An Exploration of Factors Associated with the Diagnosis and Treatment of Obstructive Sleep Apnoea in Chronic Heart Failure: A mixed methods study

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Abstract

Sleep disordered breathing (SDB) is a comorbidity that is prevalent in chronic heart failure (CHF) and associated with substantial morbidity and mortality. As it is largely under diagnosed and under treated, the overarching aim of this thesis was to explore factors associated with the diagnosis and treatment of OSA in patients with CHF, with a focus on the diagnostic accuracy of existing screening questionnaires, perceived barriers and enablers from CHF patients' and clinicians' perspectives, and clinician knowledge, attitudes, and clinical practices.

In the first study, the accuracy and clinical utility of existing OSA screening questionnaires were evaluated and compared. While the STOP-Bang questionnaire had a high sensitivity to detect OSA in both the sleep clinic and surgical cohorts, it lacked specificity.

In the second study, the diagnostic accuracy of the STOP-Bang questionnaire was evaluated in a sleep clinic cohort with co-existing CHF. Findings indicated a high sensitivity of the STOP-Bang questionnaire to detect OSA in a sleep clinic population with co-existing CHF, however, precision of these findings was limited by a small sample size.

In the third study, qualitative analysis of interviews was utilised to explore perceived barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives. Several barriers and enablers were identified across the OSA diagnostic pathway.

In the fourth study, an online survey evaluated the knowledge, attitudes, and clinical practice of heart failure clinicians. Results demonstrated a knowledge deficit in the diagnosis and treatment of OSA and variable practice among HF clinicians.

This thesis highlights several barriers associated with the diagnosis and treatment of OSA in CHF that could form the foundation of targeted interventions to aid the diagnosis and treatment of OSA in CHF, should the evidence change in the future.

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Abbreviations

AASM	American Academy of Sleep Medicine
ACEi	Angiotensin converting enzyme inhibitor
AF	Atrial fibrillation
AHI	Apnoea hypopnoea index
ARB	Angiotensin receptor blocker
ASV	Adaptive servo ventilation
BANCC	British Association for Nursing in Cardiovascular Care
BCS	British Cardiology Society
BMI	Body mass index
BSH	British Society for Heart Failure
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CHF	Chronic heart failure
CO_2	Carbon dioxide
COM-B	Capability, opportunity, motivation, and behaviour
CPAP	Continuous Positive Airway Pressure
CRT	Cardiac resynchronisation therapy
CSA	Central Sleep Apnoea
CSR	Cheyne Stokes Respiration

CV	Cardiovascular
ECG	Electrocardiogram
EDS	Excessive daytime sleepiness
EEG	Electroencephalogram
EF	Ejection fraction
EMG	Electromyogram
EOG	Electro-oculogram
ESS	Epworth sleepiness scale
HCP	Health care professional
HF	Heart failure
HFmrEF	Heart failure with midrange/mildly reduced ejection fraction
HFpEF	Heart failure with preserved ejection fraction
HFrEF	Heart failure with reduced ejection fraction
HSAT	Home sleep apnoea testing
ICD	Implantable cardioverter defibrillator
LV	Left ventricular
LVEF	Left ventricular ejection fraction
LVSD	Left ventricular systolic dysfunction
MMR	Mixed methods research
NICE	National Institute for Health and Care Excellence
NYHA	New York Heart Association

OSA	Obstructive Sleep Apnoea
OSAHS	Obstructive Sleep Apnoea Hypopnoea Syndrome
OSAKA	Obstructive Sleep Apnea Knowledge and Attitudes
PAT	Peripheral arterial tonometry
PSG	Polysomnography
RDI	Respiratory Disturbance Index
SROC	Summary Receiver Operating Characteristic
RP	Respiratory polygraphy
SDB	Sleep Disordered Breathing
TA	Thematic Analysis
TDF	Theoretical Domains Framework
UK	United Kingdom
USA	United States of America

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Chronic Heart Failure and Sleep Disordered Breathing

1.1 Introduction

Heart Failure (HF) is a clinical syndrome underpinned by various aetiologies and associated with "current or prior symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by at least elevated natriuretic peptide levels or objective evidence of cardiogenic pulmonary or systemic congestion" (Bozkurt *et al.,* 2021). Characterised by renin angiotensin aldosterone system and sympathetic nervous system activation, HF is a significant health problem that affects 64.3 million individuals worldwide and is associated with a considerable burden of disability that includes frequent hospital admissions and a high risk of mortality (Brenner *et al.*, 2008; Kasai & Bradley, 2011; Coats, 2019).

With high prevalence and incidence rates, an estimated 2.2% of the population with chronic HF (CHF) in developed countries and up to 600 000 incident cases diagnosed annually, CHF remains one of the costliest conditions to manage and is the leading cause of unplanned hospitalisation in Europe and the United States of America (USA) (Go *et al.*, 2014; Biermann *et al.*, 2012). Unsurprisingly, the global economic impact of CHF has been estimated at $108 billion per year with an estimated economic impact of $26.6 billion in the USA and accounting for at least 2% of total health care expenditure in the UK (Vazir *et al.*, 2007; Mant *et al.*, 2009; Cook *et al.,* 2014).

Despite the impact of pharmacological and device therapies on CHF related deaths and disability, many patients with CHF continue to experience persistent symptoms and will die from progressive CHF. This may be exacerbated by the presence of comorbidities associated with CHF that contribute to both the development and progression of CHF (Arzt *et al.*, 2016).

Although diabetes, hypertension, atrial fibrillation (AF), renal impairment, and many other conditions frequently co-exist in patients with CHF, the importance of sleep disordered breathing (SDB) has increasingly been recognised (Coats, 2019). Acknowledged as a cause of substantial morbidity, mortality, and health care expenditure, SDB occurs in 46% of patients with CHF optimised on evidence-based treatment (Wang *et al.,* 2007; Leger *et al.,* 2012).

SDB is associated with CHF in various ways. Firstly, obstructive sleep apnoea (OSA) is characterised by upper airway obstruction with cessation of airflow in the presence of ongoing abdominal and thoracic wall movement and associated with cardiovascular (CV) morbidity and mortality through several mechanisms including sympathetic nervous system activity, oxidative stress, inflammation, endothelial dysfunction, and metabolic abnormalities, mediated through chronic, intermittent hypoxia (Coniglio & Mentz, 2020). In turn, a shift of fluid from the legs to the upper body during recumbency causes oedema of the pharynx and surrounding tissue that contributes to airway narrowing and subsequent development or worsening of OSA (Yumino *et al.,* 2010). Secondly, central sleep apnoea (CSA) and Cheyne-Stokes respiration (CSR), a periodic breathing pattern, is prevalent in up to 40% of patients with reduced ejection fraction (EF) and associated particularly with male sex, reduced left ventricular (LV) function, AF, and a poor prognosis in patients with CHF (Lyons & Bradley, 2015; Perger *et al.,* 2017).

Despite the high prevalence of SDB in CHF and the association with the development and progression of CHF, SDB remains under diagnosed and under treated.

1.2 Aim

The aim of this chapter is to provide context to this thesis. It will review the epidemiology and clinical consequences of SDB in CHF. An overview of the evidence relating to the use of screening questionnaires and the treatment of SDB in the context of CHF, will be provided. Differences in the presentation and management of OSA in the general population and in patients with CHF, will be highlighted.

1.3 Epidemiology of Heart Failure and Sleep Disordered Breathing

1.3.1 Heart failure

HF is categorised into three categories, namely HF with reduced EF (HFrEF; EF ≤ 40%), HF with mildly reduced EF (HFmrEF; EF 41-49%) and HF with preserved EF (HFpEF; EF ≥ 50%) (McDonagh *et al.,* 2021). Considering potential differences in study populations and diagnostic criteria, it is estimated that at least 50% of all CHF patients in the general population have HFpEF (Bursi *et al.,* 2006; Gerber *et al.,* 2015).

CHF is prevalent in approximately 1-2% of adults in developed countries with an estimated 64.3 million individuals living with CHF globally (Groenewegen, 2020). For individuals over 65 years of age, prevalence of CHF is reported at around 11.8% (Van Riet *et al.,* 2017). In the USA, CHF prevalence was estimated as 2.5% based on self-reported data, whilst, in the UK, prevalence of CHF was estimated at 1.6%, based on the UK Clinical Practice Research Datalink information (Conrad *et al.,* 2018). Differences in estimated prevalence in echocardiography screened studies (4.2%) and registries (2%), suggests that HF remains undetected in over half of cases. Over 76% of unrecognised cases are individuals with HFpEF, likely due to misclassification as chronic obstructive pulmonary disease, ageing, obesity, and other conditions (Caruana *et al.,* 2000; Van Riet *et al.,* 2017).

The incidence of CHF in Europe and the USA has been ranging from 1 to 9 cases/1000 person-years. Despite a decline in incidence rates in developed countries, the total number of new cases has increased by 12%, because of an ageing population, population growth and improved survival (Dunlay & Roger, 2014; Roth *et al.,* 2015).

In the western world, ischaemic heart disease is viewed as the predominant cause of CHF, however, as it is now felt that HF can be viewed as the “chronic stage” of any disease that results in cardiac impairment, it is far more challenging to allocate a specific cause of CHF due to multiple causes, multi-morbidity, and shared risk factors (Groenewegen *et al.,* 2020). Some of the

most common conditions with a predisposition to CHF include coronary artery disease (CAD), hypertension, diabetes, obesity, and smoking.

Despite the downward trends in both the severity and incidence of hospitalised myocardial infarction, ischaemic heart disease remains a key contributor to the incidence of CHF in the context of an ageing population and improved survival post myocardial infarction (Yeh *et al.*, 2010; Rosamond *et al.,* 2012).

Hypertension is the most common risk factor in women, compared to CAD in men (Daubert and Douglas, 2019). Although there has been an improvement in hypertension awareness and treatment, hypertension control appears to have plateaued (Zhou *et al.*, 2019). Furthermore, the presence of hypertension in incident HF cases has increased from 54% to 76%, whilst the presence of elevated blood pressure in incident HF has been associated with adverse outcomes (Lip *et al.*, 2015 Conrad *et al.*, 2018).

Diabetes and obesity can affect heart function independently without the presence of other risk factors such as hypertension or CAD (Iribarren *et al.*, 2001). Despite a high prevalence of diabetes in patients with CHF, there appears to be a sustained decline in diabetes incidence rates, possible due to effective screening and disease detection (Selvin & Ali, 2017). In contrast, the rate of obesity is rapidly on the rise with an estimated 20% of the global population classified as obese by 2025 (Reis *et al.,* 2015; NCD Risk Factor Collaboration, 2016).

Socio-economic status is recognised as additional risk factor for CV disease. The prevalence of HF in socioeconomically deprived is higher (2%), compared (1.2%) to the least deprived, likely explained by behavioural factors such as physical inactivity, poor diet, smoking and others in the deprived group (Havranek *et al.*, 2015). There is also a significant difference in age at first diagnosis and low socioeconomic status was also associated with a 62% increase in incident HF (Potter *et al.*, 2019).

Over the past three decades, many key pharmacological studies were conducted in HFrEF (>30 studies) and in HFpEF (>15 studies) which produced at least 13 classes of HF evidence-based medication in CHF with improved

survival, however, an aging population and increased risk factors as discussed above, has contributed to an increased prevalence of HF (Lewis *et al.,* 2017).

A survival analysis looking at HF survival and hospitalisation trends showed a significant reduction of CHF hospitalisation and CHF mortality. However, there were no improvement in population-level or gender specific CHF-related mortality (Vasan *et al.,* 2019). Women generally have a better prognosis than men and are less likely to die from CV disease (Taylor *et al*., 2020). They also have a greater survival than their male counterparts when CHF was diagnosed in the community setting rather than during a hospital admission.

Despite widely reported comorbidities in CHF, there are extensive gaps in the evidence and guidelines for the management of multimorbid CHF patients. One of the key issues is that the reporting of comorbidities in CHF trials remain low and incomplete (Khan *et al.,* 2020). Christiansen (2020) reported that CV comorbidities such as cerebrovascular disease and ischaemic heart disease were most prevalent in the oldest age group compared to the youngest age group. Furthermore, in CHF patients with more than one non-CV comorbidity, mortality at 1-year was the highest amongst CHF patients, compared to controls. For patients younger than 50 years of age, population attributable risk was the greatest for hypertension, cancer, and alcohol abuse, whilst for patients older than 74, it was the greatest for hypertension, cerebrovascular disease, and cancer (Christiansen *et al.*, 2020). A higher comorbidity burden is associated with adverse clinical outcomes, extended hospital stays and significant economic impact. Generally, older patients with HFpEF tend to have a higher burden of comorbidities compared to patients with HFrEF which in turn is associated with increased health care costs, extended length of hospital stay and poor clinical outcomes (Bhatt *et al.*, 2020).

SDB is a comorbidity that is highly prevalent in CHF and associated with substantial morbidity and mortality, however, it is largely under diagnosed and under treated. The next section of this chapter will review the pathophysiology, diagnosis, and treatment of SDB in the context of CHF and consider differences in presentation and treatment between the general population and CHF population, particularly in relation to OSA.

1.3.2 Sleep Disordered Breathing

1.3.2.1 Definition and Classification of Sleep Disordered Breathing

SDB is characterised by interruptions in breathing during sleep with consequent effects on the CV system mediated through chemical, autonomic, mechanical, and inflammatory pathways (Coniglio & Mentz, 2020). Key subgroups include obstructive (OSA), central (CSA) and Cheyne-Stokes respiration (CSR). OSA is characterised by upper airway obstruction with cessation of airflow in the presence of ongoing abdominal and thoracic wall movement. Although obstructive events are associated with oxygen desaturation, hypoxia and hypercapnia, CSA is characterised by centrally medicated cessation of airflow and cessation of abdominal and chest wall movement (Oldenburg *et al.,* 2007; Javaheri & Dempsey, 2013; Lyons & Bradley, 2015). CSR is a subtype of CSA, characterised by fluctuations in speed and depth of breathing with intermittent periods of breathing cessation (Perger *et al.*, 2017). A combination of obstructive and central events is often present in the same patient and described as mixed apnoeas. When >50% of events are obstructive, it will be classified as OSA and vice versa.

The severity of SDB is commonly described by the apnoea hypopnoea index (AHI), a measure that considers the average number of apnoea and hypopnoea episodes per hour of sleep. The American Academy of Sleep Medicine (AASM) (2012) describes an ‘apnoea’ as a ≥90% drop in airflow for ≥10 seconds and a ‘hypopnoea’ as a 30% drop in airflow for ≥10 seconds associated with ≥3% desaturation or arousal (Berry et al., 2012). From a diagnostic perspective, an AHI< 5/hr is considered as normal, AHI 5 to 15/hr indicates mild OSA, AHI>15 to 30/hr moderate to severe OSA and AHI>30 severe OSA (Berry *et al.,* 2015).

Despite being the metric of choice, AHI has been limited by its ability to capture the physiological abnormality that underpins the related complications. These predictive limitations are associated with the precision with which the AHI reflects the true OSA exposure and consequent adverse outcomes (for example measurement error from night-to-night variation), and individual responses to OSA, which may be affected by genetics, age or comorbid conditions (Malhotra *et al.,* 2021).

Alternative metrics for OSA severity have been proposed based on advanced signal processing and analyses. These include hypoxic burden, arousal intensity, odds ratio product, cardiopulmonary coupling and apnoea-hypopnoea event duration (Kahn *et al.,* 2013; Amatoury *et al.,* 2018; Penner *et al.,* 2019; Thomas *et al.*, 2009; Butler *et al.,* 2019).

Due to heterogeneity related to the underlying mechanism and clinical manifestation of OSA, it is likely that a single metric will not suffice, requiring a combination of measures to assess the scale of the OSA stimulus, the individual response to the stimulus and the individual response to treatment (Malhotra *et al.,* 2021). Novel measures, able to capture the variability of OSA endophenotypes and to facilitate robust interventional RCTs, are required to improve upon AHI for severity classification and diagnosis of OSA. Despite being criticised for its limitations, AHI remains the current metric of choice for OSA severity.

The prevalence of SDB in the general population was first reported by Young (1993). Estimated at 4% of men and 2% of women with SDB, OSA was found to be the predominant form of SDB in this population. Compared to the findings of Young *et al.* (1993), a systematic review by Senaratna *et al.* (2017) demonstrated higher prevalence of OSA in the general population, ranging from 9%-38%. Prevalence increased with age and was found to be the highest in the oldest stratum. For an AHI of ≥15, the prevalence in the general population was 6%-17%, whilst in the older age groups as high as 49%. Prevalence remained greater in men than women, older adults and in obese individuals (Punjabi, 2008).

