discussion

Scoring respiratory events in bariatric patients can be particularly challenging due to the tendency for waxing and waning of airflow and frequent desaturations which occur with sub-criterion changes in ventilation in this patient group. Despite this, the analysis has shown high levels of agreement between data scored at two time points and by two raters. Intra-rater reliability was lower for AHI than for ODI but was within the acceptable range and agreement levels for both values were above that previously reported in the literature.

Chapter 5: Validation of PAT for preoperative screening for OSA: A pilot

Background and rationale

As outlined in Chapter 1, the prevalence of OSA in patients undergoing bariatric surgery is high at 71% (Peromaa-Haavisto et al., 2016) and consensus among anaesthetists working in this area is that patients should be screened for OSA and treated peri-operatively (de Raaff et al., 2017). As previously discussed, an unpublished audit of our own data showed that 5.2% of RP studies carried out over a 9-month period were requested for pre-surgical screening in bariatric surgery candidates. These patients are typically asymptomatic and have low motivation to achieve a technically adequate test with traditional RP. It is therefore important to consider simpler ways to rapidly and accurately screen for OSA in this population.

WatchPAT® is a potential candidate due to its relatively simplicity and there is a growing body of evidence showing that it had good concordance with more traditional tests such as PSG and RP (see chapter 2 for a detailed review). However, studies to date have rarely reported a mean BMI >35; a pre-requisite for bariatric surgery and no studies have investigated the feasibility of using WatchPAT® in bariatric surgery candidates.

The aim of the studies described here, and in Chapter 6, is to assess and validate WatchPAT® against the clinical gold standard, RP, in patients requiring bariatric surgery. The data described here form an initial pilot study, which was

used to inform the power calculation for the main study in Chapter 6.

A secondary aim was to use this phase as an opportunity to learn and test the feasibility of the protocol before rolling out a larger study. Some of the challenges in delivering this and the learning that ensued are included in the discussion.

Methods

Adult patients referred to the Sleep Service at ICHNT for pre-operative screening prior to bariatric surgery (planned or being considered) and with a BMI ≥35 kg/m^2 were eligible to take part. There was no upper age limit. Exclusion criteria included a history of sympathectomy, the use of alpha-blockers and/or long-acting nitrates.

Patients simultaneously wore the WatchPAT® 300 (Itamar, Israel) and Embletta® MPR (Natus Embla, USA), the gold standard comparator in this study.

Patients elected to have their sleep study either as a planned in-patient test or as an out-patient at home according to routine clinical procedure and patient preference. Patients who had their sleep study at home received a practical demonstration and written instructions in the use of the devices. Those having the test on an in-patient basis had the devices fitted to them by the researcher prior to sleep. All patients were encouraged to keep the devices on all night and to aim for a minimum of 6 hours of sleep.

The WatchPAT® data was automatically analysed with CloudPAT® (Version 2.8.0; Precise MD, USA). Embletta®

data was analysed using RemLogic® 3.4 (Natus, USA) and was manually re-scored by the researcher as per usual clinical protocol using AASM guidelines (Berry et al., 2018). Apnoeas were defined as a reduction in airflow of ≥80% of the pre-event baseline for ≥10 seconds. Hypopnoeas were defined as a reduction in nasal airflow of greater than 30% from baseline and for a duration of 10 seconds or longer plus an oxygen desaturation of greater than 3% from pre-event baseline.

The start and stop times of the analysed Embletta® data were manually input to match those on the WatchPAT® device, since the patient is required to start the recording themselves before they go to bed. This meant the analysed time was the same between the two devices.

Incomplete datasets were analysed in line with routine clinical protocol which aims to make use of available signals; if flow was lost for part if the night, a surrogate signal derived from the respiratory effort bands was used provided these were of sufficient quality and the total loss of signal was less than 10% of the overall study. Loss of oximetry for less than 10% was also accepted provided other signals were of good quality. A total sleep time of less than 1.5 hours is considered insufficient for a valid analysis on the WatchPAT® and all data for that patient was therefore excluded. Only patients with valid and complete data for both devices were included in the final analysis.

Patient involvement

Patients were involved in the planning of the studies described in this thesis. Specifically the patient information sheet was reviewed by members of the Respiratory Patient

Involvement Group at ICHNT and by patients with OSA who attend the Sleep Centre at ICHNT. Both groups gave feedback on the content and clarity of the information sheet, which was incorporated into the final version.

HRA and Trust approvals

Relevant HRA, MMU and ICHNT approvals were in place prior to commencement of data collection. The study was sponsored by MMU. It received a favourable ethical opinion following review by the Central London Research ethics committee (appendix 2). Capacity and Capability was assessed and granted by the Research and Development Department at ICHNT. All patients were gave full informed consent to participate.

Results

Figure 18 shows the recruitment flow for the study. 11 patients gave informed consent and completed the protocol. However, after review of the data, two were excluded due to technical failures (One patient removed the device prematurely, resulting in insufficient data for analysis. The second patient forgot to turn the WatchPAT® device on to start the study). The final dataset on which the sample size calculation was based contained 9 patients.

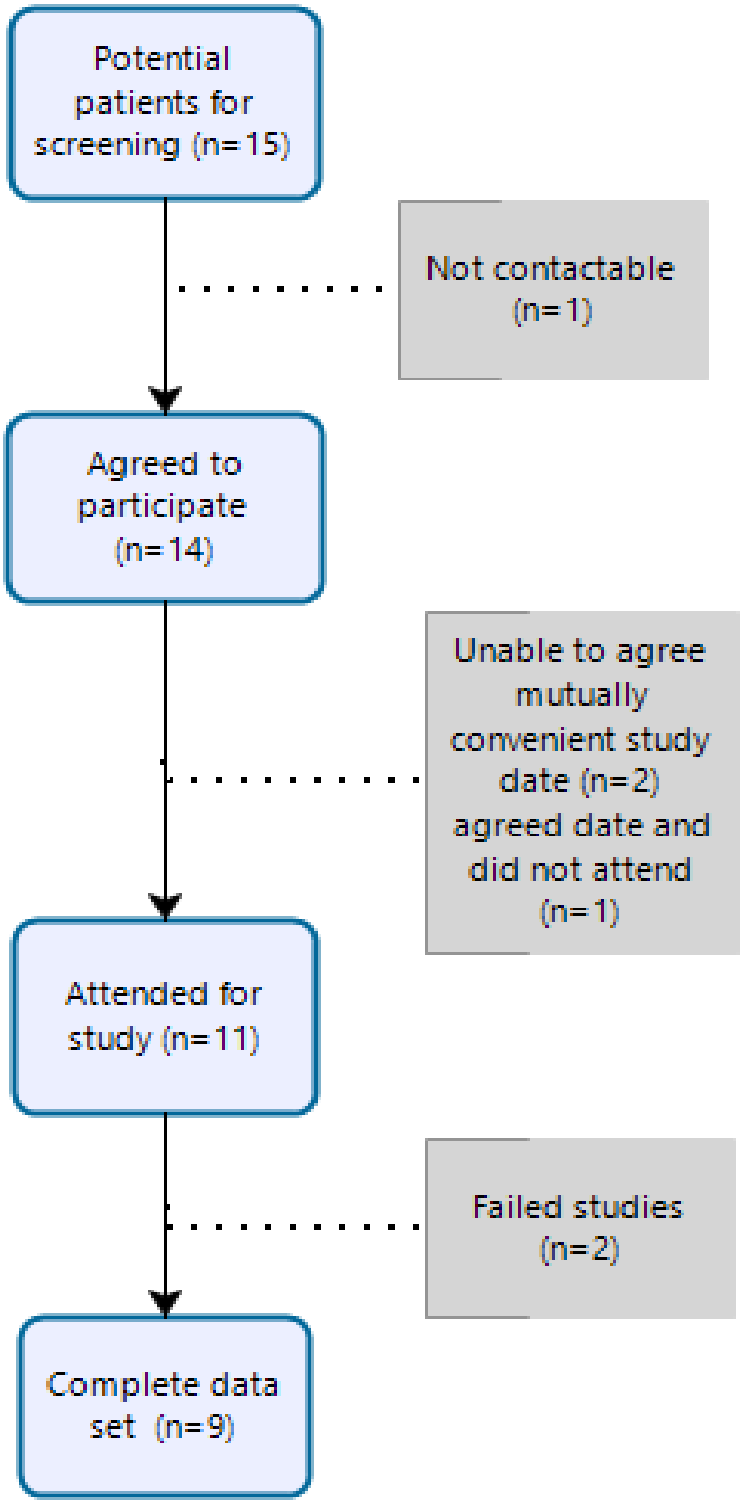

Figure 18: Flow diagram showing recruitment

Patient demographics

The sample included 5 males and 4 females. The mean ± SD age for the group was 41.0 ± 13.1 and the BMI was 50.5 ± 11.4.

The group mean ± SD AHI calculated by Embletta® after manual rescoring and WatchPAT (automatic scoring) were as follows: Embletta AHI 30.98 ± 28.78; WatchPAT AHI 44.66 ± 33.56 events per hour.

Sample size

The data from the pilot study were given to a statistician who performed a sample size calculation for the study. For the purpose of the sample size calculation, α was set to 0.05 and β to 0.85 and the correlation of interest was set to moderate (r=0.4). The sample size required after exclusions was 53.

Discussion

This was a pilot study with the primary purpose of generating data for a power calculation, which will forms the basis of the main study described in Chapter 6. The results are not discussed in detail here. The focus of this section will be to address the methodological challenges arising from this study and the learning that came from them.

There were two tests with insufficient data in this small pilot sample, representing 18% of the total sample. In one case, the test failed because the patient forgot to turn the WatchPAT® device on. In the other case, the patient

removed and replaced the uPAT® sensor after the test started which resulted in a truncated study with insufficient data for analysis. Although patients were provided with the manufacturer set-up guides for both devices and were trained in their use prior to taking the devices home, the failure rate early in this study suggested that this was not sufficient. As a result, I created a simple set-up guide for patients to use which included the step by step set up of both devices for the study and saw no further failures after this.

Chapter 6: Validation of WatchPAT® for pre-operative assessment of OSA screening in bariatric patients: Full study

Introduction

The context and background to this study is described in previous chapters and will therefore not be repeated here.

The primary aim of this study was to validate WatchPAT® as a test to screen for OSA in patients undergoing bariatric surgery. A secondary aim was to evaluate acceptability and ease of use in this patient group.

Methods

The protocol was as described in Chapter 5 with some minor amendments based on learning from the pilot study. Specifically, patients doing the sleep study at home were given a written step-by-step set-up guide in addition to a face to face demonstration of the equipment. The aim of this intervention was to reduce the risk of failed studies through user error.

The protocol was amended after a few studies had been carried out due to the discovery that a small number of patients across the clinical and research populations were suffering pain and blisters when using WatchPAT®. Further details are included in the adverse events section. The amendment to the protocol comprised of advising patients to wear the WatchPAT® probe on the 5th finger and the patient information leaflet and instructions were amended accordingly. The amendment was approved by the HRA

(Appendix 2). As the PAT signal can be taken from any finger, this change is unlikely to have affected the results.

Research Governance

This study and the amendments described above received a favourable ethical opinion form the HRA and Heath and Care Research Wales and was also approved by the Research and Development Department at ICHNT where the study was conducted and MMU who were the study sponsor. All patients received written information about the study and gave informed consent. Copies of approval documents are included in appendix 2.

Statistical Analysis

Statistical analysis was carried out using SPSS (version 26). Descriptive statistics are presented as mean ± SD or median (range). Normality of the data was assessed visually by constructing histograms and QQ plots and statistically with Shapiro Wilk. AHI from WatchPAT® and Embletta® was compared with Wilcoxon Signed Ranks test. Correlation between WatchPAT® and Embletta® AHI was assessed with Spearman's Rho. Statistical significance was set at $p<0.05$. A Bland Altman plot was constructed to assessment agreement between the WatchPAT® and Embletta® AHI. Optimal sensitivity and specificity for AHI ≥5, ≥15, and ≥20 and ≥30 events per hour were calculated with ROC analysis.

Results

Timeline of recruitment

The final data set contained 28 patients from a population of 41 patients referred to the Sleep Clinic during the time that the study was recruiting. This was less than the recruitment target of 53 patients recommended from the power calculation.

Figure 19 illustrates the recruitment timeline and impact of the COVID-19 pandemic on the project. Following ethical and Trust approvals, the first patient was recruited to the pilot study in January 2020. Opportunities for recruitment were limited by the number of eligible patients being booked to my clinic and my own capacity to study them within the NHS target waiting times. There were also some early failed studies which have been discussed previously in Chapter 5. I had aimed to recruit 10 patients for the pilot study but the study was halted abruptly in mid-March 2020 when the Trust made the decision to pause all elective out-patient and surgical activity, study leave and research. I had 9 useable datasets at this stage and decided to terminate the study prematurely to enable me to send the pilot data to the statistician and prepare the ethical application for the main study. Sleep clinics were paused for a total of 3 months during which I was briefly re-deployed to a COVID-CPAP unit before being asked to return to service to work on the reset and recover plans. I received favourable ethical opinion for the main study described in this chapter in July 2020 but research and non-essential study leave remained paused at the Trust for a further two months and I was required to seek additional Trust approvals before I was allowed to re-start. I finally received Trust approval to re-start with home studies only

in August 2020. Although my clinics re-started, opportunities for recruitment were severely limited as elective surgical pathways at the Trust remained paused to free up theatre space for urgent patients and the bariatric service discharged patients who were not yet listed for surgery. These included patients who would have populated my own clinic lists. My own service took a different approach and did not discharge booked patients and therefore my lists were filled up with GP referrals. In order to ensure I was able to catch up on missed recruitment opportunities, I decided to work with the bariatric team to promote my study among patients who would be referred to me and run additional *ad-hoc* clinics specifically for bariatric patients who were interested in participating in my study. I also purchased an additional Embletta MPR to enable me to double my research slots. These measures initially helped and I saw a steady increase in recruitment. However, between Christmas and New Year of 2021 London hospitals saw an unprecedented further surge in COVID-related admissions and the Trust board made the decision to once again pause all elective out-patient, surgical and research activity and study leave with immediate effect. I was redeployed to provide remote monitoring support for patients in the early weeks following discharge. I was not allowed to re-start the research until March 2021, after which I once again maximised recruitment opportunities with the aim of getting as close as possible to my recruitment target by late August. At this point I had to pause the study to allow myself sufficient time to analyse and write up the results for submission in late September.