SDB in CHF is far more prevalent compared to the general population and is commonly seen in HFrEF, HFpEF and patients with acute decompensated HF. Despite a similar prevalence in HFrEF and HFpEF patient groups, it can be higher (44-97%) in patients with decompensated HF (Cowie, 2017).

A landmark study by Javaheri *et al.* (1998) first reported on the prevalence of SDB in CHF. Although this study showed the prevalence of SDB in CHF as 51%, several subsequent studies confirmed the high prevalence of SDB in CHF, ranging between 45% and 81%. Most studies reported CSA as the main

SDB phenotype in CHF. The SCHLA-HF registry demonstrated a 46% overall prevalence of moderate to severe SDB in patients with CHF. Prevalence was dependent on both age and sex with sex differences constant across age groups. The findings of this study were consistent with previous prevalence studies with populations >100 patients (Arzt *et al.*, 2016).

Discrepancies between prevalence studies are commonly due to methodological differences, differences in population characteristics, choice of sleep study and SDB diagnostic criteria. Although many of the prevalence studies summarised in **Table 1** enrolled unselected patients from CHF and cardiology clinics, Sin *et al.* (1999) recruited patients from a selected, symptomatic sleep clinic population. It is likely that results from this study might have been influenced by an element of selection bias.

Though many of the prevalence studies used in-lab polysomnography (PSG) for the diagnosis of SDB, a similar number used respiratory polygraphy (RP) with mixed reviews on the use of RP for the diagnosis of SDB in CHF. Smith (2007) reported that RP underestimates AHI and consequently could result in under diagnosis of SDB. Conversely, Pinna (2014) showed a high degree of agreement between AHI recorded with home PSG compared to RP. A possible contributing factor to the differences in findings is that Smith (2007) did not consider night to night variation in respiratory events, that are marked particularly in patients with OSA.

A diagnostic threshold of AHI≥15/hour is commonly used for moderate to severe SDB, however, many of the prevalence studies used a threshold of AHI≥10/hour and consequently the prevalence of SDB will be increased in some of the studies (Javaheri, 2007). Furthermore, the criteria for scoring hypopnoea events were variable across studies. Some studies used a 30% reduction in airflow compared to 50% in others. Similarly, a 3% reduction in oxygen saturation was used in some studies, compared to 4% in others (Berry *et al.*, 2012). Consequently, variability among studies is likely to result in misclassification of obstructive and central events and at least in part account for differences in prevalence of SDB.

Table 1 Prevalence of SDB in CHF

Author	Year	*N*	Male (%)	Age (Years)	BMI (kg/m^2)	NYHA		LVEF %	Sleep Study	AHI	SDB %	CSA %	OSA %
						I-II%	III-IV%						
Heart Failure with Reduced Ejection Fraction													
Javaheri	1998	81	100	64±11	27.8±6	70	30	<45	PSG	≥15/hour	51	40	11
Sin	1999	450	85	60±13	29.3±5.8	62	38	27.3±15.6	PSG	≥15/hour	61	29	32
Ferrier	2005	53	77	60.1±9.8	27.9±5.53	75	25	34±8.5	PSG	≥10/hour	68	53	15
Schulz	2007	203	75	65.3±1.1	27.6±0.6	55	45	28.0±1.0	RPG	≥10/hour	71	43	28
Oldenburg	2007	700	80	64.5±10.4	26.7±4	NS	NS	28.3±6.8	RPG	≥15/hour	52	33	19
Vazir	2007	55	100	61±12	29.4±5	100	0	30.6±10.1	PSG	≥15/hour	53	38	15
MacDonald	2008	108	85	57±11	26.8±5.8	62	38	20	RPG	≥15/hour	61	31	30
Hagenah & Beil	2009	50	88	63±12	26.6±4.3	NS	NS	26±6	PSG	≥10/hour	64	44	20
Yumino	2009	218	77	55.6±12.7	29.2±5.3	54	46	24.7±10	PSG	≥15/hour	47	21	26
Paulino	2009	316	83	60±13	28±6	NS	NS	30±11	RPG	≥10/hour	81	30	70
Ferreira	2010	103	79	66	27	NS	NS	NS	PSG	≥15/hour	45	NS	NS

Author	Year	*N*	Male (%)	Age (Years)	BMI (kg/m^2)	NYHA		LVEF %	Sleep Study	AHI	SDB %	CSA %	OSA %
						I-II%	III-IV%						
Jilek	2011	273	89	NS	NS	NS	NS	NS	PSG	≥10/hour	64	50	14
Dolliner	2013	176	85	65.1±33.1-88.2	28.4±5.1	NS	NS	25	RPG	≥15/hour	50	35	15
Arzt	2016	6876	84	69±11	28.9±5.2	27	73	32.8±8.3	RPG	≥15/hour	46	NS	NS
Heart Failure with Preserved Ejection Fraction													
Herrscher	2014	44	31	62.8±10.0	51.7±5.2	95	5	51.7±5.2	RPG	≥15/hour	81	27	54

BMI: body mass index; NYHA: New York Heart Association; LVEF: left ventricular ejection fraction; AHI: Apnoea hypopnoea Index; SDB: sleep disordered breathing; CSA: central sleep apnea; OSA: obstructive sleep apnoea, NS: not stated; RPG: respiratory polygraphy; PSG: polysomnography

1.3.2.2 Risk Factors

Several risk factors have been identified from prevalence studies and are summarised in **Table 2**. The SCHLA-HF registry, the largest and most recent multicentre study to investigate the prevalence of SDB in stable CHF, reported male sex, older age, higher body mass index (BMI; kg/m^2), lower left ventricular ejection fraction (LVEF), higher New York Heart Association (NYHA) functional class, and AF as clinical predictors for at least moderate SDB (Arzt *et al.,* 2016).

The prevalence of SDB varied across age groups with progressive increase into older age. SDB was two-to three-fold more prevalent in men than women, however, this difference decreased after menopause (Cowie, 2017). Interestingly, there were no sex differences in the predictors of SDB and AHI, despite relevant analysis, suggesting similar disease mechanisms in both men and women (Arzt *et al.*, 2016). Prevalence in African American and Asian populations appear to be higher than the European population, likely due to genetic factors related to body fat distribution, craniofacial shape, and receptor sensitivity. A high proportion of patients with OSA is overweight which causes a vulnerability to upper airway collapse. In CHF, an accumulation of fluid in the upper airway when in supine position, increases the susceptibility to upper airway collapse (Cowie, 2017).

Table 2 Risk Factors for Sleep Disordered Breathing in Chronic Heart Failure

Author	Year	*N*=	Sleep Study	Risk factors for SDB
Sin	1999	450	PSG	CSA: male, age ≥60yrs, hypocapnia (PCO_2 ≤ 38mmHG), AF OSA: BMI in men; Age in women
MacDonald	2008	108	RGP	SDB: AF, NYHA functional class
Yumino	2009	218	PSG	CSA: male, age, AF, hypocapnia, diuretic use OSA: male, age, BMI
Herrscher	2014	115	RPG	CSA: BMI OSA: BMI
Arzt	2016	6876	RPG	SDB: male, age, BMI, LVEF, AF (no sex differences for significant risk factors.

SDB: sleep disordered breathing; CSA: central sleep apnoea; OSAHS: obstructive sleep apnoea hypopnoea syndrome; BMI: body mass index; LVEF: left ventricular ejection fraction, PSG: polysomnography; AF: atrial fibrillation; NYHA: New York Heart Association; pCO_2: partial pressure of carbon dioxide

1.3.2.3 Impact on morbidity and mortality

Several population-based studies reported that both OSA and CSA are independently associated with increased risk of mortality in patients with CHF, despite the limitation of small sample sizes, selection bias and failure to consider obesity and related confounding factors (Cowie, 2017). Lavie (2007) reported an association of severe SDB with all-cause mortality in young and middle-aged men. Despite highlighting SDB as a risk factor for mortality, the study findings were limited by the exclusion of women, referral bias and lack of consideration for treatment effects.

These findings were further supported by the Wisconsin Sleep Cohort that demonstrated a 3-fold greater risk of all-cause mortality in severe SDB, compared to participants without SDB (Young *et al.,* 2008). Similar studies by Punjabi (2009) and

Jilek (2011), also reported an association between severe SDB and all-cause and CV mortality, independent of confounding factors.

Unlike previous cohorts, the Busselton Sleep Cohort included both men and women and was free from referral bias. Findings showed that moderate to severe OSA was associated with 33% mortality over 14 years follow-up, compared to 6.5% and 7.7% mortality in those with mild or no sleep apnea, after correction for confounding variables (Marshall et al., 2008). Despite the exclusion of women in several of these studies, Campos-Rodrigues (2012) demonstrated that severe OSA was associated with increased risk of CV death in women.

1.4 Pathophysiology of Sleep Disordered Breathing and Heart Failure

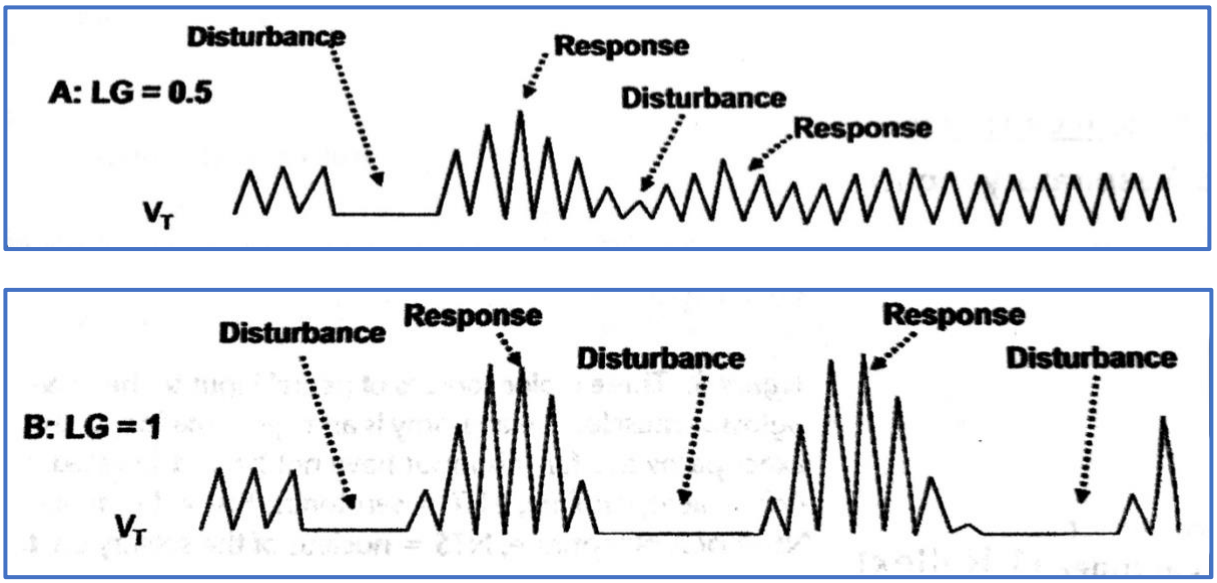
1.4.1 Pathophysiology of Central Sleep Apnoea in Heart Failure

CSA is characterised by dysfunction of the ventilatory control system and associated with centrally mediated cessation of airflow and cessation of abdominal and chest wall movement in the presence of a patent upper airway tract (Lyons & Bradley, 2015; Naughton, 2016).

1.4.1.1 Apnoeic threshold and CO2 reserve

Ventilation is tightly regulated through feedback loops, chemoreceptors, intrapulmonary receptors, and muscle afferents to maintain oxygen (O_2) and carbon dioxide (CO_2) levels. During wakefulness, a change in CO_2 level will initiate several responses to correct the change, however, during sleep, the set point for CO_2 increases and the ventilatory control mechanisms will fail. Therefore, systems that are regulated by feedback loops have the potential to become unstable. The overall gain of any system controlled by feedback loops is called “loop gain” and can be defined as the response to a disturbance (hyperpnoea) over the disturbance itself (apnoea/hypopnoea) (**Figure 1**):

Loop Gain = (response to disturbance) / the disturbance itself



LG: loop gain; VT: tidal volume (White, 2005)

Figure 1 Ventilatory Response to an Apnoea with Loop Gain 0.5 and 1.0

In a low loop gain system where the size of the response is less than the disturbance, stability is restored (A), however, in a high loop gain system where the size of the response exceeds the disturbance, an oscillatory breathing pattern will occur (B).

A high gain system will respond quickly to any changes, whereas a low gain system will exert a slow and weak response. The two main variables that influence ventilatory stability are controller and plant gain. Controller gain plays a role in chemo responsiveness to hypoxia and hypercapnia, whereas plant gain reflects a specific level of ventilation to eliminate CO_2. A high plant gain refers to a small change in ventilation that produces a large change in pCO_2 and is associated with low functional residual capacity, low dead space, low cardiac output and a high pCO_2 (Khoo et al., 1982).

For a system to become unstable, there must be a delay between the effector and the sensor for the system and the loop gain must be greater than 1. For example, there is usually a delay between blood gas changes in the lung and the detection of any changes at the sensor. In CHF, a prolonged circulation time amplifies this delay and may cause further destabilisation of ventilation (Xie *et al.,* 2002).

CSA can be classified as a cyclic or sustained form of breathing instability that are characterised by increased sensitive chemo responses and prolonged circulation

time (Eckert *et al.*, 2007). Cyclic forms of CSA are typically seen in the first few weeks of infancy, in adults at high altitude or in patients with CHF. CSA can also manifest in patients with OSA once airway patency is restored, a condition called complex sleep apnoea (Orr, Malhotra & Sands, 2017).

During an episode of CSA, a reduction in pCO_2 results in withdrawal of the central drive to the respiratory muscles. LV volume and filling pressure in conjunction with pulmonary congestion, stimulate the pulmonary vagal irritant receptors. Increased chemoreceptor sensitivity and arousals from sleep results in hyperventilation that causes a reduction in pCO_2 below the apnoea threshold. Consequently, airflow will stop until the metabolic CO_2 production causes the pCO_2 to increase above the apnoea threshold. This will trigger hyperventilation which will again reduce the pCO_2 level below the apnoea threshold (Kasai, 2012).

CSR is frequently seen in patients with CSA and is characterised by fluctuations between hypopnoea/apnoea and hyperventilating phases (Eckert *et al.,* 2007; Somers *et al.,* 2008; Linz *et al.,* 2015). CSA with CSR commonly occurs in patients with advanced CHF secondary to increased CO_2 (high controller gain), hypocapnia from lung oedema and high filing pressures, and prolonged circulation time. A combination of these characteristics destabilises ventilation and results in a characteristic crescendo-decrescendo pattern of breathing (Javaheri, 1999). Apnoea/hypopnoea episodes during CSR are associated with an increase in sympathetic nervous system activity including an increased heart rate, reduced heart rate variability, raised blood pressure, and increased oxygen demand (Bradley & Floras, 2003; Somers *et al.,* 2008; Gottlieb *et al.,* 2010; Cowie *et al.,* 2015). Additionally, pathological myocardial remodelling can occur because of regular episodes of hypoxemia and reoxygenation (Bitter *et al.*, 2011; Kasai, Floras & Bradley, 2012; Lévy *et al.,* 2015).

1.4.1.2 The role of fluid shift in CSA

Recumbent position at night contributes to rostral shift of fluid from the lower extremities to the thorax which can increase pulmonary capillary wedge pressure and pulmonary oedema (Van Lieshout *et al.,* 2005). Yumino (2010) demonstrated in men with HFrEF that the greater amount of rostral shift of fluid overnight, the lower the nocturnal PCO_2 and the higher the AHI. Findings suggest that fluid accumulation

in the lungs stimulates the pulmonary vagal irritant receptors which in turn causes hyperventilation and a consequent drop in $PaCO_2$ below apnoea threshold. When the patient's head is elevated, it reduces the severity of the CSA-CSR by reducing pulmonary congestion and ventilation and subsequently increase the PCO_2 (Soll *et al*., 2009).

In CHF patients who present with mixed apnoeas (both OSA and CSR-CSR), it is possible for patients to shift from predominantly OSA to CSA-CSR during the night because of a decrease in CO_2 and an increase in CSA-CSR cycle duration and circulation time, likely because of increased pulmonary congestion and decrease in cardiac output (Tkacova *et al.,* 2001). Therefore, the potential for the dominant apnoea type to change over time should be considered when planning treatment for SDB in CHF, particularly in HFrEF.

1.4.2 Pathophysiology of Obstructive Sleep Apnoea in Heart Failure

1.4.2.1 Symptoms

In the general population, OSA has been associated with an array of symptoms which includes snoring, witnessed apnoeas, unrefreshing sleep, headaches, unexplained excessive sleepiness, tiredness, or fatigue, nocturia, choking during sleep and more (National Institute for Health and Care Excellence (NICE), 2021). In patients with CHF, snoring has been independently associated with OSA, whilst excessive daytime sleepiness (EDS), is less common compared to the non-HF SDB population (Bitter *et al*., 2012). Artz (2006) reported that despite longer sleep onset latency and shorter sleep time, patients with CHF had lower Epworth Sleepiness Scores (ESS) with no association between the OSA severity and the ESS score. It is possible that superimposing OSA on CHF causes an exaggerated effect on sympathetic nervous system activity and is therefore likely to play a role in lack of reported EDS in CHF.

Symptoms of fatigue and nocturia are commonly reported in both OSA and CHF. Therefore, a cross-over of symptoms between OSA and CHF, in addition to lack to EDS, is likely to challenge the recognition of OSA in CHF.

1.4.2.2 Upper airway collapse

OSA is characterised by upper airway obstruction with cessation of airflow in the presence of ongoing abdominal and thoracic wall movement. Usually, airway

patency is maintained by increased pharyngeal dilator muscle activity, however, during sleep, reflex muscle activation is reduced. Therefore, when the airway is compromised, it will lead to complete or partial airway obstruction that relies on episodes of hypoxia and hypercapnia to stimulate ventilation and subsequent arousal to re-establish the airway (White, 2005).

In the general population, OSA is often anatomically predisposed to a smaller pharyngeal airway due to increased soft tissue or a small bony compartment around the airway. In patients with CHF, rostral shift of fluid from the lower legs to the chest and neck area during night-time recumbency, provides an additional mechanism for OSA.

Obesity and fat deposition around the pharynx contribute to pharyngeal narrowing. Due to a lack of rigid support, the upper airway depends on specific dilating forces to maintain airway patency (Remmers *et al.,* 1978). Collapse of the airway is influenced by intraluminal negative pressure, generated by the diaphragm during inspiration, and extra luminal tissue pressure, usually resulting from bony or tissue pressure around the airway. These forces are counteracted by the action of pharyngeal dilator muscles (Stanchina *et al.,* 2003).

Pharyngeal patency is also dependent on the airway anatomy. During muscle activity inhibition, the airway requires about -5 cmH_2O to collapse (Isono *et al.*, 1997). Therefore, the soft tissue pressure around the airway must be 0 cmH_2O to overcome the elasticity of the airway wall. Soft tissue situated in the bony area of the mandible and spinal column is sufficiently small and does not cause airway collapse (Shelton *et al.,* 1993). However, in patients with OSA, the airway collapses during muscle relaxation and require positive airway pressure to maintain patency. Increase in tissue pressure in the bony compartment, sufficient to cause collapse, may be due to fat deposition or crowding of the normal pharyngeal structures in a smaller bony compartment. Physical structure that can partially or completely fill the airway include tonsils and adenoids, vascular perfusion, position, or airway secretions (White, 2005).

To maintain airway patency and to overcome collapsing forces, the activation of the pharyngeal dilator muscles is required. The genioglossus muscle is the most well-known and may activate during inspiration. Furthermore, pharyngeal patency can be

influenced by changes in lung volume. During lung inflation longitudinal tension on the pharyngeal airway the caudal traction on the trachea and larynx stiffens the airway and reduce collapsibility (Schwab *et al.,* 1995)**.**

Therefore, specific characteristics such as upper airway anatomy, upper airway dilator muscle responsiveness during sleep, arousal threshold secondary to respiratory stimulation, and ventilatory control instability, are key determinants of the development and severity of OSA.

1.4.2.3 The role of fluid shift in OSA

In CHF, rostral shift of fluid might be an important mechanism for OSA. A shift of fluid from the legs to the upper body, causing oedema of the pharynx and surrounding tissue when lying down at night may be a contributing factor to airway narrowing. Not only was overnight rostral shift of fluid associated with a reduction in leg volume that inversely correlated with increased neck circumference and AHI, but it was also associated with increased pharyngeal collapsibility and a reduction in pharyngeal calibre during sleep in patients with CHF (Yumino *et al.,* 2010; Carlisle *et al.,* 2017). A study by Kasai (2013) demonstrated an increase in neck circumference and upper airway resistance, a reduction in minute volume and increase in PCO_2 due to fluid displacement when anti-shock trousers were inflated, further demonstrating the role of rostral shift of fluid in upper airway obstruction.

Patients with CHF and co-morbid OSA are also likely to have a higher sodium intake than CHF patients without OSA (Kasia et al., 2011). A study by Yadollahi (2014) demonstrated that the infusion of 2l of saline in male participants not only increased neck circumference, but also a 3-fold increase in AHI.

These studies demonstrate that rostral shift of fluid is likely to contribute to the pathogenesis of OSA in CHF.

1.4.2.4 Respiratory control

A crescendo-decrescendo pattern of hyperventilation is usually associated with CSA-CSR due to a low cardiac output and delayed lung-to-chemoreceptor time (Ryan and Bradley, 2005). This periodic breathing pattern can also be displayed in OSA, suggesting that there is a possibility that instability in respiratory control and high loop gain, might contribute to the pathogenesis of OSA in CHF, however, supporting evidence is lacking.

1.4.3 Impact of Obstructive Sleep Apnoea on Heart Failure

OSA can contribute to the progression of CHF through several mechanisms described in the section below.

1.4.3.1.1 Negative Intrathoracic Pressure

Inspiratory effort against an occluded airway generates increased negative intrathoracic pressure as low as -80cmH_20, resulting in increased LV transmural pressure and consequent increase in LV afterload (Bradley *et al.*, 2001). Similarly, negative intrathoracic pressure changes augment venous return and right ventricular preload, whilst hypoxic pulmonary vasoconstriction increases right ventricular afterload (Bradley & Floras, 2009).

Secondary to right ventricular distension, leftward septal displacement reduces LV filling during diastole. Increased LV afterload in conjunction with a reduced LV preload progressively reduces stroke volume and cardiac output. These changes are more marked in HFrEF than individuals with normal LV function (Bradley *et al.*, 2001).

Increased transmural pressure raises myocardial oxygen demand whilst generating a fall in coronary blood flow and can cause myocardial ischemia in those with pre-existing CAD (Bradley *et al.*, 2001; Bradley *et al.,* 2003). A fall in cardiac output can further cause a significant decline in cerebrovascular blood flow during apnea episodes, predisposing patients with OSA to nocturnal cerebral ischemia (Bålfors & Franklin, 1994). Over time, the increase in wall stress result in LV hypertrophy and ventricular dilatation which are closely linked to the severity of OSA (Shivalkar *et al.,* 2006). Negative intrathoracic pressure also increases atrial and intrathoracic aortic wall stress and subsequently the likelihood of nocturnal atrial arrhythmias and thoracic aortic dissection (Sampol *et al.,* 2003).

1.4.3.1.2 Autonomic dysregulation

OSA has a profound effect on the sympathetic nervous system mediated through apnoea-induced hypoxia and hypercapnia. Similar to the negative intrathoracic pressure changes, sympathetically mediated peripheral vasoconstriction further contributes to the increase in afterload and blood pressure (Somers *et al.,* 1995). On termination of an apnoeic episode, arousal from sleep is associated with increased sympathetic activity, in the presence of reduced vagal tone resulting in an increase in

blood pressure and heart rate. These effects can be observed into wakefulness resulting in higher blood pressure and reduced heart-rate variability (Somers *et al.,* 1995; Narkiewicz *et al.,* 1998). Cardiac vagal withdrawal specifically reduces heart rate variability which is a marker of malignant arrhythmias. Heart rate is further increased by sympathetic over activation resulting in cardiac ß-adrenoreceptor desensitisation, peripheral vasoconstriction, myocardial injury, and necrosis and promotion of sodium retention (Floras, 2009).

1.4.3.1.3 Oxidative Stress, Inflammation and Endothelial Dysfunction

Intermittent hypoxia can induce oxidative stress and activate inflammatory pathways that impair vascular endothelial function and promote atherogenesis with consequent increase in blood pressure independent of sympathetic nervous system activation (Vongpatanasin *et al.*, 2007). Low plasma nitrate and high levels of oxidative stress markers are present in individuals with OSA. Intermittent hypoxia activates nuclear transcriptional factors such as nuclear factor kappa-B which stimulate the production of inflammatory mediators and adhesion molecules that facilitate endothelial damage and atherogenesis. Several non-randomised uncontrolled studies showed that raised levels of inflammatory markers, including C-reactive protein, Interleukin-6, tumour necrosis factor-kappa B and interleukin-8, in patients with OSA decreased with the use of continuous positive airway pressure (CPAP) (Yokoe *et al.*, 2003; Ryan *et al.,* 2006).

1.4.3.1.4 Platelet Activation and Hypercoagulability

In patients with OSA, platelet activation and thrombotic risk increase during sleep. Barcelo (2011) showed that increased platelet activation at night improved with consistent use of CPAP. In addition, both fibrinogen and plasminogen activator inhibitor type-1 increased in the presences of OSA, although both have shown decreased concentrations with the use of CPAP (Chin *et al.*, 1996; Von Känel *et al.,* 2006; Mehra *et al.,* 2010). It is therefore possible that increased platelet activation and hypercoagulability may play a role in thromboembolic events such as stroke.

1.4.3.2 Subclinical Consequences and Disease Endpoints

1.4.3.2.1 Hypertension

Of all CV conditions related to OSA, hypertension is the best established with a particularly strong association with resistant hypertension (Nieto *et al.,* 2000;

Gonçalves *et al.*, 2007). During an OSA event, the termination of an apnoea or hypopnoea is followed by an increase in blood pressure and heart rate which corresponds with a cerebral arousal and decline in oxygen saturation. Blood pressure patterns associated with OSA are usually characterised by a non-dipping pattern that is often associated with CV disease (Cowie, 2017).

Findings from the Wisconsin Sleep Cohort described a linear, dose-dependent relationship between OSA severity and the risk of developing hypertension, with OSA prevalence much higher (71%) in patients with resistant hypertension compared to those with essential hypertension (38%) (Peppard *et al.,* 2000; Gonçalves *et al.*, 2007).

Findings from multiple RCTs reported a reduction in blood pressure with CPAP treatment. Furthermore, a meta-analysis by Lui *et al.* (2016) supported these findings and not only found a significant reduction in 24-hour ambulatory blood pressure, but also in mean nocturnal diastolic blood pressure with CPAP treatment.

1.4.3.2.2 Metabolic Syndrome

The role of OSA in the development of metabolic syndrome has been widely recognised (Drager *et al.*, 2015). Regardless of BMI, patients with OSA are often insulin-resistant with an increase in type-2 diabetes. The severity of insulin resistance was found to directly correlate with nocturnal hypoxia (Borel *et al.,* 2013; Murphy *et al.*, 2017). Disturbances in lipid metabolism are also found in patients with OSA with the desaturation index as an independent contributing factor to hypercholesterolaemia and other disturbances in lipid metabolism (Adedayo *et al.,* 2014).

Despite the benefits of CPAP for the treatment of OSA, a meta-analysis by Jullian-Desayes (2014) concluded that CPAP did not significantly improve glucose, lipids, insulin resistance or the number of patients with metabolic syndrome.

1.4.3.2.3 Cerebrovascular Disease

OSA has been independently associated with an increased risk of stroke. Yaggi (2005) reported an increase in risk of stroke and all-cause mortality with an AHI of ≥35/hour, independent of other risk factors. These findings were further supported by Munoz (2006) who reported an increase in risk of ischaemic stroke with an AHI ≥30 in elderly men. Although the Sleep Heart Health study found that AHI increased the

risk of stroke by 6%, in men there was an increased risk of stroke with mild-moderate OSA, whilst in women, increased risk of stroke was only linked to severe OSA (Redline *et al.,* 2010). A reduction in risk of CV events was reported with CPAP treatment (Marin *et al.,* 2005).

1.4.3.2.4 Coronary Artery Disease

OSA has been associated with CAD with the related mechanisms of sympathetic nervous system activity, oxidative stress, and endothelial dysfunction (described in section 2.3.4.2) (Patt *et al.,* 2010). CPAP intervention has been shown to mitigate these pathological processes and therefore offering treatment that could influence CV outcomes (Tietjens *et al.*, 2018). Early observational studies supported the efficacy of CPAP treatment on CV outcomes.

1.4.3.2.5 Arrhythmias

Cardiac arrhythmias, including bradycardia and atrioventricular block, are commonly associated with OSA and can occur because of vagal stimulation associated with apnoeas and hypopnoea during rapid eye movement sleep (Patel *et al.,* 2017).

OSA is prevalent in most patients with persistent AF with findings from the Sleep Heart Health Study reporting a four-fold increase in odds of AF in patients with moderate to severe OSA. In patients with AF and untreated OSA, there is not only an increased risk of AF recurrence post- cardioversion, but also after pulmonary vein isolation (Kanagala *et al.*, 2003; Ng *et al.,* 2011).

Findings from the Sleep Heart Health Study also reported a three-fold increase in non-sustained ventricular tachycardia and twice the odds of complex ventricular ectopy in patients with OSA, independent of confounding factors. Furthermore, nocturnal arrhythmias were associated with OSA and hypoxia (Cowie, 2017).

OSA associated arrhythmias have been correlated with an increase in sudden cardiac death during sleep which in turn has been directly correlated with nocturnal hypoxaemia, independent of other risk factors. An AHI of ≥ 20 was identified as an independent and significant risk factor (Gami *et al.,* 2013). Sympathetic nervous system activation and alterations in ventricular repolarisation have been identified as proarrhythmogenic mechanisms in patients with OSA (May, Van Wagoner & Mehra, 2017).

1.4.3.2.6 Heart Failure

OSA is a significant risk factor for HFrEF. From the subclinical consequences and disease endpoints described above, it appears that there are also several similarities between the effects of OSA and other aetiologies of HFpEF. Intermittent hypoxia, consequent stimulation of the sympathetic nervous system and renin-angiotensin-aldosterone system, and inflammation are associated with oxidative stress which is likely to contribute to the development of HFpEF (Sanderson *et al.,* 2021).

The mechanisms of OSA related CV and metabolic disease are summarised in **Figure 2**.