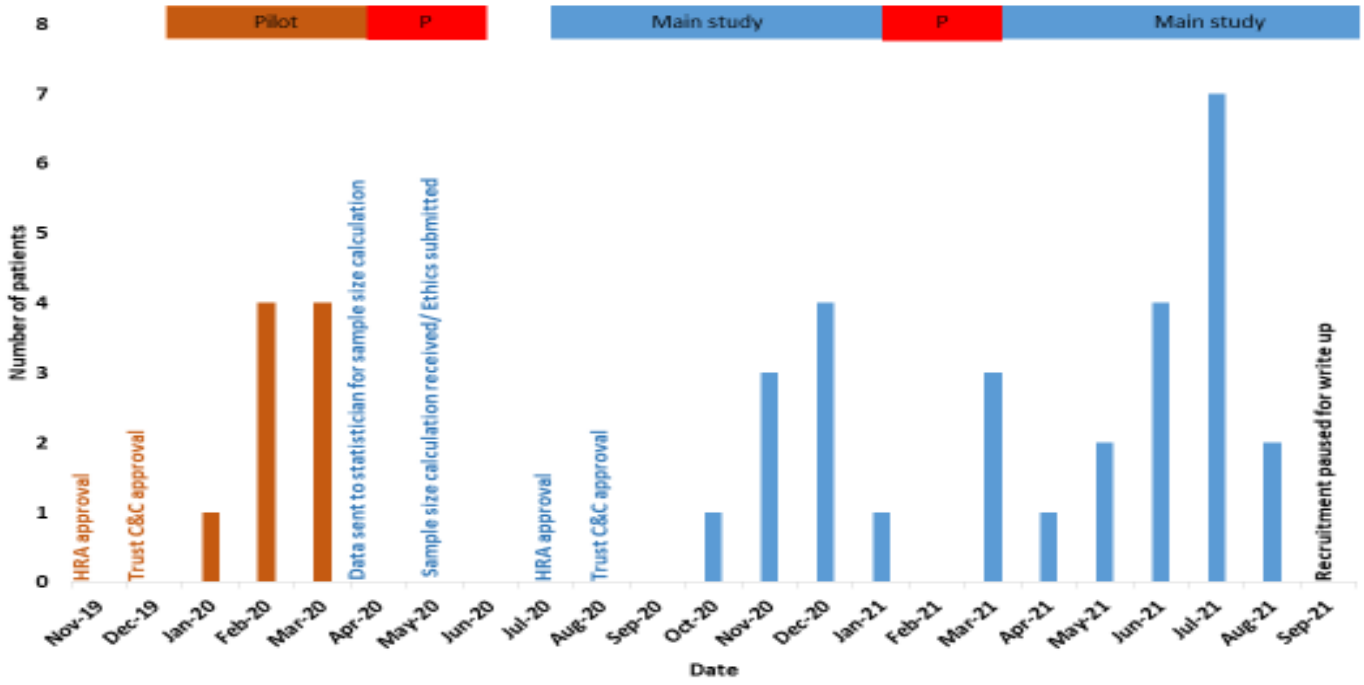

Figure 19: Study timeline showing recruitment numbers by month, major milestones and covid-related interruption

Figure 20 shows a breakdown of the recruitment process. Of those invited to take part, 81% consented and completed the protocol.

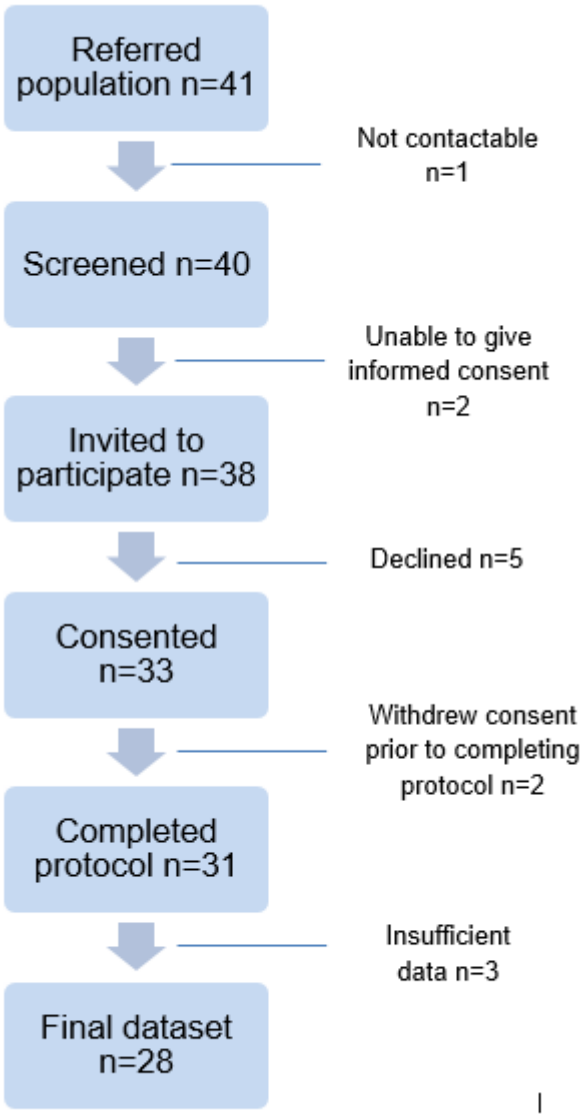

Figure 20: Recruitment flow diagram

Three datasets were excluded from analysis due to insufficient data: Two had inadequate Embletta® data (one patient wore the kit on a different day to that which it was programmed for and the other had inadequate oximetry data). One dataset was excluded due to insufficient data recorded on the WatchPAT®. On questioning, it transpired that the patient removed and replaced the WatchPAT® probe a few minutes into the study as they believed the device wasn't recording. The overall failure rate of WatchPAT® in this study was therefore 3%.

Patient demographics

28 patients (6 males and 22 females) completed the protocol and were included in the study. 26 patients completed the studies at home and 2 were carried out as in-patient studies according to the patients' preference.

The mean ± SD age of the participants was 44.1±11.6 years and BMI was 45.7±7.5 kg/ m^2.

Medical co-morbities

Table 4 lists the rate and type of medical co-morbidities in the study population. The most common type of co-morbidity was mental illness, which affected 71% of patients. 54% were diagnosed with depression or anxiety and smaller numbers were effected by other mental health issues including personality disorders (7%) PTSD (7%) and ADHD (4%). Next most common was systemic hypertension (39%) followed by chronic pain (32%), type II diabetes and GORD (each effecting 29%). 4 patients (14%) met the criteria for metabolic syndrome with a combination of diabetes, hypertension and obesity.

Table 4: Co-morbidities in the study population

Co-morbid diagnosis	**N**	**%**
Mental health disorders	20	54
Systemic hypertension	11	39
Chronic pain	9	32
Type II diabetes	8	29
GORD	8	29
Asthma	7	24
Polycystic ovary syndrome	7	24
Hypercholesterolemia	4	14
Fatty liver	4	14
Anaemia	4	14
Hypothyroidism	4	14
Vitamin D insufficiency	4	14
Migraine/ headache	4	14
Dyslipidaemia	3	11
Polycythaemia	2	7
Hiatus hernia	2	7
Endometriosis	2	7
AF	1	4
Intracranial hypertension	1	4

Sjogren's syndrome	1	4
Osteoporosis	1	4
Calcified coronory artery plaque disease	1	4
Sialadenos	1	4
Charcot foot	1	4
Chronic venous insufficiency	1	4
Menieres disease	1	4
Pre-diabetes	1	4
Folic acid deficiency	1	4
IBS	1	4
Lipodema	1	4
Detrusor hyperreflexia	1	4
Pulmonary and cutaneous sarcoidosis	1	4
Type one diastolic dysfunction	1	4
Ulcerative colitis	1	4
carpel tunnel syndrome	1	4
Lichen sclerosis	1	4
Non-diabetic hyperglycemia	1	4
Renal colic	1	4
Unspecified skin condition	1	4

Sleep study summary data

Mean ± SD for oxygen saturation, nadir SpO_2 and % time with SpO_2 below 90% are shown in Table 5. The 3% ODI calculated by WatchPAT was significantly higher than that on Embletta. The average SpO_2 on the WatchPAT was also significantly higher than Embletta. The values for nadir SpO_2 and percentage time with SpO_2 below 90% were not significantly different.

Table 5 Summary data on oxygen saturation

	Embletta	WatchPAT	P value
3% ODI (events/hr)	18.37 ± 13.22	27.82 ± 16.74	0.02
4% ODI (WatchPAT only)	-	16.53 ± 15.31	-
Average SpO_2 (%)	93.44 ± 2.10	94.43 ± 1.53	0.05
Nadir SpO_2 (%)	79.5 ± 10.73	81.36 ± 9.78	0.50
Time below 90% SpO_2 (% of recording time)	7.86 ± 15.05	2.84 ± 6.27	0.11

Comparison of AHI in the Embletta® and WatchPAT®

Visual inspection of the data suggested that AHI was positively skewed for both Embletta® and WatchPAT®. The Shapiro Wilk test for normality was carried out and the results are presented in Table 6 below.

Table 6: Shapiro Wilk test for normality

	Statistic	df	p
AHI Embletta	0.886	28	0.002
AHI WatchPAT	0.918	28	0.031

The null hypothesis is therefore rejected at the 0.05 level of significance and there is evidence that the data is not normally distributed.

PAT AHI (3% analysis) was higher than Embletta AHI (Median (range) 23.5 (3.9-70.6) versus 11.7 (0.7-46.5) events per hour; z=-4.623, p=0.000. When applying the 4% oxygen desaturation threshold to the PAT analysis the AHI was closer to that derived from Embletta but remained statistically significant (median (range) PAT 4% AHI: 14.3 (0.4-65.2) events per hour (p=0.002)).

For the remainder of this section, comparisons are made using the 3% threshold for both the WatchPAT and Embletta. The AHI from the WatchPAT (automated analysis) and Embletta MPR (re-scored) showed a strong positive correlation (r=0.849; p=0.000) (figure 21).

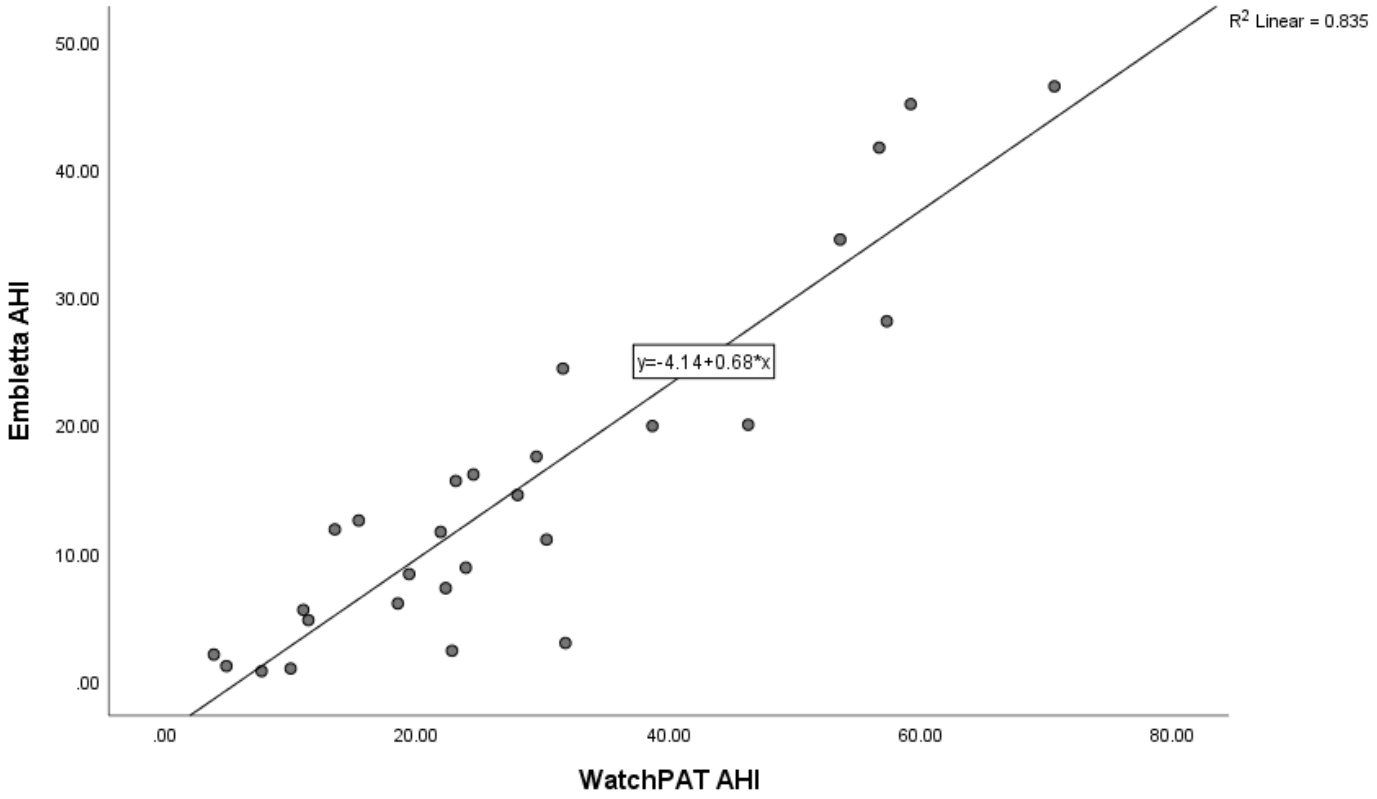

Figure 21: Correlation between AHI as measured by WatchPAT® and Embletta®

WatchPAT® AHI is plotted (X axis) against Embletta® AHI (Y-axis). The data show a strong positive correlation between the AHI measured by the two devices

A bland-Altman plot was constructed to examine the level of agreement across the range of data (Figure 22). The AHI generated automatically by WatchPAT® was persistently higher than that on the manually re-scored Embletta®. The mean bias in AHI was 13.1 events per hour. The difference in AHI tended to widen with increasing severity levels.