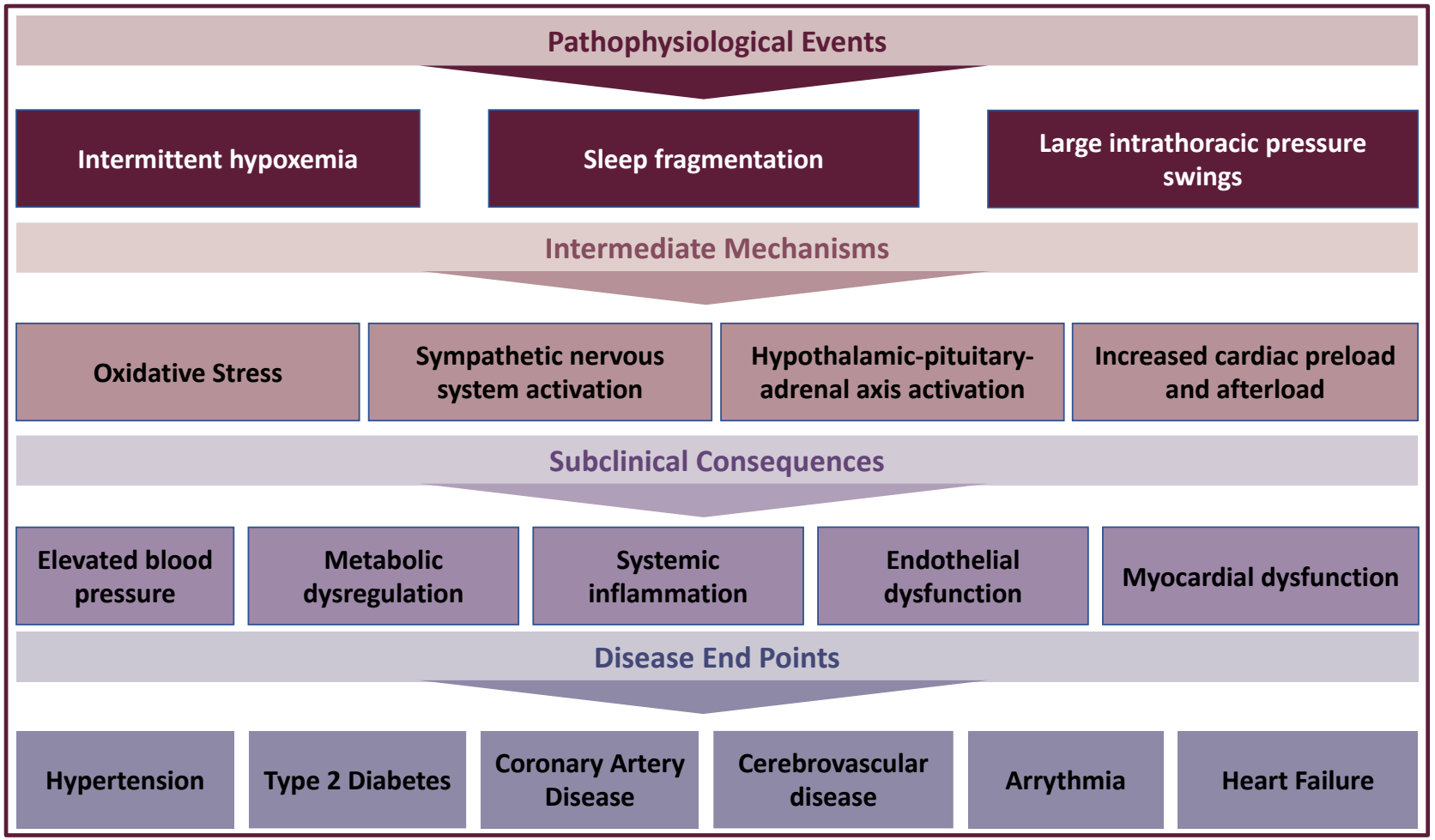


Figure 2 Mechanisms of Obstructive Sleep Apnoea (adapted from Gottlieb & Punjabi, 2020)

In summary, a bidirectional relationship exists between OSA and CHF. OSA is likely to unsettle CHF through the above-described mechanisms, whilst fluid accumulation in the neck can narrow the pharynx and increase propensity of upper airway collapse during sleep, contributing to the severity of OSA.

1.5 Diagnosis of Sleep Disordered Breathing in Heart Failure

1.5.1 Symptoms

Cluster analysis of the Icelandic Sleep Apnoea Cohort identified three distinct phenotypes of OSA which include disturbed sleep, minimally symptomatic and the EDS groups (Ye *et al.,* 2014).

Individuals with OSA in the general population generally fall in the EDS group and commonly report unrefreshing sleep and up to 90% of sleep clinic patients reported EDS, usually because of sleep fragmentation (Chervin, 2000; Kapur *et al.*, 2005; Gottlieb & Punjabi, 2020). Other general symptoms include loud snoring, awakening with gasping or choking, nocturia, morning headaches, irritability, erectile dysfunction, poor concentration, and witnessed apnoeas reported by partners (Martin *et al.,* 2016; Russel, Kristiansen & Kvaerner, 2014; Parthasarathy *et al.*, 2012). Although awakenings are typically without any additional symptoms, those associated with gasping or choking are found to be a more reliable indicator of OSA (Myers, Mrkobrada & Simel, 2013).

Atypical symptoms commonly reported by women include insomnia, impaired memory, mood disturbance, reflux, and nocturnal enuresis (Björnsdóttir *et al.,* 2013; Lim, Morgenthaler & Katka, 2018). This association between OSA and mood disorders has been strengthened by reports that CPAP therapy sustained improvement in depression scores in patients with moderate-severe OSA (Edwards *et al.*, 2015). OSA related cortical arousals, sleep fragmentation, EDS and nocturnal intermittent hypoxia have been associated with impaired cognitive function whilst impaired reaction time and distractibility has been contributing to motor vehicle accidents (MVAs) with a dose-response relationship between OSA severity and MVAs (Young *et al.*, 1997; Strohl *et al.*, 2013).

Although snoring is a common feature of OSA in CHF, clinical recognition of OSA in patients with CHF is often challenging. Patients with CHF commonly present with

minimal sleepiness and would fall into the minimally symptomatic group. In patients with OSA, the probability of co-morbid hypertension and CV disease were the highest in this group, and the lowest in the EDS group (Ye *et al.,* 2014). Lack of reported EDS in CHF is likely explained by wakefulness due to increased sympathetic nervous system activity (Pak *et al.*, 2019). This patient group is likely to have around 10% less sleep and score 2 points lower on the ESS, compared to OSA patients without CHF (Naughton & Kee, 2017). Furthermore, symptoms of fatigue and nocturia are commonly reported in both CHF and OSA. Therefore, lack of EDS in conjunction with a crossover of symptoms between CHF and OSA are likely to complicate the recognition of OSA in CHF.

CSA-CSR is often associated with delayed onset of sleep, insomnia, nocturia, orthopnoea, paroxysmal nocturnal dyspnoea, hyperpnoea, daytime fatigue and feeling of unrefreshed sleep (Costanzo, 2020). Like OSA, patients may report fatigue, but not usually EDS.

1.5.2 Screening Questionnaires

While laboratory-based PSG is the recognised gold standard test for the diagnosis of OSA, access to and availability of sleep services are often limited by geographical variation and inequity associated with cost and long waiting times (Rejón-Parrilla, Garau & Sussex, 2014). To support risk stratification, several screening questionnaires and clinical prediction tools have been developed. Whereas clinical prediction formulae are limited by complexity and the requirement for a computer or mathematical calculations, OSA screening questionnaires are less complicated and may provide an alternative to clinical prediction formulae for the identification of individuals at risk of OSA (Rowley, Aboussouan & Badr, 2000).

OSA screening questionnaires commonly used in clinical practice include the Epworth Sleepiness Scale (ESS), Berlin, STOP and STOP-Bang questionnaires (Johns, 1991; Netzer *et al.,* 1999; Chung *et al*., 2008). Due to differences in symptoms, risk factors and lack of validation of these questionnaires in patients with CHF, clinical utility, and accuracy of these questionnaires in this patient population are not well established (Arzt *et al.,* 2006).

1.5.2.1 Epworth Sleepiness Scale

The ESS was developed by Dr Murray Johns in 1990 to assess daytime sleepiness in adults. It is a self-administered questionnaire that consists of eight questions that takes between 2-3 minutes to complete **(Figure 3).** For each question, respondents are asked to rate (scale of 0-3) their chances of falling asleep during eight different activities. The overall ESS score can range from 0-24; the higher the indicated score, the higher the individual's sleep propensity (Johns, 1991). The ESS questions were selected to represent a wide range of activities with different capacity to facilitate sleep onset and that was confirmed by analysis of variance and Rasch analysis (Johns, 2010).

Sleep propensity refers to the probability, ease, or speed of changing from being wakeful and alert, through drowsiness to sleep under specific circumstances, whilst fatigue refers to the sense of tiredness from exertion (Johns, 2010). The ESS specifically distinguishes between sleepiness and feelings of fatigue. Although fatigue and sleepiness are related concepts, they are often confused (Johns, 2003). The ESS does not enquire about an individual's subjective feelings of alertness or drowsiness, nor does it determine frequency or length of an individual's daytime sleep (Johns *et al.,* 2008). To reduce the number of invalid ESS scores due to missed-item scores, the ESS was updated in 1997 to include an additional sentence in the instructions ("it is important that you answer each question as best you can").

The normal range for ESS scores (0-10) has been agreed in several countries including Australia, United Kingdom, Italy, and Turkey, however, it is unclear if this range applies to other populations (Manni *et al.,* 1999; Izci *et al.,* 2008). Although age and gender did not affect ESS scores in adults, it was found that African Americans had a significantly higher ESS scores than Caucasian Americans (Mihăicută *et al.,* 2013). ESS scores of 11-24 are associated with high levels of EDS which are commonly seen in patients with narcolepsy who often have at least moderate to severe EDS.

Although the ESS has been developed in English, it has since been translated in many languages, including Arabic and Chinese. Since the development of the ESS, it has been validated in numerous clinical cohorts, including those with insomnia, restless legs, SDB, narcolepsy, Parkinson's disease, and healthy subjects. Despite

being widely used in clinical practice and research, a systematic review by Kendzerska (2014) highlighted several limitations. Firstly, there appeared to be a lack of high-quality studies reporting on the psychometric properties of the ESS. Secondly, the internal consistency of the ESS suggested that it can be utilised for group comparisons but not individual comparisons. Thirdly, there was only limited evidence on the test-retest reliability of the ESS. Fourthly, there was uncertainty about the one-dimensionality of the ESS scale, specifically in relation to items that may occur infrequently or situations with low probability of falling asleep, such as talking or in traffic. Fifthly, despite known-group construct validity, it was likely that differences across groups of comparison may not be of clinical significance. Finally, it was also found that it was likely that the ESS underestimates sleepiness severity in older patients, due to many older adults not being able to answer all the ESS items (Onen *et al.,* 2013).

How likely are you to doze off or fall asleep in the following situations in contrast to feeling just tired? This refers to your usual way of life in recent times. Even if you haven't done some of these things recently, try to work out how they would have affected you.

Use the following scale to choose the most appropriate number for each situation:

0 = would **never** doze

1 = **slight** chance of dozing

2 = **moderate** chance of dozing

3 = **high** change of dozing

Situation	Chance of dozing			
Sitting and reading	0	1	2	3
Watching TV	0	1	2	3
Sitting inactive in a public place (eg. movie theatre or a meeting)	0	1	2	3
As a passenger in a care for an hour without a break.	0	1	2	3
Lying down to rest in the afternoon when circumstances permit.	0	1	2	3
Sitting and talking to someone.	0	1	2	3
Sitting quietly after lunch without alcohol.	0	1	2	3
In a car, while stopped for a few minutes in the traffic.	0	1	2	3

ESS Score Interpretation of daytime sleepiness

0-5 Lower Normal

6-10 Higher Normal

11-12 Mild Excessive

13-15 Moderate Excessive

16-24 Severe Excessive

Figure 3 Epworth Sleepiness Scale

1.5.2.2 Berlin Questionnaire

The Berlin questionnaire was developed to identify patients at risk of OSA and was first validated in a primary care population. The questionnaire consists of ten questions that are arranged into three categories. Category one has five questions on snoring and cessation of breathing, category two has four questions on symptoms of EDS, BMI and hypertension, and category three has one question about height and weight (**Figure 4**) (Netzer *et al.,* 1999).

The Berlin questionnaire was developed in English and has been translated into several languages, including Arabic, Chinese, Dutch, French, Greek, Indian and more, and is widely validated in several study populations, including the general population, sleep clinic, occupational groups, surgical patients, pregnant women, primary care patients and patients with cardio- or cerebrovascular disease or risk factors. Test characteristics are dependent on setting, location, AHI threshold and disease prevalence (Netzer *et al.,* 1999).

In the sleep clinical population, validation of the Berlin questionnaire showed a pooled sensitivity ranging from 79%-82%, whilst pooled specificity ranged from 32% to 39% at AHI thresholds for mild, moderate, and severe OSA. In the surgical population, sensitivity across AHI thresholds (≥5; ≥15, ≥30) were 69%, 79%-82% and 87%, and specificity were 56%, 50-62%, and 46%, respectively. In the general population for AHI ≥5 and ≥15, sensitivity was 69% and 89% and specificity was 83% and 63%, respectively. In the primary care population for AHI ≥5 and AHI≥30, sensitivity was 76% and 93%. In the other populations, such as the idiopathic intracranial hypertension and pregnant women populations, participants were much younger than compared to the other study populations (Senaratna *et al.,* 2017).

Although the Berlin questionnaire has a good sensitivity to detect moderate-severe OSA in the sleep clinical population, specificity was low across all study populations. The questionnaire is time consuming to complete and has not been validated in African American or Hispanic populations. Being one for the few questionnaires validated in a primary care population, the Berlin was validated against home portable sleep study rather than PSG.

BERLIN QUESTIONNAIRE

Height (m) _____ Weight (kg)_____ Age_____ Male / Female
Please choose the correct response to each question.

CATEGORY 1

1. **Do you snore?**
_ a. Yes
_ b. No
_ c. Don't know

If you snore:

2. **Your snoring is:**
_ a. Slightly louder than breathing
_ b. As loud as talking
_ c. Louder than talking
_ d. Very loud – can be heard in adjacent rooms

3. **How often do you snore**
_ a. Nearly every day
_ b. 3-4 times a week
_ c. 1-2 times a week
_ d. 1-2 times a month
_ e. Never or nearly never

4. **Has your snoring ever bothered other people?**
_ a. Yes
_ b. No
_ c. Don't Know

5. **Has anyone noticed that you quit breathing during your sleep?**

_ a. Nearly every day
_ b. 3-4 times a week
_ c. 1-2 times a week
_ d. 1-2 times a month
_ e. Never or nearly never

CATEGORY 2

6. **How often do you feel tired or fatigued after your sleep?**
_ a. Nearly every day
_ b. 3-4 times a week
_ c. 1-2 times a week
_ d. 1-2 times a month
_ e. Never or nearly never

7. **During your waking time, do you feel tired, fatigued or not up to par?**
_ a. Nearly every day
_ b. 3-4 times a week
_ c. 1-2 times a week
_ d. 1-2 times a month
_ e. Never or nearly never

8. **Have you ever nodded off or fallen asleep while driving a vehicle?**
_ a. Yes
_ b. No

If yes:

9. **How often does this occur?**
_ a. Nearly every day
_ b. 3-4 times a week
_ c. 1-2 times a week
_ d. 1-2 times a month
_ e. Never or nearly never

CATEGORY 3

10. **Do you have high blood pressure?**
_ Yes
_ No
_ Don't know

Figure 4 Berlin Questionnaire

1.5.2.3 STOP and STOP-Bang Questionnaires

The STOP and STOP-Bang questionnaires were developed by Dr Frances Chung in 2008 **(Figure 5)**. The STOP questionnaire was based on previous work conducted with the Belin questionnaire and following consensus with anaesthetists and sleep

specialists and a subsequent literature review. Following the initial work, a four-question tool was designed to include questions related to snoring, daytime fatigue, episodes of breath holding during sleep and hypertension. These four questions were combined with the Berlin questionnaire and administered to 278 patients. Factor analysis was based on 254 responses and after a significant level of association was observed, the four questions then formed the STOP Questionnaire. As a self-reported, pencil and paper questionnaire that took 1 minutes to complete, the questionnaire consisted of four questions with yes/no answer options.

The STOP questionnaire was piloted in 592 pre-operative clinic patients. The reliability of the questionnaire was reviewed by allowing 55 patients to complete the questionnaire twice, however, due to the questions reflecting four different dimensions of OSA morbidity, it was not required to evaluate internal consistency of the questionnaire (Chung *et al.,* 2008).

The STOP questionnaire was then validated against overnight PSG in 1875 participants from pre-operative clinics. It demonstrated a moderately high sensitivity and PPV across AHI thresholds (≥5; ≥15, ≥30), however, when clinical characteristics of male gender, age, BMI>35kg/m^2 and neck circumference were incorporated to form the STOP-Bang questionnaire, sensitivity and NPV were significantly higher. For the STOP questionnaire for AHI ≥5, ≥15 and ≥30, sensitivity was 65.6%, 74.3% and 79.5% and PPV were 78.4%, 51% and 30.4% respectively. For the same AHI thresholds, specificity was 60%, 53.3% and 48.5% and NPV was 44%, 76% and 89.3%. For the STOP-Bang questionnaire for AHI ≥5, ≥15 and ≥30, sensitivity was 83.6%, 92.9% and 100% and PPV was 81%, 51.6%, and 31%. For the same AHI thresholds, specificity was 56.5%, 43% and 37% and NPV was 60.8%, 90.2% and 100% (Chung *et al.,* 2008).

Originally developed in English, the STOP-Bang questionnaire has since been translated into 23 different languages. It has been widely validated in pre-operative clinics, sleep clinics, general population, and other special populations such as highway bus drivers and renal failure patients. A systematic review and meta-analysis conducted by Nagappa (2015) showed in the sleep clinic population for AHI ≥5, ≥15 and ≥30 a sensitivity of 90%, 94% and 96% and specificity of 49%, 43% and 25% respectively. In the surgical population for AHI ≥5, ≥15 and ≥30, sensitivity was 84%, 91% and 96% and specificity was 43%, 32%, and 29% respectively.

The STOP-Bang questionnaire is a simple, easy to remember, self-reporting screening tool for OSA. Although the validation studies are of high methodological quality, the screening questionnaire is limited by low specificity and consequent high number of false positive test findings.

STOP		
Do you **SNORE** loudly (louder than talking or loud enough to be heard through closed doors)?	Yes	No
Do you often feel **TIRED**, fatigued, or sleepy during the daytime?	Yes	No
Has anyone **OBSERVED** you stop breathing during your sleep?	Yes	No
Do you have or are your being treated for high blood **PRESSURE**?	Yes	No
Bang		
BMI more than 35kg/m^2	Yes	No
AGE over 50 years old?	Yes	No
NECK circumference>16 inches (40cm)	Yes	No
GENDER: Male?	Yes	No
TOTAL SCORE*	……/8 points	

BMI: body mass index; (Chung *et al.* 2008); *Total number of "yes" answers out of 8

STOP-Bang interpretation:

Low Risk of OSA: Yes to 0-2 questions

Intermediate Risk of OSA: Yes to 3-4 questions

High Risk of OSA: Yes to 5-8 question

Figure 5 STOP-Bang Questionnaire

This section presents an overview of questionnaires commonly used in a wide variety of clinical settings to identify patients at risk of OSA. The use of a combination of the ESS and STOP-Bang questionnaires is recommended by NICE (2021), however, these questionnaires are unlikely to be effective in a CHF population. Firstly, patients with CHF do not usually present with EDS, which means that the ESS, designed to assess sleep propensity, will not be effective in this group. Secondly, both the Berlin and STOP-Bang questionnaires also enquire about sleepiness which might result in misclassification of risk and a subsequent lower score due to absence of EDS. Thirdly, many validation studies have been conducted in sleep clinic populations. These studies are often exposed to a high degree of selection bias and spectrum effect. As such, diagnostic validation and clinical utility is therefore not transferable to other clinical cohorts due to differences in prevalence and disease spectrum. Patients referred to sleep services are also likely to have more severe disease and validation in the sleep clinic does not necessarily reflect the questionnaire performance in an unselected clinical cohort where the questionnaire is intended to be used.

1.5.3 Sleep Studies

1.5.3.1 Polysomnography

PSG is considered the gold standard for the diagnosis of SDB. It requires a comprehensive monitoring system to accommodate sleep staging, limb movements, airflow, respiratory effort, heart rate and rhythm, oxygen saturation and body position. PSG is a type 1 sleep study that is usually conducted in a sleep laboratory with a sleep technician present for the duration of the study. It is expensive, time-consuming, and associated with long waiting times (Flemons *et al.*, 2004). To overcome these barriers, portable home sleep apnoea testing (HSAT) devices have been developed for the detection of SDB (Corral-Peñafiel *et al.,* 2013).

Historically, the AASM classified sleep studies into four types, however, in 2011, a new SCOPER (Sleep; Cardiovascular; Oximetry; Position; Effort; Respiratory) categorisation (**Table 3**) was introduced (Ferber, *et al.*, 1994; Collop *et al.*, 2011).

Table 3 SCOPER Categorisation

Sleep	Cardiovascular	Oximetry	Position	Effort	Respiratory
S1: 3 EEG channels with EOG and chin EMG	C1: >1 ECG lead	O1: Oximetry (recommended sampling)/ O1x: Oximetry without recommended sampling or not described	P1: Video or visual position measurement	E1: Two RIP belts	R1: Nasal pressure and thermal device.
S2: <3 EEGs with/without EOG or chin EMG	C2: Peripheral arterial tonometry	O2: Oximetry with alternative site	P2: Nonvisual position measurement	E2: One RIP belt	R2: Nasal pressure
S3: Sleep surrogate: actigraphy	C3: Standard ECG measure (1 lead)	O3: Other oximetry	n/a	E3: Derived effort	R3: Thermal device
S4: Other Sleep measures	C4: Derived pulse (from oximetry)	n/a	n/a	E4: Other effort measures (including piezo belts)	R4: End-tidal CO_2
n/a	C5: Other cardiac measures	n/a	n/a	n/a	R5: Other respiratory measures

(Reproduced from Collop *et al.*, 2011); EEG: electroencephalogram; EOG: electro-oculogram; EMG: electromyogram; RIP: respiratory inductance plethysmograph

Portable HSAT devices, ranging from 1-2 channels (oximetry) to multi-channel cardiopulmonary signals, are associated with improved patient access, cost effectiveness and greater acceptability to patients (Collop *et al.*, 2007; Corral-Peñafiel *et al.*, 2013; Ferber *et al.,* 2018). Type 3 monitors are commonly used as HSAT devices and when compared to in-lab PSG, it has shown positive results and good concordance in patients with a high pre-test probability of moderate-severe OSA, suggesting that unattended RP is a feasible alternative to in-lab PSG. Furthermore, type 3 monitors demonstrated a high sensitivity and specificity in patients with CHF and suspected SDB and due to a high agreement between AHIs recorded by PSG and RP, this makes RP a useful alternative to portable PSG for the diagnosis of SDB in CHF (Quintana-Gallego, *et al.*, 2004; Pinna *et al.*, 2014).

Scoring of SDB events vary depending on the technology and number of signals that are recorded. HSAT devices do not record the same signals as full PSG, however, they attempt to provide an index of OSA severity that is comparable to PSG derived AHI (Collop *et al.*, 2011).

A key limitation of HSAT devices is the inability to detect arousal in the absence of electroencephalogram (EEG) recording. In turn some devices utilise surrogate measures such as change in snoring, pulse rate and movement to identify hypopnea events. To calculate the AHI, the majority of HSAT devices utilise the recording time instead of total sleep time with typically a 20% difference between recording time and total sleep time with a consequent lower AHI value in the HSAT (Light *et al.*, 2018).

To accommodate these differences, the AASM recommends the use of Respiratory Event Index. Some HSAT devices can distinguish between sleep and wake stages by using limited EEG or alternative technology, such as arterial tonometry providing an estimated measure of total sleep time (Kapur *et al.,* 2017; Popovic *et al.*, 2014; Zhang *et al.,* 2020).

Validation studies comparing HSAT devices with in-lab PSG demonstrated a fair agreement between OSA severity metrics and adequate diagnostic parameters (Mulgrew *et al.,* 2007; Chang *et al.*, 2019). Whilst most devices rely on the measurement of airflow, technologies such as peripheral arterial

tonometry (PAT) have been identifying SDB events without airflow. OSA indices from PAT devices are referred to as pAHI and pRDI and have been reported as equivalent to PSG derived AHI (Hedner *et al.*, 2004; Hedner *et al.,* 2011).

1.5.3.2 Scoring of Events

The 2007 AASM manual for the scoring of sleep and associated events was updated in 2012 (Berry *et al.,* 2012). The definitions of respiratory events have continued to evolve over time and are summarised in **Table 9**.

Table 4 Timeline of Hypopnoea Definitions

Date	Criteria
1979	First description of 'hypopnoea': 4% oxygen desaturation (Block *et al.*, 1979)
1988	Description of 'Sleep Apnoea Syndrome' (Gould *et al.*, 1988)
1999	Chicago Criteria description of hypopnoea: 50% reduction in air flow or clear air flow amplitude reduction with 3% oxygen desaturation and/or arousal. (AASM, 1999)
2007	Recommended: 30% airflow reduction + ≥4% oxygen desaturation Alternative: 3% oxygen desaturation and/or arousal (Iber *et al.*, 2007)
2012	30% airflow reduction + ≥3% oxygen desaturation and/or arousal. (Berry *et al.,* 2012)

The apnoea rule for adults includes a drop in airflow of ≥ 90% from baseline, lasting ≥10 seconds and ≥90% of the event's duration meets the amplitude reduction criteria for an apnoea. In turn, despite difficulties in selecting a single definition for hypopnoea, a consensus was reached on the definition of a hypopnoea rule in adults and included a 30% drop in nasal pressure excursion

for ≥10 seconds associated with ≥30% desaturation or arousal. Changing from ≥4% to ≥3% desaturation criteria increased the AHI considerably (Berry *et al.,* 2012).

1.6 Treatment of Sleep Disordered Breathing in Heart Failure

Optimisation of HF evidence-based treatment is an essential first approach to the management of SDB in patients with CHF (Tsai & Khayat, 2018). Angiotensin converting enzyme inhibitors, beta-blockers and mineralocorticoid receptor antagonists form the cornerstone of HFrEF treatment with the aim to improve the clinical status, functional capacity, and quality of life in this patient group, whilst preventing hospitalisation and reduce mortality. The utilisation of diuretics for relief of congestion is particularly important to reduce the night-time rostral shift of fluid from the lower extremities to the thorax and throat which is likely to worsen both OSA and CSA-CSR (McDonagh *et al.,* 2021). A study by Bucca (2007) demonstrated that diuretic therapy increased the upper airway calibre in patients with severe OSA and CHF with a significant decrease in AHI and improvement in SDB.

Additionally, cardiac resynchronisation therapy (CRT) may reduce the AHI in CSA-CSR, but not in OSA. Stro (2004) reported that CRT did not only increase sleep quality in patients with CHF, but also reduced the AHI and consequently the severity of CSA. A meta-analysis reported that CRT is associated with a clinically significant reduction in AHI in patients with CSA, however, not in patients with OSA (Lamba *et al.,* 2011).

1.6.1 Treatment of Central Sleep Apnoea in Heart Failure

1.6.1.1 Positive Airway Pressure

The two positive airway pressure (PAP) devices used in clinical trials to investigate the treatment of CSA-CSR in patients with HFrEF are CPAP and adaptive servo ventilation (ASV). The main difference between these devices is that CPAP delivers a set amount of air pressure during the night to maintain upper airway patency, whilst ASV utilises algorithms that adapt the air pressure to deliver both inspiratory and expiratory airway pressure in response to the individual's breathing patterns as required (Cowie *et al.,* 2015)

The use of CPAP for the treatment of CSA-CSR in HFrEF was first investigated by Bradley (2005) with the Canadian Continuous Positive Airway Pressure for Patients with Central Sleep Apnoea and Heart Failure Trial (CANPAP). The trial tested the impact of CPAP on survival without heart transplantation in CSA-CSR and HFrEF. The study randomly assigned 258 participants with HFrEF and CSA-CSR who were medically optimised to receive either CPAP or no CPAP with a mean follow-up of two years. Follow-up assessments included sleep studies, measurements of EF, exercise capacity, quality of life and neurohormones. Results at three months showed that the CPAP group had a greater reduction in AHI and norepinephrine levels whilst reporting an increase in oxygen saturation, EF, and six minutes' walk distance. Findings showed no difference in hospitalisation events, quality of life or atrial natriuretic peptide levels. Despite early differences in survival rate without heart transplant between the control and treatment arm, there were no difference in the overall event rate between the two groups. Regardless of the abovementioned improvements, treating CSA-CSR with CPAP did not affect survival in patients with HFrEF and findings from this trial therefore does not support the use of CPAP for CSA in this patients group.

The Adaptive Servo Ventilation for Central Sleep Apnoea in Systolic Heart Failure (SERVE-HF) trial investigated the effect of ASV in patients with HFrEF and predominantly CSA. The trial randomised 1325 patients with HFrEF (LVEF≤ 45%) and predominant CSA (AHI≥15) to receive guideline-based medical treatment and ASV or guidelines-based medical treatment alone (control). It utilised time-to-event analysis with a primary end point of the first event of composite of all-cause mortality, lifesaving CV intervention (cardiac transplant, long-term ventricular assist device, sudden cardiac arrest, shock for ventricular arrhythmia) or unplanned hospitalisation for worsening CHF. Secondary end points included time to death from any cause, time to death from CV causes, change in NYHA class and 6-minute walk distance. The median follow-up period for this study was 31 months. Findings showed that the ASV group had a mean AHI of 6.6/hr at 12 months. There was no significant difference between participants assigned to the ASV and those assigned to the control group for the primary end point (p=0.10). However, the

ASV group experienced significantly higher all-cause and CV mortality, compared to the control group (HR 1.28; p=0.01; HR 1.34; p=0.006) with no improvement in quality of life (Cowie et al., 2015; Bradley and Floras, 2015). Therefore, with no significant effect on the primary end point and increase in all-cause and CV mortality in patients with HFrEF and predominantly CSA-CSR, clinical guidelines advise against the use of ASV in this patient group (NICE, 2018; McDonagh *et al.,* 2021).

The reason for the increased mortality in the ASV group is unclear. Several postulates have been suggested. Firstly, it is possible that CSA-CSR is an adaptive or compensatory mechanism in HFrEF and that reversal might be harmful (Naughton, 2012). Secondly, it is possible that the positive airway pressure generated by ASV treatment might reduce venous return and subsequent cardiac output in individuals who already have reduced cardiac reserve (Bradley *et al.,* 1992) and thirdly, ASV generated inspiratory support could result in hyperventilation, alkalosis and hypokalaemia that could increase the risk of cardiac arrhythmias (Al-Abri and Olson, 2013). However, due to lack of data recorded at the time of death, it is not possible to ascertain if deaths occurred whilst using the ASV device.

It is important to note that there are different ASV devices available that utilise different algorithms to suppress CSA-CSR. SERVE-HF used an algorithm (ASV minute volume; ASVmv) that set the minute volume target to 90% of the participants own ventilation, using relatively high default pressures with a minimum end-expiratory PAP of 5 cmH_2O and minimum inspiratory pressure support of 3 cmH_2O, likely to have contributed to low adherence to ASV treatment during the trial (Cowie *et al.,* 2013).

The Effect of ASV on Survival and Hospital Admissions in Heart Failure (ADVENT-HF) trial is the latest trial to investigate the effects of ASV on hospitalisation and mortality in patients with CHF. The trial has completed follow-up and data analysis is underway with publication of results awaited.

This multicentre, multinational, randomised, parallel group, open label trial investigated the effect of ASV peak flow (ASVpf) against no ASVpf in HFrEF with either OSA or CSA-CSR. The study included patients with stable HFrEF

(LVEF≤ 45%) and SDB (AHI >15), either predominant OSA or predominant CSA-CSR. A further criterion for patients with OSA is an ESS score of ≤ 10 with minimal or no daytime sleepiness. Unlike SERVE-HF, ADVENT-HF used the ASVpf algorithm which uses lower default pressures with a minimum expiratory PAP of 4 cmH_2O and minimum pressure support of 0 cmH_2O. The primary endpoint in this trial is the cumulative incidence rate of composite of all-cause mortality, first hospitalisation for CV diseases, new onset AF or flutter requiring anticoagulation or appropriate discharge from an implantable cardioverter defibrillator (ICD) device. Secondary endpoints include cumulative incidence rate of all-cause mortality, CV hospitalisations, new-onset AF or flutter or ICD discharge; number of days alive and not hospitalised; LV end-diastolic volume; LV mass; LVEF; NT-proBNP levels, CRT/ICD implantations; changes in NYHA class, AHI, quality of life and ESS (Lyons *et al.*, 2017; Perger *et al.,* 2019).

In view of the SERVE-HF study findings, treatment of CSA-CSR with positive pressure airway devices, is contra-indicated and considered harmful in HFrEF.

1.6.1.2 Oxygen

The use of nocturnal oxygen therapy has been associated with an increase in oxygen saturation and reduced sympathetic drive in CSA-CSR and HFrEF. Earlier small, randomised trials have shown that the use of nocturnal oxygen in patients with HFrEF and CSA-CSR can reduce the AHI by around half (Hanly *et al*., 1989; Javaheri *et al.*, 1999). However, it had no effect on plasma B-type natriuretic peptide, neurocognitive function, or quality of life.

The Congestive Heart Failure-Home Oxygen Therapy randomised trial (CHF-HOT) demonstrated that the use of low flow oxygen caused a decrease in AHI and improvement in the LVEF and mean NYHA class in severe CSA (Nakao *et al.*, 2016). Despite these earlier findings, there is no consistent evidence that the use of oxygen improved CV function or clinical outcomes in this patient group and therefore evidence does not currently support the use of supplemental oxygen for the treatment of CSA-CSR in this patient group.