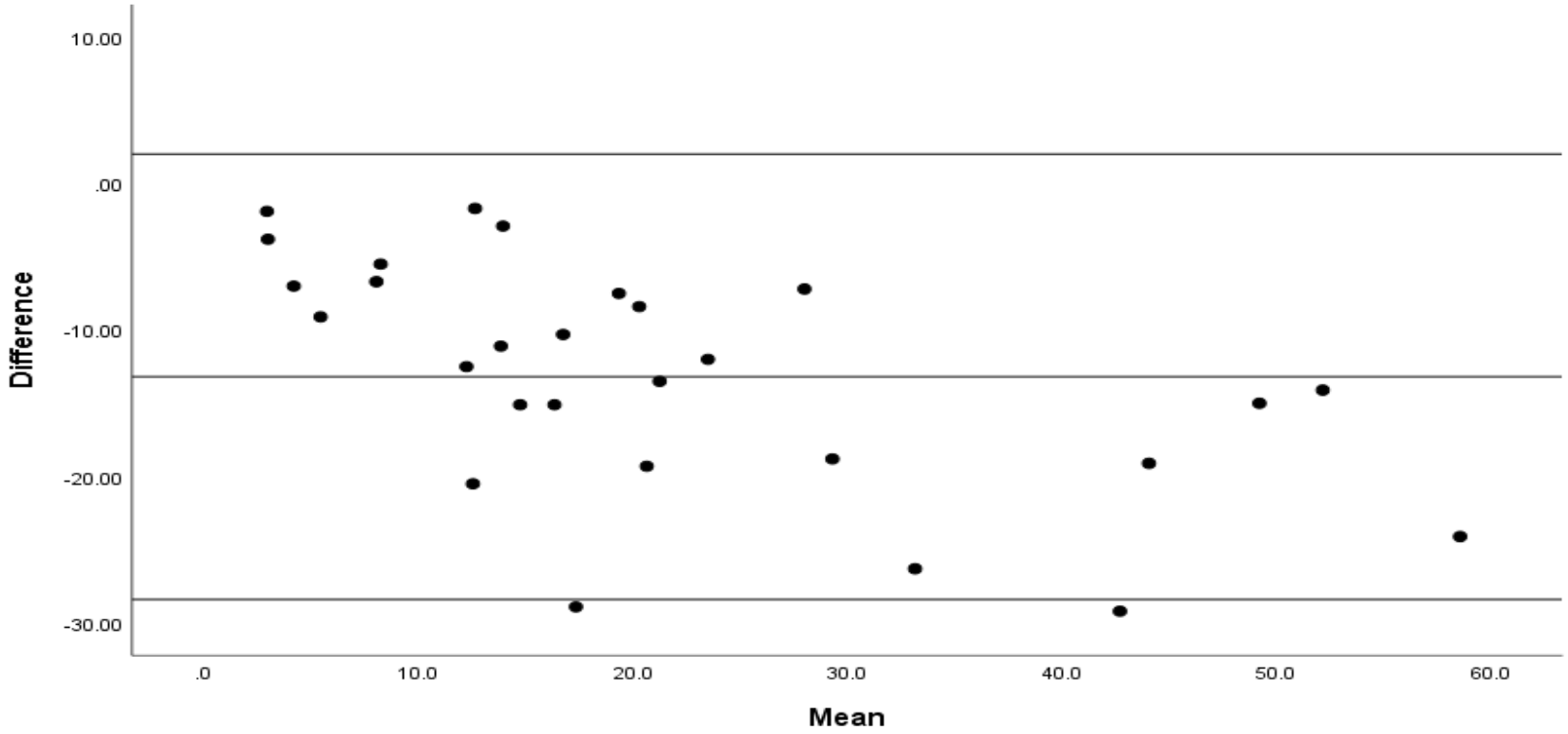

Figure 22: Bland Altman Plot showing the agreement between the WatchPAT® and Embletta® on AHI

The mean of WatchPAT® and Embletta® AHI for each patient is plotted against the difference in AHI (WatchPAT-Embletta). The horizontal bars represent the mean of the differences and 2 SDs above and below the mean difference (upper and lower horizontal bars). The plot shows a mean bias of 13.1 events per hour with a tendency for data points to diverge at AHIs >30 events per hour showing that the difference between WatchPAT® and Embletta® AHI may be greater at increasing severity levels.

The Bland-Altman plot suggests that the difference between the AHI Embletta® and AHI WatchPAT® is greater with higher mean AHI values. Therefore the relationship was explored further by plotting the difference (WatchPAT-Embletta AHI) against the Embletta® AHI (figure 23). There was a weak but significant correlation between the values ($r=0.39$; $p=0.04$).

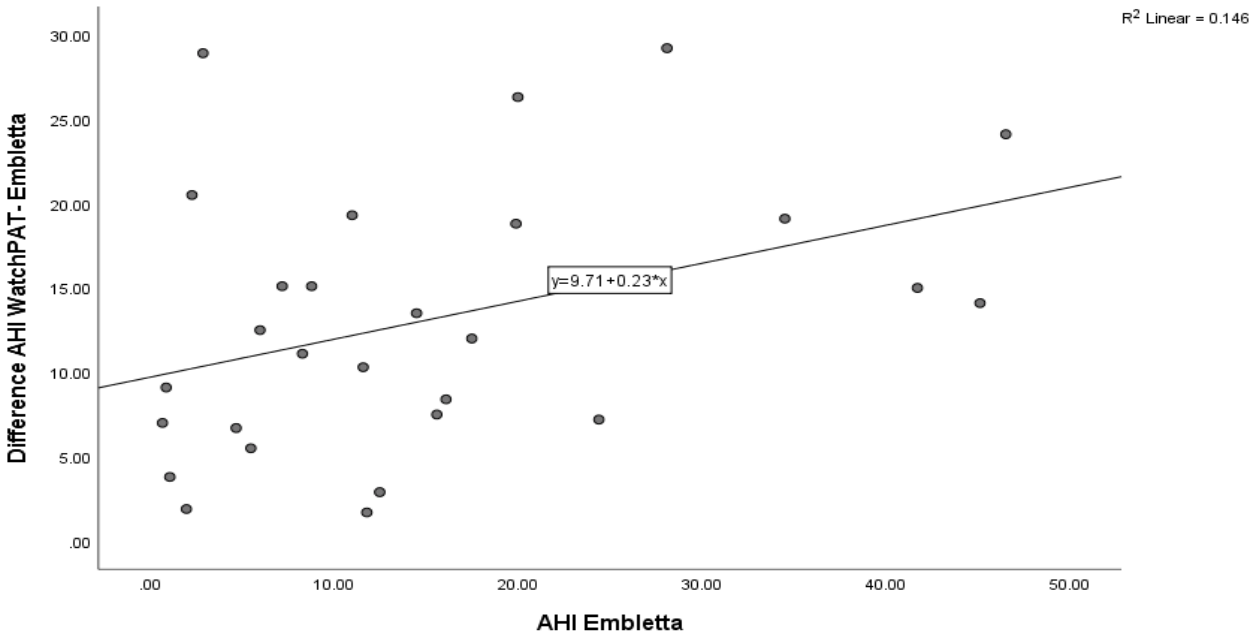

Figure 23: A scatter plot showing the relationship between the differences in AHI (WatchPAT - Embletta) to the AHI recorded on Embletta®

Embletta® AHI is plotted (X axis) against the difference in AHI (WatchPAT-Embletta) (Y-axis). A weak positive correlation is shown.

Assessment of sensitivity and specificity

Clinically relevant OSA is usually defined as an AHI ≥15 and therefore the ability of WatchPAT® to discriminate patients with an AHI above this value was of interest. Table 7 shows the classification of patients based on the Embletta® AHI (columns) and WatchPAT® (rows). WatchPAT® showed 100% sensitivity and 41.2% specificity in discriminating an AHI ≥15.

Table 7: Sensitivity and specify of WatchPAT for an AHI ≥15 events per hour

		Embletta AHI >15 events/hr		
		No, n (%)	**Yes, n (%)**	**Total**
WatchPAT AHI >15 events/hr	**No, n (%)**	7 (41.2)	0 (0)	7(25)
	Yes, n (%)	10 (58.8)	11 (100)	21 (75)
Total		17	11	28

A ROC plot was constructed to assess optimal sensitivity and specificity of the WatchPAT® to detect an AHI >15 (moderate OSA) (figure 24). The Area under the curve was 0.947 ($p<0.05$).

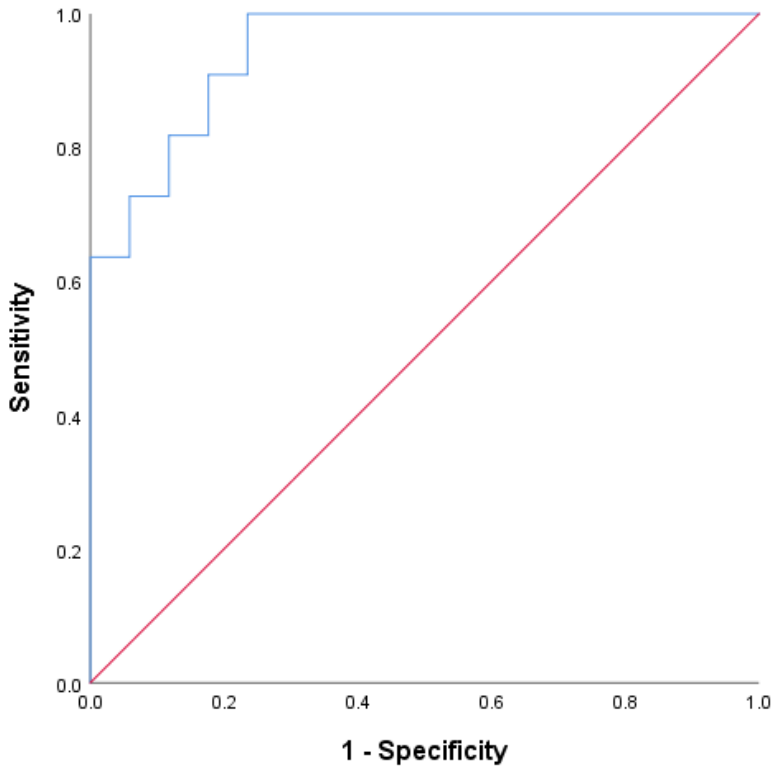

Figure 24: ROC Curve for an AHI over 15 events per hour

Sensitivity (true positives) of WatchPAT® to detect an AHI ≥15 events per hour (as defined by Embletta® AHI) is plotted against 1-specificity (true negatives) to form an ROC curve (blue line). A test with good sensitivity and specificity will have a curve close to the top left hand corner of the graph. A test with no sensitivity or specify would follow or closely follow the red diagonal line. The area under the curve AUC) is used to compare the sensitivity and specify at different cut-offs of AHI. AUC for this plot is 0.947

In order to assess the change in sensitivity and specify at alternative values, ROC curves were also constructed for an AHI ≥5 events per hour (the definition of OSA), ≥20 events per hour and ≥30 events per hour (severe OSA).

The AUC was highest for an AHI ≥20 (0.986) and AHI ≥30 (0.979), while for AHI ≥5 the AUC was 0.850.

Classification of OSA severity based on AHI

Table 8 shows the number of patients classified according to severity of AHI using established ranges (normal <5; mild 5-14.9, moderate 15-29.9; severe ≥30 events/ hour) according to Embletta® and WatchPAT® respectively.

WatchPAT® and Embletta® placed the AHI within the same severity classification in 11 patients. Where there was a mis-match in AHI classification this was consistently in the direction of WatchPAT> Embletta. Of those patents placed in a different severity category by WatchPAT® compared to Embletta®, the majority (14 patients) moved up by one severity category (i.e. from normal-mild, mild-moderate or moderate-severe). 3 patients moved by ≥2 severity categories; 2 patients had a normal AHI on Embletta® and were classified as moderate and severe by WatchPAT® respectively while 1 had a mild AHI on Embletta® and was severe on WatchPAT®.