1.6.1.3 Phrenic Nerve Stimulation

Newer approaches, such as unilateral transvenous phrenic nerve stimulation are under development (Ponikowski *et al.,* 2012; Abraham *et al.,* 2015). A study

by Constanzo (2018) showed that the use of phrenic nerve stimulation in patients with CHF and CSA improved oxygen desaturation and quality of life, however this study was not powered for CV events and further research is therefore required.

1.6.1.4 Respiratory stimulants

The use of the carbonic anhydrase inhibitor, acetazolamide, has been considered for the treatment of CSA-CSR. Acetazolamide stimulates respiration through metabolic acidosis and although it has shown to improve oxygenation and AHI events, further research is required (Javaheri, Sands & Edwards, 2013) The study by Javaheri and Dempsey (2013) demonstrated an improvement in CSA in CHF, however, it was associated with an increase in hypercapnic ventilatory response, a key mechanism opposing the effective resolution of CSA

1.6.2 Treatment of Obstructive Sleep Apnoea in Heart Failure

There are several treatment options for the treatment of OSA in the general population. Depending on OSA severity, treatment approaches may include sleep position restriction, lifestyle therapy, mandibular advancement devices, positive airway pressure or surgery (NICE, 2021).

The use of CPAP for the treatment of clinically significant OSA in the general population has been clearly established and supported by clinical guidelines (NICE 2008; NICE, 2021). Due to differences between the CHF population and the general population, particularly in relation to EDS, there is currently no evidence to indicate CV hospitalisation or mortality benefit when treating OSA with CPAP in CHF.

The Sleep Apnea Cardiovascular Endpoints (SAVE) study is one of the largest studies to date to investigate if treatment of OSA with CPAP in patients with HFrEF would reduce CV morbidity and mortality.

The primary endpoint of the study was a composite of death from CV causes, myocardial infarction, stroke or hospitalisation for HF, acute coronary syndrome, or transient ischaemic attack. Secondary endpoints included other composites of CV events which included revascularisation procedures, new-onset AF, new-onset diabetes mellitus and all-cause mortality. Additional

secondary end points included OSA symptoms, health related quality of life and mood. The study randomised 2717 participants from 89 sites with minimal sleepiness, moderate to severe OSA and coronary or cerebrovascular disease to receive usual care and CPAP (CPAP group) or usual care alone (control). With a mean follow-up period of 3.7 years, 229 primary end-points events were recorded for the CPAP (17%) group and 207 in the control group (15.4%). Although CPAP significantly reduced snoring and daytime sleepiness, and improved quality of life and mood, none of the individual or composite CV endpoints were met. The study concluded that CPAP and usual care did not prevent CV events in patients with CV disease and moderate-severe OSA (McEvoy *et al.,* 2016).

There are several considerations regarding the conduct of the SAVE trial. Firstly, approximately 60% or participants were from Chinese study sites. Secondly, there was a large under representation of women in the study; 80% of participants were male in line with increased risk of OSA in men. Thirdly, CPAP adherence during the trial was modest with an average adherence of 3.3 hours per night. In a pre-planned per protocol analysis of 651 participants with acceptable adherence of ≥4hrs/night, compared to a similar number of participants in the usual care group, no statistically significant benefit of CPAP was evident in relation to CV events as stated in the primary endpoint. However, this sub-group analysis did show a trend towards lower risk of stroke in good CPAP use. It was recognised that there might be a possibility that longer treatment could have showed treatment benefit. It was also noted that the SAVE trial reflected current “real world” clinical experience and that it is possible that suitable training of clinical staff could provide the skill set to adequately manage EDS in clinical practice (Qui *et al.,* 2017).

In summary, although the SAVE trial was unable to demonstrate CV benefit for treating OSA with CPAP in CHF, it did show an improvement in quality of life, reduction in depression and improvement in workplace productivity. As described in section 1.6.1.1, the ADVENT trial investigated the effect of ASV on both CSA-CSR and OSA. It is anticipated that the findings from the ADVENT-HF trial will provide further insight into the management of OSA in patients with HFrEF.

1.7 Description and Structure of Thesis

The primary aim of this thesis is to explore factors associated with the diagnosis and treatment of OSA in CHF. Specific objectives include:

- To evaluate the accuracy and clinical utility of existing questionnaires, when used alone, as screening tools for the identification of OSA in adults in different clinical cohorts.
- To prospectively evaluate the ability of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of CHF.
- To identify barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives.
- To evaluate HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

To achieve the objectives, a convergent parallel mixed methods research (MMR) design was utilised consisting of both qualitative and quantitative components. Whilst data collection and analysis were conducted simultaneously, integration of findings are presented in the discussion chapter.

To provide context to this thesis, **Chapter 1** reviewed the epidemiology and clinical consequences of SDB in CHF. This chapter highlighted differences between the general and CHF populations in relation to OSA, the challenges in detecting OSA in patients with CHF due to lack of typical OSA symptoms and overlap of symptoms in OSA and CHF. Evidence relating to OSA screening questionnaires and the treatment of SDB in the context of CHF were reviewed. Additional context will be presented in each chapter where necessary.

Chapter 2 will describe the methodology utilised in this study. The chapter will focus on the study design, the rationale for sampling, data collection and data analysis methods, including a description of relevant regulatory approval and ethical considerations.

Chapter 3 will describe a systematic review and meta-analysis of existing OSA screening questionnaires in adults in different clinical cohorts. The chapter will report the diagnostic accuracy of the Berlin, STOP and STOP-Bang

questionnaires, validated against the gold standard PSG, across the sleep clinic, surgical and resistant hypertension cohorts.

Chapter 4 will describe a diagnostic validation study of the STOP-Bang questionnaire in a sleep clinic population with co-existing stable CHF.

Chapter 5 will describe the perceived barriers and enablers to the diagnosis and treatment of OSA in CHF from both patients' and clinicians' perspectives.

Chapter 6 will describe the web survey study evaluating HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

Chapter 7 will provide a summary and integration of the findings of the different study components, the implications of the research findings, limitations, and future directions.

2

Overview of Methodology

2.1 Aims

The aims of this chapter are to:

- Describe the design of the study including the purpose, priority, and sequence of methods,
- Provide the rationale for the selected sampling, data collection and analysis methods, and
- Describe the regulatory approvals and ethical considerations of this study.

2.2 Methodological Approach

2.2.1 Study Objectives

The objectives of this thesis are:

- To evaluate the accuracy and clinical utility of existing questionnaires, when used alone, as screening tools for the identification of OSA in adults in different clinical cohorts (*quantitative component*).
- To evaluate prospectively the ability of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of CHF (*quantitative component*).
- To identify barriers to and enablers of the diagnosis and treatment of OSA from HF patients' and clinicians' perspectives (*qualitative component*).
- To evaluate HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA (*quantitative component*).

2.2.2 Mixed Methods Research

Characterised by the utilisation of a combination of quantitative and qualitative components, a convergent parallel mixed methods design was utilised to achieve the study objectives. Johnson (2007, p. 123) defines MMR as

"The type of research in which a researcher or team of researchers combines elements of qualitative and quantitative research approaches for the broad purposes of breadth and depth of understanding and corroboration".

MMR combines the statistical trends in quantitative data with the lived experiences of qualitative data, utilising the collective strength of the combination of the two data types to provide a more informed understanding (Bryman, 2006). Considered to be closely related to multiple method research, MMR utilises a combination of quantitative and qualitative components whilst multiple method research tends to utilise either multiple quantitative approaches or multiple qualitative approaches, but not a combination of the two approaches in the same study (Schoonenboom & Johnson, 2017).

An overview of the quantitative and qualitative components of this thesis is displayed in **Figure 6.**

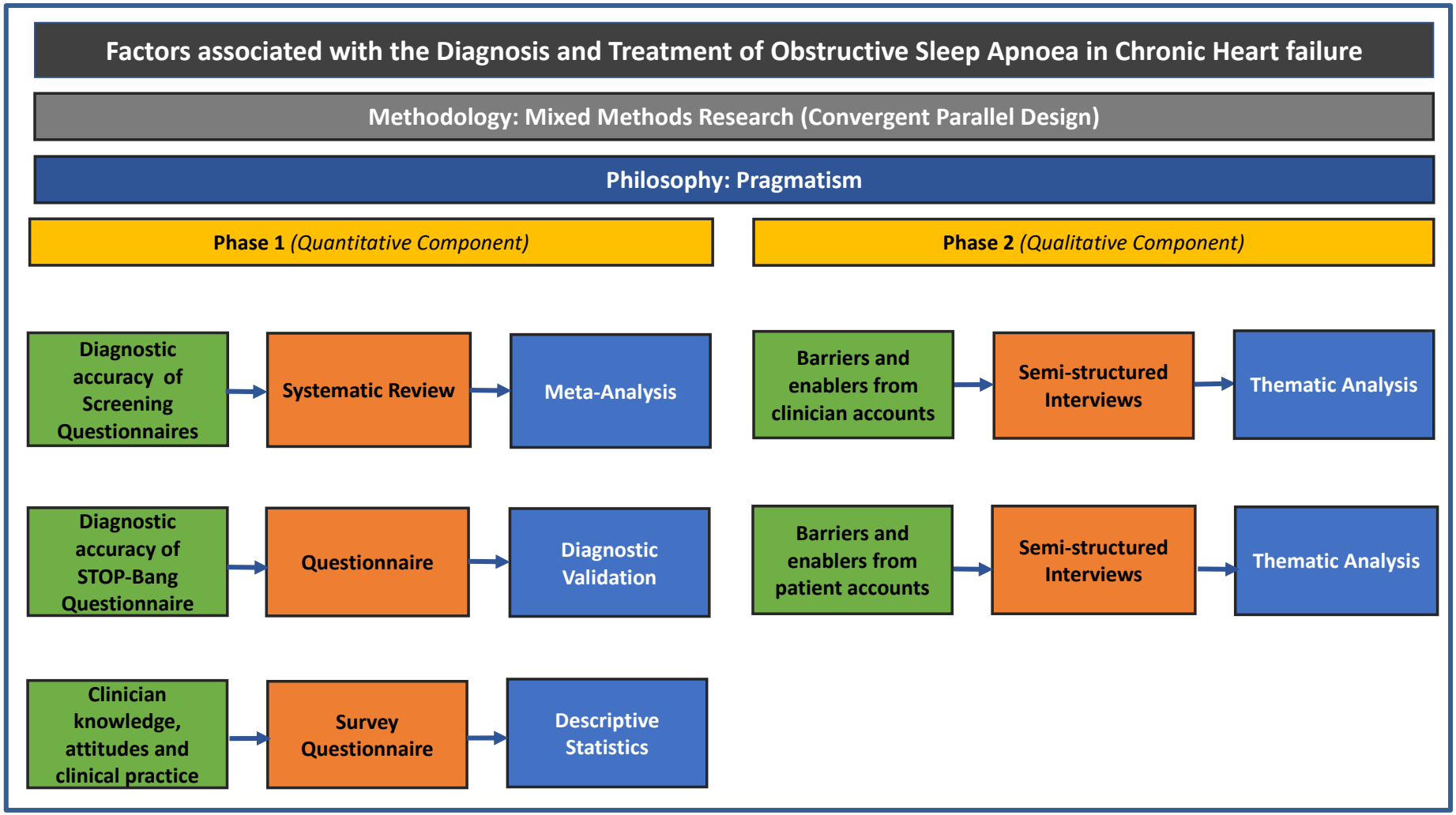


Figure 6 Overview of Study Components

2.2.3 Philosophical Stance

MMR emerged as a third research paradigm in response to the debates about the benefits and limitations of quantitative versus qualitative research, also known as the 'paradigm wars' (Feilzer, 2010). First described by Kuhn (1970), a research paradigm refers to the set of beliefs and assumptions that the researcher holds in relation to what they consider as reality (ontology), their beliefs about what is knowledge (epistemology) and what procedures can be used to gain knowledge (methodology) (Denzin & Lincoln, 2005).

The key paradigms of positivism/postpositivism and constructivism/interpretivism are situated at opposite poles of the research continuum (Creswell & Plano Clark, 2011). At the one end of the continuum, positivists believe in a singular, discoverable reality appreciated by means of deductive, objective and value-free inquiry and in support of quantitative research methods. At the other end of the continuum, constructionists reject the idea of a single objective reality and in turn believe in multiple realities through inductive and subjective inquiry and in support of qualitative research methods (Creswell & Plano Clark, 2011; Tashakkori & Teddlie, 2010).

Since MMR does not fall within either quantitative or qualitative worldviews, advocates of MMR have constructed several alternative frameworks to accommodate the nature of MMR (Tashakkori & Teddlie, 1998; Greene, Benjamin & Goodyear, 2001; Creswell & Plano Clark, 2011; Teddlie & Tashakkori, 2009). Offering an alternative paradigm to positivism/postpositivism and constructivism/interpretivism, pragmatism is frequently associated with MMR, with a focus on the research problem and research consequences (Miller, 2006; Creswell & Plano Clark, 2011). Pragmatists advocate the use of specific research methods whilst excluding others. The researcher's choice of research questions and methods will therefore reflect their epistemological understanding of the world, and their interpretation of the research findings often reveal their underlying philosophies.

Derived from the works of Peirce, James, Mead and Dewey, pragmatists are not committed to one system of philosophy or reality, but instead, utilise both quantitative and qualitative assumptions in their research and a choice of

research methods that they deem best suited for the research purpose (Denzin 2017). Assuming a mixed approach to research, pragmatists will consider both positivist and interpretivist epistemologies with a focus on similarities of the different philosophies (Johnson & Onwuegbuzie, 2004; Onwuegbuzie & Leech, 2005).

Pragmatism avoids the issues of truth and reality and accepts that there may be multiple realities. Furthermore, pragmatists evade the constraint of having to choose between positivism and constructivism or a specific research method or technique and choose to focus on "solving practical problems in the real world" (Feilzer, 2010). Therefore, pragmatists align with MMR that uses both quantitative and qualitative methodology in the same study, recognising the multiple realities are better than a single reality.

Rather than subscribing to a set of abstract philosophical beliefs, pragmatists focus on those beliefs that are connected to actions. For them, reality is ever changing, depending on our actions and will therefore focus on the method that works best to answer the related research question (Feilzer, 2010).

Pragmatism ignores the divide between quantitative and qualitative paradigms and instead suggests that the most important factor is whether the research has supported the researcher to find the knowledge that they were seeking (Hanson, 2008). Therefore, pragmatists are not determinist or rigid about the research methods that they use but apply flexibility to answer a research question.

2.2.4 Purpose

Based on Green, Caracelli and Graham's (1989) classification of MMR purposes, the primary purpose of using MMR for this study was to allow for "expansion". The use of different methods for different components of the research study did not only extend the breadth and depth of our inquiry, but also strengthened the study conclusions. Furthermore, considering Bryman's (2006) rationale for the use of MMR, the combination of qualitative and quantitative approaches in this study added enhanced credibility and strengthened the integrity of the study findings.

2.2.5 Theoretical Drive

This study included multiple objectives that were underpinned by several theoretical drives. The diagnostic validation and survey components of the study were underpinned by a ‘deductive’ or ‘quantitative’ drive, whilst the interview studies of patients and HF clinicians were underpinned by an ‘inductive’ or ‘qualitative’ theoretical drive. Because it was difficult to privilege one theoretical drive above the other, an equal status was assigned allowing both components to interact with the outcomes integrated at the end of the research process (Greene, 2015).

2.2.6 Timing and dependence

The concurrent-independent MMR design of this study meant that data collection for the quantitative and qualitative components were conducted simultaneously, whilst data analysis was performed independently. Furthermore, analysis of one component did not depend on the results of the other component (Onwuegbuzie & Johnson, 2006).

2.2.7 Point of integration

Described by Morse and Niehaus (2009) and Guest (2013), a vital component of a MMR study is the point where the qualitative and quantitative components are integrated. Differentiating between simple or complex MMR designs, Guest (2013) described simple designs as a study with a single point of integration and complex designs as a study with multiple points of integration. Requiring at least one point of intersection, integration, can occur within any or all the research components, for example study purpose, research questions, theoretical drive, methods, data analysis or results (Schoonenboom & Johnson, 2017). Considered as a simple MMR design, integration of the data sets for this study occurred through the utilisation of a theoretical framework and will be presented in the discussion chapter of this thesis (**Figure 7**).

2.2.8 Design typology

MMR designs can be further categorised into a specific MMR typology often used to direct practice, generate new ideas or as an educational tool (Teddlie & Tashakkori, 2009). Many and diverse MMR designs are available, each with strengths and limitations. Specifically, MMR designs proposed by Morse and

Niehaus (2009) appeared unsuited for this study, given an absence of equal-status designs. Instead, Creswell and Plano Clark's (2011) 'convergent parallel' design was selected which describes the conduct of the quantitative and qualitative components in the same phase of the research process, applies equal weight to the methods, analyses the components independently with integration of the results in the overall interpretation of the study.

Although the study was originally designed as a 'planned' MMR design, as it evolved it was felt that the addition of the HF clinician perspective to that of the patient perspective would add richness to the understanding of the barriers and enablers associated with the diagnosis of OSA in CHF. As such, the clinician interview study was added at a later stage, changing the MMR design from a planned to an emergent design (Creswell and Plano Clark, 2011).

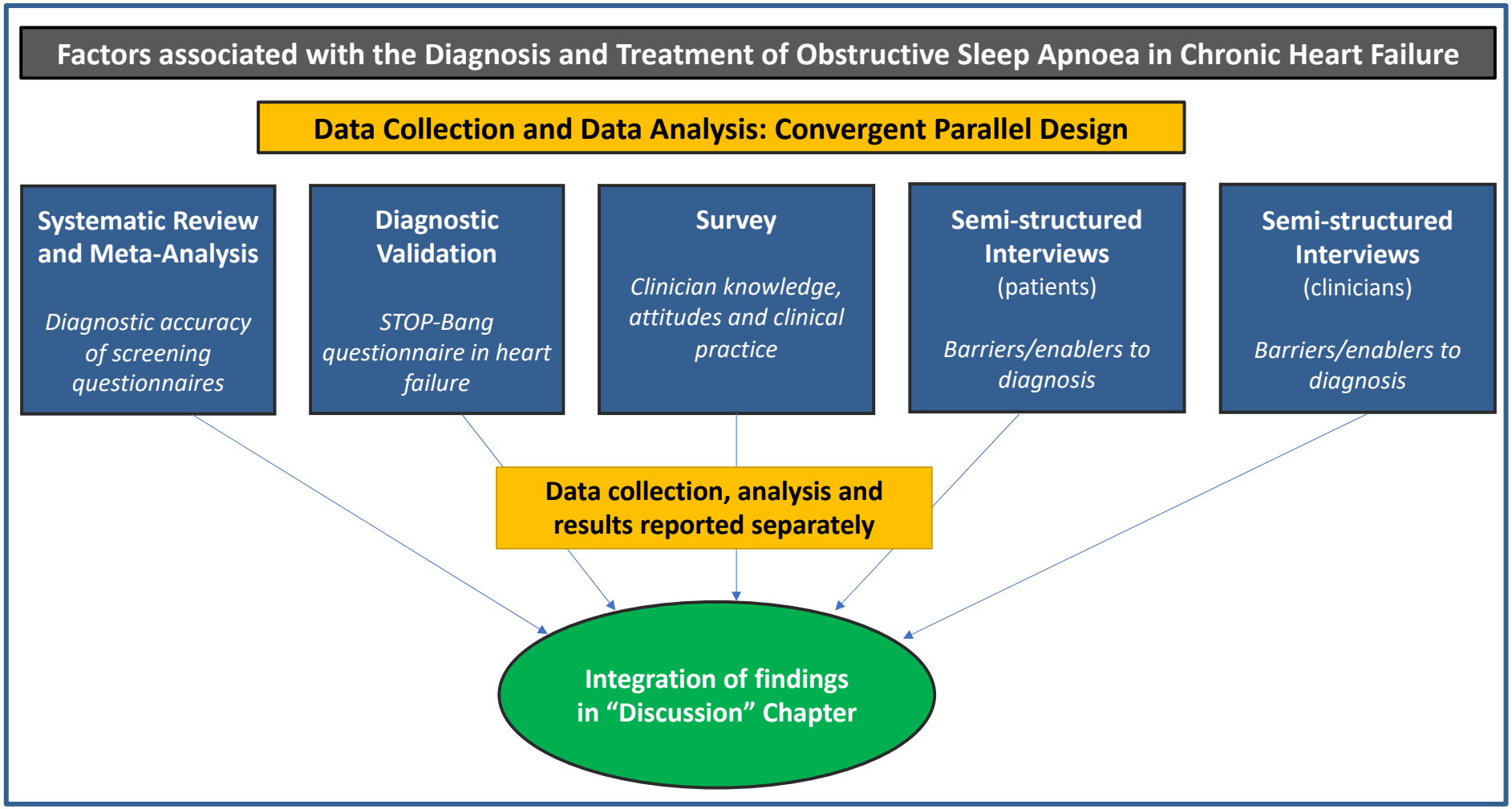


Figure 7 Overview of Study Design

2.3 Sampling Strategy

The key sampling strategies are broadly described as probability and non-probability sampling techniques. In probability sampling, every participant has an equal probability to be selected from the population utilising a random selection process (Fink, 2002). In contrast, random selection of the study sample is less important in non-probability sampling. Instead, subjective methods or judgement are utilised to select the study sample and therefore not every individual has an equal chance to be included in the study sample (Etikan *et al.,* 2016).

In this study, a non-probability sampling strategy was selected for all aspects of the study. For the quantitative component, consecutive and convenience sampling strategies were utilised for the diagnostic validation and the web survey studies, respectively. For the qualitative component of the study, purposive sampling, a non-probability sampling technique widely used in qualitative studies, was utilised (Patton, 2002).

2.3.1 Quantitative Component

Consecutive patients who attended the Sleep Disorders Service at the Leicester General Hospital for the assessment of suspected OSA and who met the selection criteria, were invited to participate in the diagnostic validation study. Consecutive non-probability sampling includes all available participants and is considered the best non-probability sampling method to control sampling bias (Thewes *et al.*, 2018). Additionally, it is a cost-effective and convenient approach with participants readily available (Etikan *et al.,* 2016). Considering the underdiagnosis of OSA across clinical specialities, consecutive sampling was selected to maximise our sample size and therefore giving every patient meets the selection criteria the opportunity to be included in the study. With consecutive sampling, the main assumption is that the population is homogeneous, and was ensured through stringent selection criteria. Key limitations to this type of sampling technique are that there is likely to be a risk of bias and potential outliers (Mackay & Gass, 2005).

For the web-based survey, convenience sampling was utilised. Ideally, objective, and unbiased probability sampling, underpinned by random selection

of participants, would have been the sampling strategy of choice (Groves *et al.*, 2002). However, it proved difficult to access a representative list of HF clinicians in England, Scotland, and Wales. The British Society for Heart Failure (BSH) has a membership of more than 1200 HF clinicians. Access to a sample of the BSH membership would have been preferred, however, it is BSH policy not to promote individual research studies and consequently the request to distribute the survey to the BSH membership was declined by the BSH Board. A pragmatic approach was thus adopted opting for non-probability, convenience sampling. Because of the subjective judgement of the researcher, participants were likely to be selected based on convenience or the researcher's beliefs that the individuals were typical of the population being studied.

One of the limitations of non-probability sampling is that some individuals may have a very high chance of being selected, while others have no chances of being selected, hence it is not possible to make statistical inferences (Salant & Dillman, 1994). A further limitation of non-probability sampling is the lack of random selection which often pose a risk of under coverage and non-response. This means that some HF clinicians have a chance to be selected, whilst other have zero chance of being selected, therefore, this non-probability sample of HF clinicians are unlikely to be representative of the entire HF clinician study population (De Leeuw *et al.*, 2008; Dillman *et al.*, 2014). However, in view of the lack of coverage and low response rates associated with web surveys, it is uncertain if true probability samples are achieved or whether is merely consists of volunteers (Dillman *et al.*, 2014). Despite the limitations of non-probability sampling, it remains a more cost-effective sampling method that supports conduct of surveys in a short period of time (Fowler, 2014).

2.3.2 Qualitative Component

Purposive, non-probability sampling was utilised for both the patient and clinician interview studies. Comprising subjective sampling methods, purposive non-probability sampling describes the deliberate choice of a participant based on their individual characteristics. For purposive sampling, typically used in qualitative research, the researcher decides what information is required and to

find individuals who can and are willing to provide the information (Etikan *et al.*, 2016).

Therefore, in the patient interview study, patients with CHF who consented to the diagnostic validation study and had OSA confirmed on their sleep study were invited to participate, given the specific interest in patients with co-existing CHF and OSA. Similarly, in the clinician interview study, a purposively selected group of doctors, nurses and pharmacists with an interest and expertise in the active management of patients with CHF in England, Scotland and Wales were invited to participate in the study.

2.4 Data Collection Methods

2.4.1 Quantitative Component

The web-based survey was selected as the most appropriate survey design to evaluate HF clinicians' knowledge and attitudes about OSA in England, Scotland, and Wales. This cost-effective and time-efficient approach, allows for rapid collection of data, often completed within 48-72hr (Uhlig *et al.,* 2014). Additionally, direct export of survey data into statistical tools, such as SPSS and Excel, facilitates the speed and accuracy of data-analysis. From a design perspective, web-based surveys benefit from a superior questionnaire interface that encourages higher response rates using icons, colours, and graphics (Callegaro *et al.,* 2015). It permits the use of a variety of question types that can be ordered randomly and be quick to fill in. Furthermore, the level of anonymity that is associated with web-based surveys makes it more likely that respondents will be forthright with their responses.

Coverage, sampling, measurement, and response are the four cornerstones of survey research. Therefore, any errors associated with these four domains will impact on data quality (Salant & Dillman, 1994).

Coverage error is a type of non-sampling error that occurs when the sample members do not represent the population accurately (Dillman *et al.,* 2014). For example, to participate in a web survey, respondents will require access to a computer and internet, requiring some degree of computer literacy. Therefore, any individuals who lack these skills will be excluded and not covered. Coverage problems in web surveys are challenging and often difficult to solve,

particularly as the researcher has no control over respondents. Furthermore, convenience samples are often used in which case coverage cannot be determined (De Leeuw *et al.,* 2008; Groves *et al.*, 2009).

Sampling error occurs when "only a sample of the population is investigated instead of the whole population" (De Leeuw *et al.,* 2008). In probability samples, with simple random sampling, statistical techniques can be used to estimate the population value. In contrast, non-probability sampling does not use a random selection process and therefore statistical techniques, or probability theory cannot be relied on (Dillman *et al.,* 2014).

Measurement error is associated with the data collection process and can be related to the questionnaire, the respondent, and the method of data collection. When respondents are unclear or do not know what to answer, it can create errors when answering the questions. Therefore, a well-designed, pretested questionnaire with clear questions will improve the quality of the survey and reduce measurement error. Respondents can be the source of error, intentionally or unintentionally (De Leeuw *et al.,* 2008). Difficulty with recall may create an unintentional error, whilst providing incorrect information to avoid answering the question may be an intentional error. Error related to the method of data collection occurs when an interviewer is present and is therefore not relevant to web-based surveys.

2.4.2 Qualitative Component

To understand individual participant experiences rather than a collective view, interviews were selected as the method of data collection for both the patient and clinician interview studies, as opposed to focus groups.

Therefore, semi-structured interviews were used to explore the barriers and enablers to the diagnosis of OSA in CHF from both CHF patients' and clinicians' perspectives. In addition to providing a deeper understanding than a survey or questionnaire, semi-structured interviews provided a flexible option that could be conducted both face to face and via telephone. Not only did it meant that the interview studies were not limited by geographical location, but it also allowed for additional questions during the interview.

A further advantage of semi-structured interviews is that this type of interview is less rigid than structured interviews where questions and response categories are pre-specified, but more structured than unstructured interviews which only has a list of topics for discussion and is mostly guided by the participant (Gill *et al*., 2008; Braun & Clarke, 2014).

Consisting of a conversation between the researcher and the participant, semi-structured interviews are directed by a topic guide that consists of open-ended questions and enhanced by follow-up questions, probes, and comments, providing an understanding of the participants personal experiences, attitudes, and perceptions about a topic of interest (DeJonckheere & Vaughn, 2019).

Interviews are associated with a few limitations. It can be time consuming from both the participant and researcher's perspective and despite the depth of information, if often lacks breadth due to smaller sample numbers. Additionally, interviews generally lack anonymity and may not necessarily be ideal for the discussion of sensitive issues (Braun & Clarke, 2014). Some participants may be more challenging to engage in the conversation and could be reluctant to share their experiences or viewpoints. Furthermore, limited probing and follow-up questions, an underdeveloped interview guide that lack open ended questions and failure to utilise active listening could all limit the effectiveness of a semi-structured interview (DeJonckheere & Vaughn, 2019).

Several of the interviews for this study were conducted by telephone. Despite being viewed as a poor substitute of face-to-face interviews, telephone interviews provide a practical and convenient alternative to face-to-face interviews allowing the participant to undertake the interview from the comfort of their homes or a location of their choice (Sturges & Hanrahan, 2004). Many of the HF clinician participants were able to undertake their interviews from their place of work, without the need to travel. Although telephone interviews allow for partial anonymity compared to a face-to-face interview, it prevents the direct observation of emotions or other visual clues during the interview, which is possible during a face-to-face interview (Braun and Clarke, 2014).

2.5 Analysis

2.5.1 Quantitative Components

Data analysis methods for the systematic review and meta-analysis, diagnostic validation study and the web-survey are discussed in Chapters 3, 4 and 7, respectively.

2.5.2 Qualitative Component: Thematic Analysis

Thematic analysis (TA) is a method for identifying, analysing, and reporting patterns (themes) within data."

(Braun and Clarke 2006)

A reflexive approach to TA was selected as the method of data analysis for the qualitative component of the study. Through analysis and synthesis of data from various participants into a meaningful account, TA is considered an appropriate method to gain understanding of individual experiences, views, opinions, or practices and was therefore considered best suited to gain a greater understanding of barriers and enablers associated with the diagnosis and treatment of OSA in CHF from patients' and health care professionals'(HCP) accounts (Boyatzis, 1998; McLeod, 2011). Additionally, it also aids understanding of the relationship between concepts and can identify factors that might influence the area under investigation (Alhojailan, 2012).

TA provides a flexible approach to qualitative data analysis and because it is not tied to a particular epistemological or theoretical perspective, it can be applied within any ontological, epistemological, and theoretical framework that underpin qualitative research (Loyns & Coyle, 2016; Maguire and Delahunt, 2017). TA are broadly classified into three types of approaches, namely coding reliability, reflexive, and codebook. Of the three, a reflexive approach was selected, also known as Big Q qualitative, which focuses on themes that are developed from codes and 'conceptualised as patterns of shared meaning' and functions within a qualitative values framework (Braun & Clarke, 2014).

In contrast, also known as 'small q' qualitative, coding reliability approaches provides a structured approach to coding that is focused on a codebook or coding frame and are underpinned by (post) positivist research values. Due to

requiring multiple coders to overcome researcher subjectivity, this approach was not considered an ideal option for this study. The codebook approach is a blend between the coding reliability approach and the reflexive approach utilising the principles of reflexive TA and the structured approach of the coding reliability approach (Braun & Clarke, 2020)

When compared to other methods of analysis, there are several perceived limitations to TA. It is often felt that TA may lack substance when compared to theoretically driven approaches such at Grounded Theory (GT) and Interpretive Phenomenological Analysis (IPA) and as a result lack interpretative power if it is not used within an existing theoretical framework. In addition, analysis can sometimes only reflect a 'realist description' of issues with the voices of individual participants getting lost in larger data sets (Braun & Clarke, 2014).

Despite these limitations, TA has several advantages. Firstly, TA is an intuitive method of analysis that offers a flexible approach that functions across epistemologies and because it is not rooted in pre-existing theoretical frameworks, it leaves room for flexibility around the underpinning theory (Reismann, 2007). Secondly, TA can capture both overt and underlying meanings from the data (Braun & Clarke, 2014).

Alternative forms of qualitative analysis were considered, including Content Analysis, GT and IPA. Although both GT and IPA similarly search for patterns in the data, these approaches differ from TA on the grounds of being theoretically bounded. IPA is aligned with phenomenological epistemology with a focus on understanding everyday experience of reality whilst GT focuses on generating a plausible theory of the 'phenomena that is grounded in the data' (McLeod, 2001; Holloway & Todres, 2003; Smith & Osborn, 2007).