Table 8: Severity classification assigned by Embletta® versus WatchPAT® AHI

		AHI Classification from Embletta®				
		normal	mild	moderate	severe	Total
AHI classification from WatchPAT®	normal	2	0	0	0	2
	mild	3	2	0	0	5
	moderate	1	7	3	0	11
	severe	1	1	4	4	10
Total		7	10	7	4	28

Values are presented as number of cases classified as having a normal (<5 events per hour), mild (5-14.9 events per hour), moderate (15-29.9 events per hour) or severe (≥30 events per hour) AHI using Embletta® (columns) versus WatchPAT® (rows). Highlighted cells represent agreement between the severity categories based on AHI in Embletta® and WatchPAT®.

Figure 25 is a graphical representation of the data shown in Table 8 but displayed as percentages rather than numbers of cases. This shows that 100% of cases classified as severe on the Embletta® were also severe on WatchPAT®, while those with a normal AHI on Embletta® were represented in all severity categories on WatchPAT®

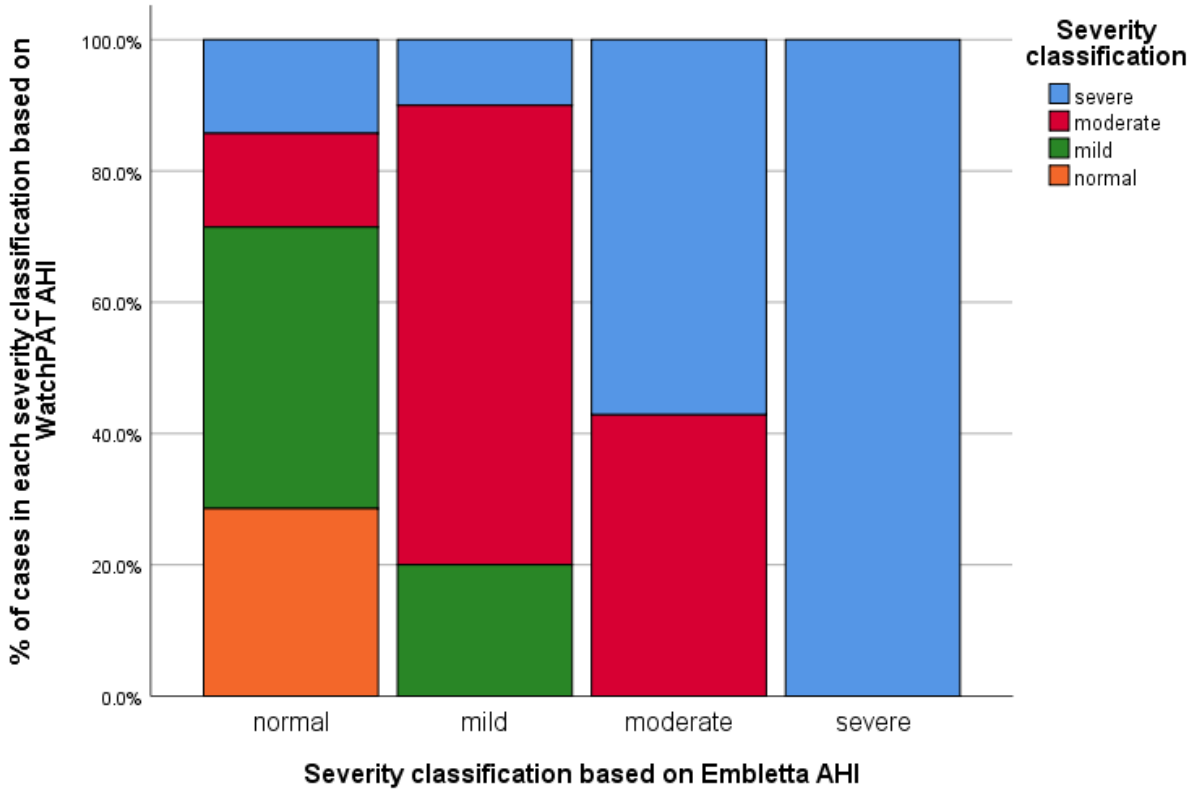

Figure 25: Percentage of patients classified as having normal, mild moderate and severe AHI on WatchPAT® as a function of Embletta® classification

The columns represent the severity classification based on the Embletta® AHI. Within each column the data is split according to the percentage of patients classified as normal, mild, moderate and severe based on the WatchPAT® AHI.

Patient Experience of Using WatchPAT®

During the course of the research, three patients shared feedback that they had experienced discomfort from wearing the WatchPAT® probe. Similar reports were received when using the device in routine clinical practice in non-bariatric patients. These reports ranged from mild and short-lived pain and stiffness to more significant levels of discomfort, including immobility of the finger lasting a few hours and painful blisters. One research participant developed a small painful blister on their finger where the WatchPAT® probe had been situated. A small number of patients in the clinical setting had also reported similar effects. The rate of these adverse events across our combined clinical and research settings was around 3%. On reporting to the manufacturer, I learned that similar events had been reported in other centres using WatchPAT®. I was advised that this could be mitigated by the patient wearing the WatchPAT® probe on the 5th finger which tends to be thinner and therefore will be less affected by the tightly fitting probe. I submitted an amendment to the HRA to include changes to the protocol and patient information sheet and this was approved. A copy of the completed amendment tool is included in appendix 2.

Study participants were invited to give optional feedback on their experience of using the WatchPAT® device. Feedback from the pilot and main study were combined and all feedback received was included in this analysis regardless of whether or not the sleep study yielded useable data. The response rate was 76%.

Ease of setting up the equipment

Patients who set up their equipment at home were asked to rate the ease of doing so using the following criteria:

- Very easy (I was able to do it myself without any help and without referring to the instructions)
- Quite easy (I needed to refer back to the instructions)
- Not very easy (I needed some help to put the equipment on)
- Not at all easy (I needed a lot of help to use the equipment/ someone put it on for me as I did not feel able to)

The responses are shown in figure 26 below. 29 patients who gave feedback were able to answer this question. Three patients scored not-applicable as they had their studies on an in-patient basis and the kit was set up for them. However two of these patients commented on their feedback form that they felt they could have done the set-up themselves without difficulty.

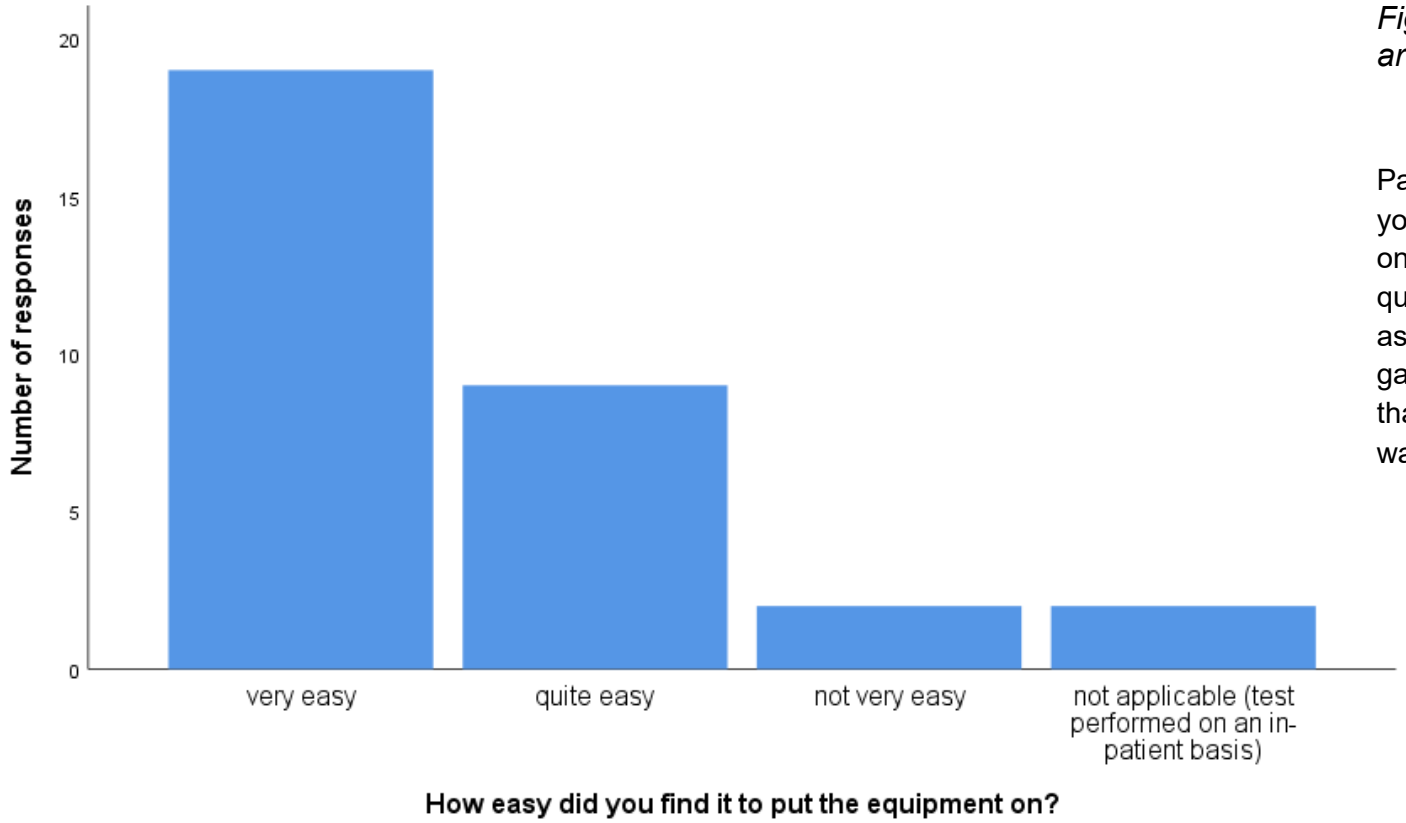

Figure 26: Feedback responses around ease of use

Patients were asked “how easy did you find it to put the equipment on?” 29 patients answered the question and the data is displayed as the total number of patients who gave each answer. The data shows that most patients felt the device was very easy or easy to put on.

Did the equipment stay on all night?

The majority of patients wore the WatchPAT® device for the whole night. 3 patients reported that they did not wear it all night. Of those who did not wear it all night, one removed it because the equipment was uncomfortable and some sensors fell off; in one case, the equipment fell off and in a third case, the patient removed it due to a perceived technical problem with the device.

How aware of the device were you during the night?

30 patients answered this question and the responses are detailed in figure 27. Options were as follows:

- Not at all aware- once it was on, I forgot it was there
- A little aware- I woke briefly and was aware of the device but it did not concern me
- Very aware- I woke a lot and found the device very intrusive/ uncomfortable

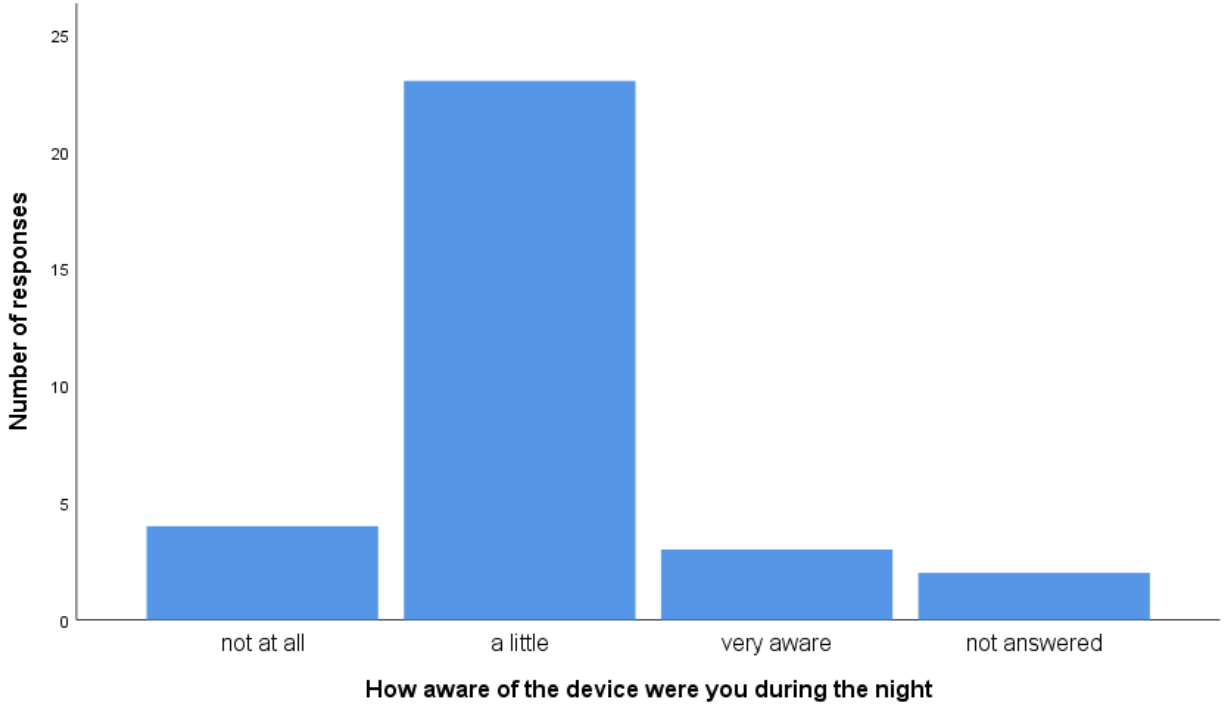

Figure 27: Feedback on device awareness

Patients were asked “how aware of the device were you during the night?” 30 patients answered the question and the data is displayed as the total number of patients who gave each answer. The data shows that most patients were a little aware”.

Acceptability of the device in clinical practice

Patients were asked to give their opinion on whether WatchPAT® could be used instead of the Embletta® device in routine screening for OSA in the bariatric surgery population. All 32 respondents answered this question and 31 said yes, they thought it would be acceptable to other patients and 1 felt it would not be acceptable.

Free text feedback

Patients were invited to give free-text feedback on their experience generally. The comments are included in Table 9 and grouped into themes.

Table 9: Free text comments

Responses have been reproduced exactly as the patient wrote them and are classified into themes for ease of reference.

Theme	**Comment**
Snoring sensor	The device, which we attach to the neck, doesn't glue much. I had to fix it with tape to keep it in place
	The sticky sensor needs to be stickier that goes on your neck/ chest
Nasal cannula (Embletta®)	Plaster on my face was not very nice to take off in the morning
uPAT® probe	Slight sore finger
	Small mark on my finger and a bit tender but no lasting issue
	Finger sore due to something digging into it
	The only issue/ concern is that the WatchPAT doesn't have an adequate facilitation for people with long nails (The Embletta does)

Comfort	It was more comfortable than the Embletta and less tangles in wires than the Embletta.
	The watch was far easier to sleep with than the traditional equipment which I find awkward and intrusive
	I managed to sleep 4-5 hours with both devices on was just uncomfortable for me.
	Impossible to sleep and half the machine came off so I had to stop. Stick pad came out. So did wires
	The equipment isn't uncomfortable
	Simple, easy to fit equipment and comfortable during the night
	more comfortable to sleep in than the other device
	The device is certainly more easier and comfortable to use. I would want this option if I had the choice

Ease of use	Much easier to use and more user-friendly
	I find the WatchPAT 300 more easy and convenient to use more than the Embletta which is more complicated and difficult to sleep with
	Did not work. Got error code 20. Got it to work after I took the device off
	WatchPAT is so compatible and light-weight, Roll it out please ☺
	Much easier than the other device
Instructions	Was not sure if I should turn it on. I couldn't remember if I had been told to or not
General	Thank you for everything
	Preferable option if it works

Patient outcomes

The nature of the bariatric pathway is such that patients may wait several years before undergoing surgery. All patients must undergo a 12-week Tier 3 weight loss

program and additionally may require psychological support to change their eating habits and optimise their chances of having a successful surgical outcome.

Figure 28 shows the outcomes for the patients included in this study. The COVID-19 pandemic has unfortunately exacerbated an already lengthy pathway and waiting times are now around two-years and many patients on the waiting list were discharged to their GP in order to manage waiting lists. At the time of writing, nine patients (32%) were on a waiting list for planned surgery. Six patients were discharged from the bariatric service without completing their pathway. Of these, two were discharged due to the pandemic, two due to non-attendances and one decided to transfer their treatment to the private sector.

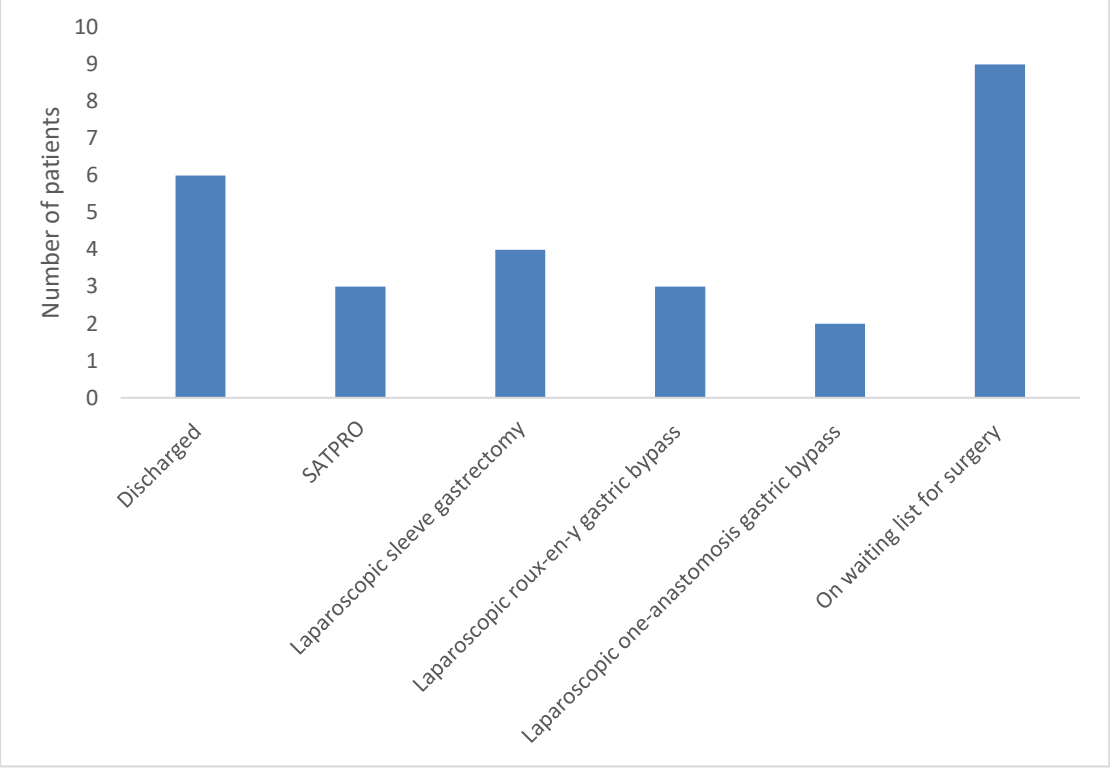

Figure 28: Outcomes for all patients

Nine patients went on to have weight loss-surgery. The most common procedure was laparoscopic sleeve gastrectomy (44% of all surgical procedures) followed by laparoscopic roux-en-Y gastric bypass (33% of all proedures) while 2 patients (22%) had laparoscopic one anastomosis gastric bypass surgery. Three of the patients had previously had a bariatric procedure (2 gastric bands, 1 sleeve gastrectomy) and one patient was intending to have revision surgery after gaining weight a year after sleeve gastrectomy but decided not to go ahead at this stage due to the burden of multiple other health issues.

Of the patients who went on to have surgery following participation in this study, none had any significant peri-operative complications. One patient had suffered intra-operative perforation of the gastric fundus during a previous surgery to remove a gastric band. They subsequently went on to have a laparoscopic one anastomosis gastric bypass which was uneventful. Another patient who had a laparoscopic roux-en-Y was noted to have a particularly lengthy procedure (>2 hours) due to adhesions from a previous caesarean section and additional surgery required to repair an umbilical hernia at the same time.

All but one patient reported some form of unwanted post-surgical side-effects at follow-up. These were generally minor and self-limiting. The most common were constipation and diarrhoea (50%) nausea or vomiting

(40%) and abdominal pain (40%). One patient reported discomfort when swallowing cold fluids. Two patients reported reflux. One patient reported a collection of symptoms including hair loss, brittle nails, low energy and headache. These were felt to be due to nutritional deficiencies and the patient was given specialist dietary advice. One patient developed biliary colic six-months after a sleeve gastrectomy and is currently awaiting laparoscopic cholecystectomy. One patient had an adverse reaction to the surgical drapes.

All patients started to lose weight following surgery but due to many of them being less than 3 months post-surgery at the time of writing, there is insufficient weight data for meaningful trend analysis. Weight loss appears to peak at around 4 months and of the 4 patients who had reached this point, the mean ± SD weight loss was 23.5 ± 4.9 % of pre-surgical weight.

3 patients did not want to have surgery and instead elected to join the SATRPO weight loss program. All three achieved reasonable weight loss (5.9, 10.0 and 15.3% respectively).

CPAP compliance

12 patients were prescribed CPAP to cover the peri-operative period and were followed up in the CPAP clinic according to routine NHS pathways. The mean ± SD AHI of patients prescribed CPAP was 26.4 ± 12.7 events/ hour compared to 6.5 ± 4.9 (p=0.0002) in those not prescribed CPAP. At the time of writing, 7 patients (58%) were still

using CPAP and 5 had decided to return it as they were unable to tolerate it.

There was no difference in the average nightly usage of those still on CPAP versus those who discontinued (mean ± SD on CPAP 4.8 ± 2.9 versus discontinued 3.03 ± 1.78 hours; p=0.25). The reasons for discontinuing CPAP were weight loss (n=1), no subjective symptomatic benefit (n=1) or intolerance (n=3). One patient did not attempt to use CPAP at all since being issued it.

Discussion

The use of PAT to identify apnoeas and hypopnoeas is a new and emerging application of this technology. There is a growing evidence base to suggest that the WatchPAT® device, which combines PAT technology with actigraphy and oximetry it is comparable to in-laboratory PSG in patients with a high pre-test probability of having OSA. The validation studies done to date and discussed in detail in Chapter 2 have typically been carried out in general sleep clinic populations. To the best of my knowledge, this is the first study to evaluate the validity of this technology in a pre-bariatric surgery population where by definition the BMI is ≥35kg/m^2. The study also used RP as the gold-standard comparator and is therefore more representative of the real-world clinical population.

Comparison of results to previous studies

This study showed a strong positive correlation between AHI in WatchPAT® and Embletta® which in line with other studies (Ayas et al., 2003, Boyd et al., 2016, Choi et al., 2010, Bar et al., 2003, Pang et al., 2007, Ceylan et al., 2012, Ioachimescu et al., 2020, Jen et al., 2020, Gan et al., 2017, Kinoshita et al., 2018, Onder et al., 2012, Penzel et al., 2004, Pillar et al., 2020, Pinto et al., 2015, Pittman et al., 2004, Pittman et al., 2006, Schöbel et al., 2018, Weimin et al., 2013, Yuceege et al., 2013, Zou et al., 2006). Whilst correlation is a useful starting point in assessing the validity of a diagnostic test, it does not provide adequate detail on how well WatchPAT® can discriminate a positive from a negative test result, an important consideration when using a diagnostic test to support clinical decision making and treatment.

This data showed a significant difference between WatchPAT® and Embletta® AHI. These findings are in direct contrast to others studies, where the AHI has been found to be similar (Ayas et al., 2003, Jen et al., 2020, Onder et al., 2012). One possible explanation for this could be differences in the gold-standard comparator device used in this study compared to others. The majority of previous studies have used PSG as the gold-standard comparator. In additional to routine respiratory signals measured by Embletta®, PSG also measures EEG, allowing sleep staging and arousals to be scored which could have a bearing on the AHI. When PSG is used, hypopnoeas can be scored when associated with an EEG arousal even if oxygen desaturation criterion is not met. Changes in the PAT signal, which is the basis of the AHI

calculation in WatchPAT® are mediated by the sympathetic nervous system and represent an autonomic arousal (Grote et al., 2003). Therefore it might be expected that the PAT AHI would more closely represent that of PSG compared to Embletta® where some events might be missed due to absence of an oxygen desaturation. One other study used RP rather than PSG as the gold-standard comparator and reported that WatchPAT® was able to detect hypopneas with high reliability (Penzel et al., 2004), though these data are only reported in abstract form with no details of the statistical approach used to back up this assertion and the sample size was small.

If the limitations of RP were the main driver behind the difference in AHI between the two diagnostic tests, it would be expected that the bias would be consistent across AHI severities. Indeed, the bland-Altman plot in this study showed that the difference in AHI between WatchPAT® and Embletta® tended to be greater in higher severity levels suggesting a cumulative effect of the bias; patients with more severe OSA might have more frequent arousals and therefore more opportunities for missed events when not using a direct measure of arousal such as PSG. Others have also demonstrated a similar divergence at higher AHI levels using the Bland-Altman plot (Pillar et al., 2020, Yuceege et al., 2013) though Gan et al. (2017) reported a tendency to over score the AHI at lower levels while underscoring at higher levels. Furthermore, plotting the difference in AHI (WatchPAT – Embletta) against the AHI measured by Embletta® showed only a modest correlation and it may be that other factors are influencing the bias.

The mean bias in AHI this study was 13.1 events per hour. Ioachimescu et al. (2020) also looked at the mean bias in

large sleep clinic population and reported a bias of +4.2 when using the 3% oxygen desaturation criteria to score AHI as we have. To further understand how the bias in AHI might change clinical practice, this study classified the patient group by severity (normal, mild, moderate and severe) using the AHI generated by WatchPAT® and Embletta® respectively. This study found that that where the two devices put patients into different severity categories, they typically moved by one severity level (normal- mild, mild-moderate or moderate-severe). In clinical practice, treatment would not normally be recommended in an asymptomatic patient with mild OSA and therefore movement across the normal- mild boundary may be of limited clinical significance. Furthermore, a change between moderate- severe OSA would not likely to be clinically significant. However a small number of patients moved by 2 or more severity categories. Two patients with a normal AHI on Embletta® were classified by WatchPAT® as moderate and severe respectively, while one patient with mild OSA on Embletta® was classified as having severe OSA by WatchPAT®. The clinical relevance for these three patients should not be underplayed; the consequence of an over-estimated AHI may be that a patient receives a life-changing diagnosis and unnecessary treatment.

The majority of studies have not looked at individual data in this level of detail and have generally used statistical processes such as ROC curves to identify the optimum sensitivity and specificity for a given AHI value. When applying this type of analysis to this study using an AHI cut-off of ≥15 events per hour (the value at which clinically significant OSA is defined), WatchPAT® had 100%

sensitivity but just 41.2% specificity, demonstrating that there was a high false positive rate in this patient group. Using ROC analysis to evaluate the AUC at different AHI cut-offs, WatchPAT® was found to have the lowest AUC at AHI values <5 events per hour and greatest AUC at AHI values >20 events per hour. The ROC analysis in this study was similar to previous reports (Ayas et al., 2003, Bar et al., 2003, Jen et al., 2020, Kinoshita et al., 2018, Pillar et al., 2020, Pinto et al., 2015, Pittman et al., 2004, Pittman et al., 2006, Tauman et al., 2020b, Weimin et al., 2013, Yuceege et al., 2013, Zou et al., 2006).

In summary, the results of this study are similar to those of other studies performing similar statistical analyses. It is important to consider the data in the context of clinical as well as statistical significance; a notion that many studies have overlooked. Outliers are a particularly interesting group which have been under-explained in other studies. In the section to follow, I will offer explore some possible reasons for the exaggerated bias in AHI seen in this study.

Potential predictors of WatchPAT® accuracy

The small sample size and small number of outliers in this study precluded detailed statistical modelling of factors which might explain why WatchPAT® over-estimated the AHI to such an extent in some patients. The three patients with significantly over-estimated AHIs were all females and one had poorly controlled diabetes. None were on any medications that would expect to alter the PAT signal. This section will therefore focus on overall bias.

The WatchPAT® does not directly measure airflow as PSG and RP do. Instead, it measures sympathetic changes in

PAT to identify arousals which the algorithm then combines with data from the pulse, oxygen saturation, snoring volume and body position signals to determine whether the PAT change was caused by an apnoea or hypopnoea or some other non-respiratory event. Higher levels of sympathetic nervous system activation have been reported in bariatric surgery patients (Guarino et al., 2017). The mechanism is unclear but a link has been reported between leptin and sympathetic nervous system activity (Eikelis et al., 2003). Leptin in turn is marker for body fat mass rather than BMI (Rosenbaum et al., 1996). High levels of sympathetic activity were anecdotally noted in the raw PAT signals of some patients in this study but accurately quantifying symapthetic activity would be challenging and is beyond the scope of this study. Nevertheless, it is possible that the WatchPAT® algorithm may be interpreting this increase in PAT signal for arousal from sleep.

In addition to having an increased sympathetic activation, patients with very high BMI such as those in this study, they tend to have a lower baseine SpO_2 and desaturate frequently and often disproportianately to the reduction in airflow (Peppard et al., 2009). In this study, there was a large range in the percentage of the recording with an SpO_2 below 90%. At saturation values below 90%, the oxyheomogolbin dissociation curve predicts that changes in ventialtion with cause a greater drop in oxygen saturation than the same change with a higher baseline SpO_2. This means that in addition to having high levels of PAT activiation, there may be desaturations which would result in the algorithm incorrectly scoring a hypopnoea whereas on the Embletta®, where flow can be measured directly,

the hypopnoea would not be scored as the atenuation in the airflow signal was either of insufficient magnitude, duration or both.

This study used a 3% oxygen desaturation criteria to score hypopnoeas in the WatchPAT®. However, in the bariatric patient group who tend to desaturate frequently, a 4% desaturation threshold may be more appropriate and result in a lesser tendancy for false positives when scoring respiratory events due to the more robust criteira. Indeed Ioachimescu et al. (2020) found that the WatchPAT® scoring bias shifted in the oposite direction when the 4% threshold was used to score respiratory events. The reason for choosing the 3% rather than 4% threshold was that a 3% threshold is used when scoring the Embletta® clincially and it was preferable to use the same threshold for scoring using both devices so as to keep potential souce of bias to a minimum.

The combination of high levels of sympathetic activation, possibly mediated by leptin, a marker of body fat mass, plus noctural hypoventilation placing patients on the steep part of the oxyheamoglobin curve may therefore come together in bariatric surgery patients resulting in scoring of additional apnoea and hypopnoea events in this patient group.

Impact of co-morbidies on WatchPAT accuracy

Patients with co-morbid conditions or taking medications known to affect the PAT signal were excluded from taking part in this study. However, as identified in Table 4, the patients included in this study had a number of co-

morbidities and the potential influence of these will be reviewed here.

Systemic hypertension was the second most common co-morbidity in the patients included in this study, affecting 39% of the sample. Weisrock et al. (2017) tested the reliability of the PAT signal in patients with arterial hypertension, heart failure and diabetic neuropathy as a tool to assess endothelial dysfunction. They reported that while test-retest reliability of natural logarithmic transformed hyperaemia index, a measurement derived from the PAT signal, was acceptable in heart failure and diabetic neuropathy, reliability was poor in hypertensive patients. Although in the context of OSA, the measurement of interest is the change in global PAT amplitude rather than the absolute value, this study does raise an important question around whether PAT is reliable and valid for use in hypertension.

There is limited data available to assess the accuracy of WatchPAT® in the context of hypertension specifically and given that it is a common co-morbidly in both obesity and OSA, it may be difficult to assess this. In a study published only in abstract form. Kinoshita et al. (2019) report that the correlation between WatchPAT® and PSG-derived AHI was lower in hypertensive compared to normotensive patients but increased with angiotensin receptor blockers. The reason for this difference is not explained and to the best of my knowledge, these data have not been published as a full paper. Previous validation studies have included hypertensive patients in their samples and found strong correlations between the WatchPAT® and PSG, (Zou et al., 2006, Yalamanchali et al., 2013b) suggesting that hypertension probably does not significantly impact the

accuracy of WatchPAT® to detect OSA. (Schnall et al., 2022).

Chronic pain was reported in 32% of patients in the study sample. To the best of my knowledge, no studies have been carried out to investigate the impact of pain on the PAT signal. However diabetic peripheral neuropathic pain has been shown to be associated with an increase in peripheral alpha-1 adrenergic receptor activation (Teasell and Arnold, 2004) and given the importance of this pathway to the PAT signal, it is plausible to assume that chronic pain might have an impact on WatchPAT® accuracy.

Finally, one patient had AF. Given that the WatchPAT® algorithm uses pulse rate rises, together with PAT amplitude as core signals in determining whether an arousal has occurred, it is important to consider whether AF should be an exclusion criteria. Tauman et al. (2020a) validated Watch PAT against PSG in 101 patients with known AF, 46 of whom had AF episodes on the night of the study. They reported a strong correlation between WatchPAT® and PSG-derived AHI with no increase in excluded signal time in those with AF episodes compared to those without.

Patient feedback

To the best of my knowledge, this was the first study to analyse patient feedback. The majority of patients gave positive feedback on their experience of using WatchPAT® and felt that it would be acceptable to use in the clinical pathway. Ease of use is an important consideration for any device that will be used by patients in a clinical pathway

and the majority of patients reported that they were able to fit the device themselves.

A small number of patients reported developing pain and/ or blisters from the tightly- fitting probe which did not recur after advising them to fit the probe on the fifth finger. This may be an important consideration in bariatric patients who may have larger swollen fingers than the average sleep clinic population. One patient gave feedback about the enclosed and rigid design of the probe, which was not accommodating to long fingernails, something that can be easily accommodated in other types of SpO_2 probe, such as the one with the Embletta®. This may be a barrier to use by some patients. Nevertheless, the majority felt that the device would be acceptable if integrated into the clinical pathway.

Impact of the COVID-19 Pandemic

The COVID-19 pandemic had a significant and lasting impact on this study. The intention was to recruit 10 patients to the pilot study but after recruiting and studying 9 patients, the Trust board at ICHNT made the decision that all elective activity and research must be paused to allow staff to be redeployed to support critical and acute care, thus preventing further recruitment. I made the decision to end the pilot study with 9 patients and use the time during lockdown to have a statistician complete the power calculation to enable me to begin to prepare the application for the main study. Elective activity resumed 3 months later but I experienced further delays in restarting the research as ICHNT put in place additional approvals to ensure that the research could resume safely in light of

new COVID precautions. Morbidly obese patients are considered more vulnerable to COVID-19 and therefore adaptations needed to be made, including ensuring that all participants had their test at home rather than in hospital. Even after securing the approval to resume the research, recruitment was slow as elective surgery remained closed for a further two months and many patients already in the system but not yet ready to have surgery were discharged to reduce pathway bottlenecks. A second wave of elective activity cancellations and redeployment of staff including myself was announced in early January 2021 and lasted for 2 months. In total, the bariatric service was closed for 8 months since the start of the pandemic and my own Sleep Service was closed for 5 months resulting both in significant disruptions to the ability to recruit at key points in the project and delays as services re-mobilised after long closures.

Due to the stage that the project was at during the first wave and the fact that any project involving patients would require further ethical approvals and because non- COVID related research was not being reviewed by research ethics committees, I made the decision that it would be better to continue with the study as planned than to attempt to change to an alternative project at that stage. However, this did lead to a sample size significantly less than planned which is clearly a limitation to the study.

Limitations

The sample size was small and significantly less than that required by the power calculation. Although consent to participation in the study in eligible patients was high, this

was not sufficient to mitigate the impact of the COVID-19 pandemic. Despite this, the study has produced data that is similar to the findings of previous studies. A larger study would have enabled further phenotyping of the data which might provide additional insight into the reason for outliers.

Another limitation was the use of RP as the gold standard comparator rather than PSG, as is commonly used in other studies. This was chosen as RP is the standard test used in routine clinical practice in this patient group and the study aimed to determine the accuracy of WatchPAT® in a clinical context but it is possible that in not measuring arousals, the difference between WatchPAT® and Embletta® AHI may be artificially elevated.

The Embletta® AHI was manually re-scored according to well-established clinical guidelines (Berry et al., 2018) while the WatchPAT® AHI was taken from the automated algorithm. This is a potential source of bias as by visually verifying and scoring the Embletta® AHI, the accuracy of scoring would be improved. On the other hand, the WatchPAT® AHI was not verified. Although there are published scoring guidelines for manually editing WatchPAT® events, expertise in interpreting the raw data in this relatively new technology is limited and where it is used within the NHS, the automated algorithm tends to be used. In the absence of an opportunity for peer-assessment of the accuracy of my scoring of the raw signals in WatchPAT®, I felt there would be a risk of bias if the WatchPAT® data were manually re-scored.

Finally, the patient group in this study was predominantly female which is typical of the bariatric surgery population but not of the general clinic population. A larger dataset

may lend itself to further phenotyping and exploration of the role of gender in this patient group which is not possible with this study due to the low number of males.

Future work

This data showed a bias in the AHI scoring which was higher than seen in previous studies with the general sleep clinic population and it would therefore be interesting to extend this study to include patients from the general sleep clinic population. For instance, comparison with those with a lower BMI may determine whether this finding is driven by obesity or the fact that this study used RP as the gold standard comparator.

As the patients in this study will have bariatric surgery in the future, resulting in rapid weight loss, it would be interesting to carry out a longitudinal study after surgery to determine whether accuracy of the AHI improves as the patient loses weight.

This study also included some patients who might have concurrent hypoventilation but the numbers were too small to draw any conclusions on whether this would have had a significant impact on the agreement of AHI. Expanding the study to include a larger patient group could allow further exploration of this question.

Conclusion

In conclusion, this study has demonstrated that WatchPAT® provides a reasonable estimation of the AHI in most patients on the bariatric pathway though there are some notable outliers that are as yet not fully explained.

Chapter 6: Validation of WatchPAT® for pre-operative assessment of OSA screening in bariatric patients: Full study

Chapter 7: General Discussion

The aim of this thesis was to assess the validity of WatchPAT® in identifying clinically significant OSA in a pre-bariatric surgery population. To the best of the author's knowledge, this is the first study to validate WatchPAT® in bariatric surgery patients. Chapter 1 set the context, identifying why this group is at risk for OSA and set out the clinical pathway that patients typically follow. The thesis discussed the challenges in assessing an asymptomatic population with high BMI and often poor mobility within the sleep clinic and the burden that rising levels of obesity and demand for pre-operative screening for OSA in bariatric surgery places in addition to GP referrals from the typically symptomatic sleep clinic population. WatchPAT® is increasingly being used clinically and has a wealth of validation literature to support this, but as identified in chapter 2, no studies to date had validated WatchPAT® to be used in pre-surgical screening for bariatric surgery. The principles and practical application of sensors used in the studies in this thesis were described in chapter 3. Chapter 4 was a small inter-rater reliability study to test the reliability of RP scoring within and between raters. Chapter 5 was a pilot study on which a power calculation was performed to determine how many patients would be required for a full study aimed at validating WatchPAT® for the detection of OSA in the pre-bariatric surgery population and chapter 6 was a full validation study comparing the AHI generated by WatchPAT® with the clinical standard, RP (Embletta®) in patients referred for bariatric surgery.

Although the final sample size was smaller than originally planned, the data presented in Chapter 6 suggest that WatchPAT® is likely to be a reliable in determining whether a patient has clinically relevant OSA (AHI≥15 events per hour). The data presented was similar to the finding in previous studies. WatchPAT® over-estimated the AHI and the difference was both higher than other similar studies and also potentially clinically significant for some patients; whilst the high levels of sensitivity for detecting moderate OSA is reassuring, the relatively high rate of false positives could result in unnecessary CPAP prescription and over-treatment in some patients. The data presented in chapter 6 showed that long-term adherence to CPAP therapy in this group was generally low at 58% and of those who did use it, nightly usage was variable and often below what would be considered therapeutically meaningful. Similar findings are reported in the literature with one study showing that in asymptomatic patients who have been prescribed CPAP for peri-operative use, just 61% of patients used CPAP consistently prior to surgery (Nguyen et al., 2017).

Non-compliant patients often take up significant Physiologist time and resources with increased follow-up requirements and therefore an increase in false positives is a significant consideration if WatchPAT® were to be introduced into the patient pathway.

On the other hand, the test was generally well tolerated and in some cases favoured by patients. Anecdotally, morbidly obese patients often report poor sleep quality, insomnia, pain and general discomfort at night. The test in routine use for screening for OSA in this patient group, the Embletta®, requires the patient to wear a range of sensors

including closely fitting bands around the chest and abdomen and a nasal cannula in the nostrils. This equipment is generally well tolerated in patients who are abnormally sleepy and are motivated to do a test to obtain a diagnosis and treatment, but for bariatric patients, the nature and multitude of sensors can feel intrusive and be less well tolerated resulting in a risk of poor quality tests. In addition, the Embletta® needs to be manually scored by a skilled Physiologist. Scoring in the bariatric surgery population is often more challenging due variable airflow, concurrent hypoventilation and frequent desaturations. Phua et al. (2021) compared the time to diagnosis and cost between WatchPAT® and in laboratory PSG and found that patients having WatchPAT® had a significantly shorter time to diagnosis and reduced cost, making it an attractive proposition for pre-surgical screening for OSA.

Implementation of WatchPAT into the bariatric patient pathway

Prior to undertaking the studies in this thesis, WatchPAT was being used clinically in a small number of patients (average 16 patients per year) in the service. The main barriers to wider take-up included cost, a reticence among clinicians to trust new technology and lack of trained staff to interpret the data. WatchPAT was predominantly used in patients who had failed or were unable to manage respiratory polygraphy at home where in-patient studies were limited during the pandemic and as a follow-up study to check efficacy in patients using a mandibular advancement device.

Following the completion of this study and the clear preference for WatchPAT over Embletta expressed by

patients, I explored how WatchPAT could be integrated into the pathway. Based on annual referral numbers, I found that using WatchPAT in place of Embletta would increase costs for the service by approximately £2129 annually with little direct benefit to the service (Table 10).

Table 10: Cost implications of WatchPAT versus Embletta assuming 76 patients are studied annually

	Embletta	**WatchPAT**
Fixed per test consumables	£7.39 Breakdown: Nasal Cannula: £128.56 for 50 RIP belts: £94.42 for 20	£50.00 Breakdown: Box of 12 uPAT probes: £600.00
Maintenance (estimated per patient share of consumables based on 76 patients and typical lifespan of consumables)	£14.59 Breakdown: Replacement snap sensor for RIP belts: £31.17 x 2 =£62.34 Elastic strap: £23.37 Oximeter X-pod: £852.60 Oximeter soft sensor: £170.92	NA (kit on loan so maintenance is manufacturer responsibility)

Estimated total cost per patient	£21.98	£50.00
Estimated annual cost	£1670.48	£3800.00

The COVID-19 pandemic significantly increased pressures on the NHS with many services pausing activity for significant periods. This has resulted in significant backlogs coupled with a rebound increase in referrals of patients who delayed seeing their GP during the pandemic. As a result, clinic waiting times have increased substantially and performance against the referral to treatment target is declining. Revisiting the patient pathway set out in figure 2, I considered whether the initial out-patient consultation added anything to the management of the bariatric surgery patient. Anecdotal clinical experience has shown that bariatric surgery patients typically present differently to those referred by their GP. These patients are frequently asymptomatic and unlike other patient groups, are offered CPAP treatment based on AHI and peri-operative risk rather than

symptoms. I therefore proposed a new pathway for suitable patients on the bariatric pathway where they could be booked directly for a WatchPAT study following vetting. Such patients could be discharged directly by letter following a normal study or if the AHI was below 20 events/ hour. If the result is abnormal, the patient would be offered a follow-up to discuss the results and rational for starting CPAP pre-operatively.

To ensure appropriate and sustainable use of resources the referral criteria were as follows:

- Accepted for a Tier 4 (bariatric surgery) pathway
- Identified as at risk of OSA and requiring pre-operative screening
- No subjective sleep complaints (such patients would benefit from being clinically assessed)
- Medication list to be included with referral (alpha-receptor blockers and long-acting nitrates are exclusion criteria)
- Must not have a pace-maker
- Must not have unstable AF

Approval to trial the pathway as a pilot was granted in May 2022 and the first patient was booked in early June 2022. The rate at which patients can be seen is currently limited by the number of WatchPAT devices the service can hold (currently one for clinical use due to low numbers of tests run) and the availability of staff able to analyse and interpret the tests (currently limited to the author and one other). To date a total of 10 patients have been referred and clinically triaged direct to study using WatchPAT.3 have had their study, 3 are booked for future appointments and a further 4 are yet to be booked.

At this stage, it is too early to draw any conclusions on the operational impact of the new pathway. However, if referrals continue at the same rate, it is likely that we will study more patients annually than we have previously. It is unclear at this stage whether this would represent a real increase in referrals or is a measure of the pathway being shortened by the removal of the initial clinic appointment. The data will be analysed in six months' time where I would expect there to be sufficient numbers to draw meaningful conclusions. The outcome measures of interest will include number of clinic appointments saved (number of patients who would have had an initial clinic assessment minus additional follow-up), overall length of pathway (referral to treatment) and satisfaction data from patients and key stakeholders. If these measures are favourable, the data will form the basis of a business case for wider implementation.

Conclusion

In conclusion, WatchPAT® has been shown to be accurate in determining the AHI in a population of bariatric surgery candidates when compared to the Embletta®. Feedback from patients has shown that the device is likely to be acceptable to patients. Further research is needed to confirm these results in a larger population before recommending its introduction into the clinical pathway. The potential benefits of doing so, if it is deemed valid have been discussed and a new and innovative patient pathway with potential to save time and reduce visits to the hospital is proposed.

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References

Appendix 1: Preparing the proposal

DClinSci C1 Unit Oral Presentation Report

Section 1: Student

Name of Student:	Gillian Twigg
Title of Project:	A validation study of a device based on peripheral arterial tonometry for the detection of obstructive sleep apnoea in patients due to undergo bariatric surgery.

Section 2: Report and Recommendation

Please provide a report on the explanation of the work and response to questions.
The student presented a very clear synthesis of the relevant scientific evidence which was appropriate for a lay audience together with explaining a clear rationale for the project and its potential clinical benefit. The examiners noted that the project was very clearly explained at a level suitable for a non-specialist audience. The examiners' noted the clinical importance of the project, which was clear from the identified gaps in the current scientific literature. The student demonstrated a sound understanding of research methodology. The panel further noted that the student responded very clearly and positively during the question and answer session with the examiners. The examiners also noted that the style of presentation was excellent.
Overall Recommendation
Pass
Feedback *In the event of a fail being awarded, please provide detailed feedback to the student on what is required in order to attain a pass mark.*

Examiners:

Dr Garry McDowell (in the Chair)
Prof Mark Slevin (Neurophysiological Science)
Dr Martin Stout (Cardiac-, Respiratory & Sleep- and Vascular Science)
Ms Jane Lynch (NSHCS External Advisor)
Mr Ray Rawlinson (Lay Representative).

Appendix 2: Research Governance approvals

This section includes copies of the relevant research governance approval documents which were obtained for the studies described in this thesis. The following documents are included:

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Dr Martin Stout
School of Healthcare Science
Manchester Metropolitan University
Chester Street, Manchester
M1 5GD

Email: hra.approval@nhs.net
HCRW.approvals@wales.nhs.uk

07 November 2019

Dear Dr Stout

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Validation of a device based on peripheral arterial tonometry (PAT) for assessment of obstructive sleep apnoea prior to bariatric surgery: A pilot study. (version 1.0 Date 26.07.2019)**
IRAS project ID:	**252272**
REC reference:	**19/LO/1658**
Sponsor	**Manchester Metropolitan University**

I am pleased to confirm that HRA and Health and Care Research Wales (HCRW) Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **252272**. Please quote this on all correspondence.

Yours sincerely,

Kevin Ahmed
HRA Approvals Manager

Telephone: 0207 104 8171
Email: hra.approval@nhs.net

Copy to: *Ms Ramona Statache*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper		12 August 2019
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only)		28 November 2018
GP/consultant information sheets or letters	1.0	25 May 2019
IRAS Application Form [IRAS_Form_23092019]		23 September 2019
Letter from sponsor		12 August 2019
Non-validated questionnaire	1.0	26 July 2019
Organisation Information Document	1.0	11 October 2019
Other [Local information pack covering email]	1.0	12 August 2019
Participant consent form	1.0	26 July 2019
Participant information sheet (PIS)	1.0	26 July 2019
Referee's report or other scientific critique report		07 June 2019
Research protocol or project proposal [Protocol V1.0]	1.0	26 July 2019
Schedule of Events or SoECAT	1.0	12 August 2019
Summary CV for Chief Investigator (CI) [Dr Martin Stout]		02 January 2019
Summary CV for student		19 May 2019
Summary CV for supervisor (student research)		02 January 2019
Summary CV for supervisor (student research)		25 March 2019
Summary CV for supervisor (student research)		25 April 2019

IRAS project ID	252272

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is not requesting and does not expect any other site agreement to be used.	No study funding will be provided to sites as per the Organisational Information Document	A Principal Investigator should be appointed at study sites	The sponsor has confirmed that local staff in participating organisations in England who have a contractual relationship with the organisation will undertake the expected activities. Therefore no honorary research contracts or letters of access are expected for this study.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Ymchwil Iechyd a Gofal Cymru
Health and Care Research Wales

NHS
Health Research Authority

Prof Mark Slevin
School of Healthcare Science
Manchester Metropolitan University
Chester Street, Manchester
M1 5GD

Email: approvals@hra.nhs.uk
HCRW.approvals@wales.nhs.uk

30 July 2020

Dear Prof Slevin

HRA and Health and Care Research Wales (HCRW) Approval Letter

Study title:	**Validation of a device based on peripheral arterial tonometry (PAT) for assessment of obstructive sleep apnoea prior to bariatric surgery**
IRAS project ID:	**284509**
Protocol number:	**23995**
REC reference:	**20/WA/0197**
Sponsor	**Manchester Metropolitan University**

I am pleased to confirm that **HRA and Health and Care Research Wales (HCRW) Approval** has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications received. You should not expect to receive anything further relating to this application.

Please now work with participating NHS organisations to confirm capacity and capability, in line with the instructions provided in the "Information to support study set up" section towards the end of this letter.

How should I work with participating NHS/HSC organisations in Northern Ireland and Scotland?
HRA and HCRW Approval does not apply to NHS/HSC organisations within Northern Ireland and Scotland.

If you indicated in your IRAS form that you do have participating organisations in either of these devolved administrations, the final document set and the study wide governance report (including this letter) have been sent to the coordinating centre of each participating nation. The relevant national coordinating function/s will contact you as appropriate.

Please see IRAS Help for information on working with NHS/HSC organisations in Northern Ireland and Scotland.

How should I work with participating non-NHS organisations?
HRA and HCRW Approval does not apply to non-NHS organisations. You should work with your non-NHS organisations to obtain local agreement in accordance with their procedures.

What are my notification responsibilities during the study?

The standard conditions document "*After Ethical Review – guidance for sponsors and investigators*", issued with your REC favourable opinion, gives detailed guidance on reporting expectations for studies, including:

- Registration of research
- Notifying amendments
- Notifying the end of the study

The HRA website also provides guidance on these topics, and is updated in the light of changes in reporting expectations or procedures.

Who should I contact for further information?
Please do not hesitate to contact me for assistance with this application. My contact details are below.

Your IRAS project ID is **284509**. Please quote this on all correspondence.

Yours sincerely,
Ann Parry

Email: HCRW.approvals@wales.nhs.uk

Copy to: *Ms Rachel Heron*

List of Documents

The final document set assessed and approved by HRA and HCRW Approval is listed below.

Document	*Version*	*Date*
Covering letter on headed paper [covering letter]		11 June 2020
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [PL cover]		27 November 2019
GP/consultant information sheets or letters [GP info sheet]	1.0	05 June 2020
Instructions for use of medical device [sleep study set up guide]		
IRAS Application Form [IRAS_Form_22062020]		22 June 2020
Letter from sponsor [letter of sponsorship]		10 June 2020
Letter from statistician [letter from statistician]		07 May 2020
Non-validated questionnaire [Feedback questionnaire]	1.0	05 June 2020
Organisation Information Document [organisation information document]	1.1	23 July 2020
Other [mNCA]	1.0	02 July 2020
Participant consent form [Consent form version 1.1 tracked changes]	1.1	17 July 2020
Participant consent form [Consent form version 1.1]	1.1	17 July 2020
Participant information sheet (PIS) [Patient information sheet version 1.1 tracked changes]	1.1	17 July 2020
Participant information sheet (PIS) [Patient information sheet version 1.1]	1.1	17 July 2020
Referee's report or other scientific critique report [C1 oral report]		
Research protocol or project proposal [Protocol]	1.0	05 June 2020
Schedule of Events or SoECAT	1	30 July 2020
Summary CV for Chief Investigator (CI) [CV for Prof Slevin]		
Summary CV for student		19 May 2019
Summary CV for supervisor (student research) [Prof Slevin]		
Summary CV for supervisor (student research) [Dr Wilson]		25 April 2019

IRAS project ID	284509

Information to support study set up

The below provides all parties with information to support the arranging and confirming of capacity and capability with participating NHS organisations in England and Wales. This is intended to be an accurate reflection of the study at the time of issue of this letter.

Types of participating NHS organisation	Expectations related to confirmation of capacity and capability	Agreement to be used	Funding arrangements	Oversight expectations	HR Good Practice Resource Pack expectations
There is only one participating NHS organisation therefore there is only one site type.	Research activities should not commence at participating NHS organisations in England or Wales prior to their formal confirmation of capacity and capability to deliver the study.	An Organisation Information Document has been submitted and the sponsor is intending to use a model non-commercial agreement with sites	No study funding will be provided to sites	A Principal Investigator should be appointed at study sites	No Honorary Research Contracts, Letters of Access or pre-engagement checks are expected for local staff employed by the participating NHS organisations. Where arrangements are not already in place, research staff not employed by the NHS host organisation undertaking any of the research activities listed in the research application would be expected to obtain an honorary research contract from one NHS organisation (if university employed), followed by Letters of Access for subsequent organisations. This would be on the basis of a Research Passport (if university employed) or an NHS to NHS confirmation of pre-engagement

					checks letter (if NHS employed). These should confirm enhanced DBS checks, including appropriate barred list checks, and occupational health clearance.

Other information to aid study set-up and delivery

This details any other information that may be helpful to sponsors and participating NHS organisations in England and Wales in study set-up.
The applicant has indicated that they do not intend to apply for inclusion on the NIHR CRN Portfolio.

Amendment Tool

v1.4 30 Nov 2020

For office use

QC: No

Section 1: Project information

Short project title*:	Validation of PAT for pre-operative screening for OSA
IRAS project ID* (or REC reference if no IRAS project ID is available):	284509
Sponsor amendment reference number*:	Amendment 1
Sponsor amendment date* (enter as DD/MM/YY):	08 January 2021
Briefly summarise in lay language the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study. If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained (note: this field will adapt to the amount of text entered)*:	It has become apparent that a small number of patients experience discomfort from wearing the WatchPAT device overnight. This ranges from very minor discomfort to some cases of patients reporting pain and imobility to the finger for a few hours after removing the device. In one case, a patient reported a small pressure blister on removing the device. we have also had one similar incidence in a patient using the devivce outside of the research setting. On reproting these adverse effects to the manufacturer, we established that these effects have been reported by others using the device, though they affect a very small minoity of patients using the device. The manufacturer has been invensitgating these incidents and advises that they are more common in patients with thick fingers where the probe would be a tighter fit. They recommend that the device is worn on the little finger in such patients. We have added a the following text to the patient information sheet (version 1.2; dated 31/12/2020). "A few patients report that their finger feels stiff for a few hours after removing the sensor. On rare occasions, people have experienced a small pressure blister on the finger where the sensor was placed. This generally goes down within a day. This is more likely in patients with large fingers and it is recommended to place the sensor on the little finger to avoid this". The protocol has also been amneded (version 1.2; dated 31/12/2020) to include the manufactuer's recommendation to wear the device on the little finger. Footers on both documents have been updated with the new version numbers.

Project type (select):	[redacted] Specific study [redacted] Research tissue bank [redacted] Research database			
Has the study been reviewed by a UKECA-recognised Research Ethics Committee (REC) prior to this amendment?:	[redacted] Yes	[redacted] No		
What type of UKECA-recognised Research Ethics Committee (REC) review is applicable? (select):	[redacted] NHS/HSC REC [redacted] Ministry of Defence (MoDREC)			
Is all or part of this amendment being resubmitted to the Research Ethics Committee (REC) as a **modified amendment** (i.e. a substantial amendment previously given an unfavourable opinion)?	[redacted] Yes	[redacted] No		
Where is the NHS/HSC Research Ethics Committee (REC) that reviewed the study based?:	England: [redacted]	Wales: [redacted]	Scotland: [redacted]	Northern Ireland: [redacted]
Was the study a clinical trial of an investigational medicinal product (CTIMP) OR does the amendment make it one?:	[redacted] Yes	[redacted] No		
Was the study a clinical investigation or other study of a medical device OR does the amendment make it one?:	[redacted] Yes	[redacted] No		
Did the study involve the administration of radioactive substances, therefore requiring ARSAC review, OR does the amendment introduce this?:	[redacted] Yes	[redacted] No		
Did the study involve the use of research exposures to ionising radiation (not involving the administration of radioactive substances) OR does the amendment introduce this?:	[redacted] Yes	[redacted] No		
Did the study involve adults lacking capacity OR does the amendment introduce this?:	[redacted] Yes	[redacted] No		
Did the study involve access to confidential patient information outside the direct care team without consent OR does the amendment introduce this?:	[redacted] Yes	[redacted] No		
Did the study involve prisoners OR does the amendment introduce this?:	[redacted] Yes	[redacted] No		
Did the study involve NHS/HSC organisations prior to this amendment?:	[redacted] Yes	[redacted] No		
Did the study involve non-NHS/HSC organisations OR does the amendment introduce them?:	[redacted] Yes	[redacted] No		
	England	Wales	Scotland	Northern Ireland
Lead nation for the study:	[redacted]	[redacted]	[redacted]	[redacted]
Which nations had participating NHS/HSC organisations prior to this amendment?	[redacted]	[redacted]	[redacted]	[redacted]
Which nations will have participating NHS/HSC organisations after this amendment?	[redacted]	[redacted]	[redacted]	[redacted]

Section 2: Summary of change(s)

Please note: Each change being made as part of the amendment must be entered separately. For example, if an amendment to a clinical trial of an investigational medicinal product (CTIMP) involves an update to the Investigator's Brochure (IB), affecting the Reference Safety Information (RSI) and so the information documents to be given to participants, these should be entered into the amendment tool as three separate changes. A list of all possible changes is available on the "Glossary of Amendment Options" tab. To add another change, tick the "Add another change" box.

Change 1				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Protocol - Non-substantial changes (e.g. not affecting safety or the scientific value of the trial)			
Further information (free text - note that this field will adapt to the amount of text entered):	Section 6.4 Study assessments. The following text has been added to mitigate against risk of a pressure blister forming from use of the research device "(little finger is recommended to mitigate risk of a pressure blister in those with thick fingers, see non-serious AEs, 7.2.1)"			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	[redacted]	[redacted]	[redacted]	[redacted]
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	[redacted]		[redacted]	

Add another change: [redacted]

Change 2				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Protocol - Non-substantial changes (e.g. not affecting safety or the scientific value of the trial)			
Further information (free text - note that this field will adapt to the amount of text entered):	Section 7.2.1 Non serious AEs. The following text has been added: "The majority of patients experience no adverse effects from the WatchPAT device, but a small number report minor discomfort and stiffness of the finger on which the device was used. Rarely, patients have experienced a small pressure blister. To reduce the likelihood of this, the manufactuer has advised that patients should wear the device on the little finger. Patients will also be reminded that they can remove the sensor if they experience significant discomfort"			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	[redacted]	[redacted]	[redacted]	[redacted]
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	[redacted]		[redacted]	

Add another change: [redacted]

Change 3				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Correction of typographical errors			
Further information (free text - note that this field will adapt to the amount of text entered):	The table of contents incorrectly included some text populated from the documentunder 11.2 peer review. This has now been corrected so only the heading is shown in the table fo contents. No change to the document text has been made			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	[redacted]	[redacted]	[redacted]	[redacted]
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	[redacted]		[redacted]	

Add another change: [redacted]

Change 4				
Area of change (select)*:	Study Documents			
Specific change (select - only available when area of change is selected first)*:	Other minor change to study documents (e.g. information sheets, consent forms, questionnaires, letters) that can be implemented within existing resource in place at participating organisations - Please specify in the free text below			
Further information (free text - note that this field will adapt to the amount of text entered):	Under the heading "What are the possible disadvantages and risks of taking part? ", the following text has been added under the heading "A few patients report that their finger feels stiff for a few hours after removing the sensor. On rare occasions, people have experienced a small pressure blister on the finger where the sensor was placed. This generally goes down within a day. This is more likely in patients with large fingers and it is recommended to place the sensor on the little finger to avoid this."			
Applicability:	England	Wales	Scotland	Northern Ireland
Where are the participating NHS/HSC organisations located that will be affected by this change?*:	[redacted]	[redacted]	[redacted]	[redacted]
Will all participating NHS/HSC organisations be affected by this change, or only some? (**please note** that this answer may affect the categorisation for the change):	[redacted]		[redacted]	

Add another change: [redacted]

Section 3: Declaration(s) and look for submission

Declaration by the Sponsor or authorised delegate

- I confirm that the Sponsor takes responsibility for the completed amendment tool
- I confirm that I have been formally authorised by the Sponsor to complete the amendment tool on their behalf

Name (first name and surname):	Rachel Heron
Email address:	ethics@mmu.ac.uk

Look for submission

Please note: This button will only become available when all mandatory (*) fields have been completed. When the button is available, clicking it will generate a locked PDF copy of the completed amendment tool which must be included in the amendment submission. Please ensure that the amendment tool is completed correctly before locking it for submission.

Look for submission

After looking the tool, proceed to submit the amendment online. The "Submission Guidance" tab provides further information about the next steps for the amendment.

Section 4: Review bodies for the amendment

Please note: This section is for **information only**. Details in this section will complete automatically based on the options selected in Sections 1 and 2.

	Review bodies																	
	UK wide:						England and Wales:				Scotland:				Northern Ireland:			
	REC	Competent Authority MHRA - Medicines	Competent Authority MHRA - Devices	ARSAC	Radiation Assurance	UKSN Governance	REC (MCA)	CAG	HMPPS	IRA and HCRW Approval	REC (AWA)	PBPP	SPS (RAEC)	National coordinating function	HSC REC	HSC Data Guardians	Prisons	National coordinating function	Category:
Change 1:						(Y)				(Y)									A
Change 2:						(Y)				(Y)									A
Change 3:						N				N									N/A
Change 4:						(Y)				(Y)									C
Overall reviews for the amendment:																			
Full review:						N				N									
Notification only:						Y				Y									
Overall amendment type:	Non-substantial, no study-wide review required																		
Overall Category:	A																		

Appendix 3- IAPS report

National School of Healthcare Science

NHS Health Education England

HIGHER SPECIALIST SCIENTIST TRAINING PROGRAMME

Independent Assessment of Professional Skills
Panel Report to Candidate

Candidate details:	
Trainee ID:	**77005930**
Title and Name:	**Gillian Twigg**
Specialty	Respiratory and Sleep Science

IAPS Panel Event	Time: 12:30pm – 4pm		Date: Friday 14th May 2021	
Location	MS Teams			
IAPS instance	First take	☒	Resit ☐	Retake ☐

The ratified outcome from your IAPS is given below followed by a detailed transcript with results from both elements of your IAPS and the examiners' comments.

Candidate outcome:	**PASS - standard met for IAPS Element 1 and Element 2**
Detail:	**Congratulations! You have demonstrated development of your practice to Consultant Clinical Scientist level.**
Next steps:	Once you have received your HSST academic qualification, you can apply for your HSST completion certificate. To do this you need to complete the HSST Exit Form on OneFile attaching evidence of your academic qualification

National School of Healthcare Science

NHS Health Education England

Candidate IAPS detailed transcript:

Showcase review prior to attendance for IAPS Professional Discussion	
Pre PD Element: Lead Examiner map of showcase evidence to HSS SoP domains	
Accepted on first submission ☒	Accepted following resubmission ☐

Professional Discussion Panel Assessment and Comments:			
Element 1: Specialist Paper review			
Specialist Paper Title	**AHI comparing the 2007 and 2012 AASM criteria in COPD/OSA overlap syndrome**		
Specialist Paper reference	**He B et al, J Thorac Dis 2020;12(Suppl2):S112-S119**		
Expected standard attained:		**Yes ☒**	**No ☐**
Examiners' Comments: You presented the content of the manuscript well, explaining the major clinical implications of changes in definitions and understanding the impact of the arousals associated with respiratory events. You discussed well the relevance and the focus on patient symptoms. You understood the limitations of the analysis and the limited outcomes, suggesting further follow up studies that could be done. The panel commended your structured approach and intuitive understanding of a large dataset.			

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Professional Discussion Panel Assessment and Comments:		
Element 2: HSS SoP Showcase Evidence	Expected standard(s) of Domain attained:	
Domain 1: Professional Practice	**Yes** ☒	**No** ☐
Examiners' Comments: You explained well your approach towards professionalism in your service. Your strong position as a Quality Lead was a cross-cutting theme through several domains, both professionalism and leadership skills were showcased well.		
Domain 2: Scientific Practice	**Yes** ☒	**No** ☐
Examiners' Comments: The panel recognised the genuine interest and the acknowledgement of data as evidence-base that you explained. It was impressive how you adjusted projects when you found that the initial approach did not work as expected.		
Domain 3: Clinical Practice	**Yes** ☒	**No** ☐
Examiners' Comments: You presented how a patient-centred approach is at the heart of everything that you do. The panel was impressed by the structured approach and drive to deliver best possible patient care. The panel discussed that you could use this energy to reach out beyond the current local service and embed the sleep service within the wider context of other contributing departments (e.g. sleep: ENT, dental, head-neck, metabolic services). National and international involvement in specialist networks (e.g. ARTP, BSS, BTS, ERS) can further help you to support your goals and achieve collaborations in future.		
Domain 4: Research, Development and Innovation	**Yes** ☒	**No** ☐
Examiners' Comments: You presented well the achievements in this domain, from your PhD to the latest projects which helped you to reflect on additional skills when approaching this topic, e.g. as PI. You presented the link between the sleep and the vent team in your Trust. Future wider collaboration with other services and wider (national/international) networks should be considered.		

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Domain 5: Clinical Leadership	Yes ☒	No ☐

Examiners' Comments:

You presented your skills and achievement in the context of a long-term vision and how you engage your team to deliver on that vision. The panel was impressed by your drive and the achievements around the funding for services, the presented increase in activity and additional staff which was commendable.

Global Assessment

Examiners' Comments:

We were impressed by your achievements and your patient focus. We acknowledge what you have already managed to achieve within your service and would recommend that you in future consider to reach out to other services within your Trust (e.g. ENT), similar to your involvement with the bariatric service. Wider engagement within the national/international societies may further allow you to realise your ideas and develop collaborative projects. You have a great long-term vision within your service and it would be great to see that you take this forward in other contexts as well.
Today's assessment confirmed your achievement at HSST as a consultant level clinical scientist.