Qualitative Content analysis (QCA) is similar to TA from an analytic perspective; however, it is considered a theoretical rather than theoretically flexible as with TA. Furthermore, post-positivist assumptions are often applied and QCA is viewed as the least interpretive of the available qualitative methods of analysis (Vaismoradi *et al.*, 2013).

In turn, IPA is underpinned by phenomenology with an emphasis on personal experience in a particular context. In contrast to TA, IPA employs a dual

analytic focus which means that the focus is not only to identify themes across cases, but also a focus on the unique details of individual cases. In addition, due to the depth of the analysis, smaller samples are required limited descriptive analysis and lack of wider social context. For this study, the breadth of analysis that TA offered were preferred rather than the depth of IPA (Braun & Clarke, 2020). Finally, because the goal of this research study was to identify, describe and interpret patterns in the data rather than develop a grounded theory from the data, GT was not selected as the method of analysis.

2.5.3 Rigour and Quality in Mixed Methods Research

Methodological quality relates to how the study is conducted and the concept of trustworthiness. In turn, trustworthiness is generally influenced by the chosen methodology and the potential biases that might exist within a study (Hong & Pluye, 2018).

Given the distinct differences between quantitative and qualitative research methodology, different sets of quality criteria apply to assess rigour in MMR. Whilst validity, reliability, replicability, and generalisability are quality criteria relevant to quantitative research methods, Lincoln and Guba's criteria of credibility, transferability, dependability, and confirmability are commonly applied to qualitative research methods (Bryman, Becker & Sempik, 2008; Lincoln & Guba, 1985).

Taking these differences into account, it is evident that MMR requires further consideration, although consensus is still lacking in this regard (Brown, *et al.*, 2015.). Despite some agreements on the importance of justification for the use in MMR and the importance of integration, consensus about quality in MMR is overall lacking (Bryman, Becker & Sempik, 2008; Onwuegbuzie & Johnson, 2006; O'Cathain, Murphy & Nicholl, 2008). Furthermore, transparency in the description of data collection, analysis, interpretation, and integration of methods to permit a judgement on quality, is required.

A previous validation framework by Leech (2010) suggested a combination of quantitative and qualitative validity criteria to assess MMR validity, and include the concepts of trustworthiness, credibility, and dependability (Onwuegbuzie &

Johnson, 2006). However, this approach presented a challenge to create an integrated definition of quality across disciplines.

A framework by O'Cathain (2008), presents the Good Reporting of a Mixed Methods Study (GRAMMS) guidelines as a useful guide to appraise rigour in MMR**.** The framework considers rigour as a subcomponent of quality and consists of six guidelines summarised in **Table 5**.

Table 5 Good Reporting of a Mixed Methods Study (GRAMMS) checklist

Guideline Criteria
Describe the justification of using a MMR approach to the research question.
Describe the design in terms of purpose, priority, and sequence of methods
Describe each method in terms of sampling, data collection and analysis
Describe where integration has occurred, how it has occurred and who has participated in it.
Describe any limitation of one method associated with the present of the other method.
Describe any insights gained from mixing or integrating methods.

(O'Cathain *et al.* 2008) MMR: mixed methods research

Furthermore, Wisdom (2012) suggests that rigour is affected by both the actions of the researchers and the reporting mechanisms to describe the steps in the scientific process of MMR, therefore the idea is not for rigour to replace quality, but rather to facilitate quality.

The latest in framework development is The Rigorous Mixed Methods Framework which builds on previous work on MMR reporting and is organised into primary and advanced components (Harrison, Reilly & Creswell, 2020). The primary component comprises the core characteristics of MMR, whilst the advanced techniques enhance MMR rigour. The Rigorous Mixed Methods Framework components are summarised in **Table 6**.

Table 6 The Rigorous Mixed Methods Framework Components

Component	Criteria
Primary components	Rigorous description of data collection of quantitative and qualitative data strands.
	Rigorous description of data analysis of quantitative and qualitative data strands.
	Description of mixing or 'integration' of quantitative and qualitative data strands.
	Description of a specific mixed methods design type.
Advanced techniques	Discussion of the aims and purpose for the use of mixed methods and therefore providing a clear rationale for conducting a MMR study through a MMR question and discussing the value of MMR.
	Include elements of the writing that aim to promote the use of mixed methods, including referencing mixed methods literature, utilising joint displays to show integration, and including mixed methods research in the title.

(Harrison *et al.*, 2020) MMR: mixed methods research

2.6 Regulatory Approval

The study protocol was approved by the Health Research Authority (HRA) and the East Midlands-Leicester South Ethics Committee (REC reference: 17/EM/0400) on 15 November 2017 and conducted in full conformity with the current revision of the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice (CPMP/ICH/135/95) July 1996 (**Appendices 1 & 2**). Sponsor Green Light was granted on 09/01/2018 (**Appendix 3**). Additionally, the study was deemed eligible for NIHR Clinical Research Network support and was

assigned to the CV Disease Speciality of the Clinical Research Network Portfolio.

Two substantial amendments to the study protocol was approved by the Health Research Authority and the Ethics Committee (**Appendices 4 & 5**).

2.6.1 Amendment 1/06.03.2018 (version 2)

The following modifications were made to the study protocol:

Survey Study: 1. Time to complete survey was amended. 2. Demographic questions were refined. 3. Additional questions were added to the clinical practice section of the survey.

Diagnostic Validation Study: 1. Letter of invitation for recruitment was added. 2. Additional recruitment department was added. 3. Inclusion criteria were amended. 3. Waist circumference was added to the anthropometric measurements. 4. Sleep history questions and Epworth score were added to the medical history section.

2.6.2 Amendment 2/18.02.2019 (version 3):

The following modifications were made to the study protocol:

Patient Interview Study: The use of telephone interviews was added.

Health Care Professional Interview Study: An interview study of HCPs was added.

2.7 Ethical Considerations

Participants in the study consisted of patients (diagnostic validation and interview study) and HCPs (web survey and interview study).

2.7.1 Diagnostic Validation Study (patients)

2.7.1.1 Risks

Participants were drawn from an older patient group with multiple comorbidities and could be considered vulnerable adults. They were made aware that participation in this research study was entirely voluntary and would not affect their care at the University Hospitals of Leicester NHS Trust. Participants could withdraw their participation from the study at any time.

2.7.1.2 Confidentiality

The participant information sheet outlined details of confidentiality used in the research process. Identifiable patient information was anonymised by use of unique identification numbers. Electronic databases had restricted access, were password protected and contained no personal identifiers.

2.7.1.3 Recruitment

Consecutive patients who attended the Sleep Disorders Service at the Leicester General Hospital for the assessment of suspected OSA were considered for participation in the study. Referrals were screened and assessed for study eligibility by a team of Sleep Medicine Consultants. Prior to the patient's appointment at the sleep laboratory or sleep clinic, a letter of invitation and participant information sheet were sent by post to the patient.

On the day of appointment, it was confirmed that the patient had received the letter of invitation and participant information sheet and that they had read the information. A full explanation of the study was given, and patients had the opportunity to ask questions. Completion of the STOP-Bang Questionnaire and study related activities were undertaken once the informed consent was received.

All participants were offered a minimum of 24 hours to consider the information, and the opportunity to question the Investigator, their general practitioner or other independent parties prior to making the decision to participate in the study.

Written and verbal versions of the participant information and informed consent were presented to all participants detailing no less than:

- the exact nature of the study,
- the implications and constraints of the protocol, and
- the known side effects and any risks involved in taking part.

Participants were free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Written, informed consent was obtained by the investigator prior to participants undertaking any study related activities. Participants personally signed and dated the latest approved version of the informed consent form. The original signed form was retained at the study site within the Trial Master File.

2.7.2 Interview Study (patients)

2.7.2.1 Risks

Risks concerns related primarily to working with a potentially vulnerable patient group. Care was taken to ensure participants were made aware that they could chose to withdraw their participation from the study at any time and could terminate the interview or decline to answer specific questions should they wish to, or if they felt uncomfortable with the subject matter. It was acknowledged that some individuals may be more susceptible to becoming concerned or upset by the interview questions, particularly those that relate to symptom burden and quality of life. Whilst it was not anticipated for any harm to come to those selecting to take part in this study, it is acknowledged that there was a possibility that participants may become upset when describing difficult or anxiety provoking issues.

Where appropriate, indicators of distress were responded to immediately and participants were asked if they want to continue with the interview process by the Chief Investigator. Signposting was offered for suggestions for sources of future or additional support. The researcher's contact details were provided for participants to report any concerns or answer questions that might arise following the interview.

Several prompts were provided for participants to remind them that there was no obligation to answer all the interview questions (both verbally during the interview and in written form in the information sheet given prior to interview).

Participants were made aware that the interviews would be audio recorded and that some verbatim quotes might be used in the research write-up to illustrate themes in the data. It was made clear that quotes used in the final would comply with protecting participant anonymity.

A debriefing period was offered at the end of the interview to provide an opportunity for participants to discuss any issues relating to the personal impact

of the interview. It was anticipated that giving this opportunity will help to manage and minimise the potential levels of distress that could be experienced by participants during the interview process.

2.7.2.2 Confidentiality

The participant information sheet outlined the details of confidentiality used in the research process to ensure participants are informed about the handling of data.

Identifiable patient information was anonymised by use of identification numbers (quantitative research) and pseudonyms (qualitative research).

During the audio recording transcription process, all personal identifiers were anonymised (eg. address, family member names, occupation etc.) and were altered during the transcription process to ensure anonymity. Audio-recorded data remained securely stored at the University of Leicester until after the dissemination of the results along with transcription material. Access to electronic databases was restricted, password protected and contained no personal identifiers.

Participants were given the opportunity to ask questions following the interview and were offered the opportunity to receive a lay summary of the key research findings.

2.7.2.3 Recruitment

Participants who consented to the diagnostic validation study had the option to participate in the patient interview study. Participants indicated on the consent form whether they were willing to be contacted for the interview study, once they have completed their sleep study. Further recruitment details are discussed in **section 6.4.**

2.7.3 Web Survey (health care professionals)

2.7.3.1 Risks

The survey study posed minimal risk to participants. Although there were no known risks associated with completing the survey, there was the potential of data breach with online related activity.

To minimise this risk, survey responses were encrypted to ensure secure data transmission. Following data export, the electronic database had restricted access and was password protected. In addition, passwords were sufficiently complicated and stored securely. User accounts were not shared, and survey data contained no personal identifiers.

The possibility of risk was addressed in the invitation email. All participants had access to a participant information sheet that was embedded in the invitation email. The participant information sheet allowed participants to make an informed judgement about participating in the web-based survey.

2.7.3.2 Confidentiality

The study utilised Jisc Online Surveys (formerly Bristol Online Surveys) to design and distribute the survey. The following measures were put in place to mitigate the risk of online data breach and ensure confidentiality:

Jisc uses an Information Security Management System (ISMS) which includes many of the processes and policies used to operate online surveys, including ISO 27001, a family of standards that help to keep information secure.

All Jisc data is stored within Amazon Web Services (AWS) in the Republic of Ireland and managed in conformance with the requirements of ISO 27001. Therefore, all connections for data transfer between Jisc and AWS are secure and encrypted.

All Jisc staff employment contracts contain a confidentiality clause and are subjected to a “Secure Working Practices Policy”, covering the physical security of information. In addition, all staff are provided with data security training and new staff undertake an induction process where their responsibility towards personal data is reiterated.

Jisc is responsible for maintaining the security of the operating system and application stack. Regular vulnerability and patch management is carried out as part of the vulnerability management processes. AWS Shield and Amazon CloudFront are services used to protect online surveys against DDoS attacks.

Data access within online surveys are strictly limited to online surveys' support and technical teams and access is only permitted at the request of the client, for operational issues or required by law.

An established process is in place for the handling of information security incidents, including data breaches. New users of online surveys choose their own passwords and are required to enter a username and password each time they log in. No cookies are used when survey respondents complete the surveys, although Online surveys issues a cookie to store session information when registered users log in but is not retained once the browser is closed.

To minimise this risk, survey responses are encrypted to ensure secure data transmission. Encrypted SSL (TLS) connections, standard technology for establishing an encrypted link, are used to collect survey responses and for communication within Online surveys, ensuring that sensitive information can be transmitted securely.

Once the data are no longer required, Jisc ensures that all data are securely erased, and any media destroyed. A contract will be in place between Jisc and any third parties, should they be required.

2.7.3.3 Recruitment

The web survey was distributed by email through CV professional societies. The email gave the rationale for the survey and invited HCPs to participate. A reminder email was sent after 2 weeks. The participant information sheet and the survey links were embedded in both emails. Completion and submission of the survey were accepted as implied consent.

2.7.4 Interview Study (health care professionals)

2.7.4.1 Risks

HCPs with an interest and expertise in the management of HF were invited to participate in the Interview Study. Participants were made aware that their decision to take part in this research was entirely voluntary and that they could choose to withdraw their participation from the study at any time, including termination of the interview or declining to answer specific questions should they wish to, or if they felt uncomfortable with the content. Participants were

also be informed that they can terminate the interview at their request at any point during the interview, without needing to state a reason. It was acknowledged that some individuals might be more susceptible to becoming concerned or upset by the interview questions.

Several prompts were provided for participants to remind them that there was no obligation to answer all the interview questions (both verbally during the interview and in written form in the information sheet given prior to interview).

Participants were reminded that the interviews would be audio recorded and that some verbatim quotes might be used in the research write-up to illustrate themes in the data. It was emphasized that quotes used in the final write-up will be anonymised by means of pseudonyms.

A debriefing period was offered at the end of the interview to provide an opportunity for participants to discuss any issues relating to the personal impact of the interview. It was hoped that a debrief would help to mitigate potential levels of distress if experienced by participants during the interview process.

2.7.4.2 Confidentiality

Identifiable participant information was anonymised using pseudonyms. During the audio recording transcription process, all personal identifiers were anonymised and were altered during the transcription process to ensure anonymity. Audio-recorded data were securely stored at the University of Leicester until after the dissemination of the results along with transcription material. All electronic databases had restricted access, were password protected and contained no personal identifiers. To ensure that participants were informed about the handling of data, details of confidentiality utilised in the research process were outlined in the participant information sheet. Participants were given the chance to ask questions following the interview and offered the opportunity to receive a lay summary of the key research findings.

2.7.4.3 Recruitment

All participants provided written consent to participate in the study.

2.8 Conduct of Research Components

2.8.1 Systematic Review and Meta-analysis

- Statistical support was provided for the following aspects:
    - Review of the protocol and methods for meta-analysis.
    - Guidance on the utilisation of the MetaDTA programme for conducting the meta-analysis.
    - Guidance on the development of the data collection tool in line with MetaDTA.
    - Meta-regression analysis conducted by statistician.
    - Review of the manuscript and refinement of the methods section of the manuscript.
- Research aspects conducted by researcher:
    - Development of protocol (supported by second reviewer and primary supervisor).
    - Searches, quality appraisal and data extraction (in conjunction with second reviewer and collaborators).
    - Meta-analysis and sensitivity analyses
    - Update of the systematic review and meta-analysis (in conjunction with second reviewer).
    - Draft of manuscript for publication and abstract for presentation.

2.8.2 Diagnostic Validation Study

- Statistical support was provided for the following aspects:
    - Sample size calculations
    - Review of results and confidence intervals that were calculated by researcher.
- Research aspects conducted by researcher:
    - All data collection and data analysis

2.8.3 Qualitative Studies

- Research aspects conducted by researcher:
    - Development of interview guides in conjunction with second supervisor.

- Conduct of interviews for both patients and clinicians
- Transcription of interviews (Armstrong Transcription Services)
- Coding and thematic analysis of interview data (reviewed by second supervisor)

2.8.4 Web survey

- Research aspects conducted by researcher:
  - Development of survey questionnaire and uploading to survey platform
  - All data collection
  - All data analysis
  - Drafting of manuscript for publication and abstract for presentation

2.9 Conclusion

The aims of this chapter were to describe the design of this study, the rationale for the sampling strategy, data collection and data analysis methods utilised and the relevant regulatory approvals and ethical considerations relevant to this study. A convergent parallel MMR design was utilised to achieve the study objectives and was described with reference to the purpose, theoretical drive, timing and dependence and design typology.

Non-probability sampling was used for both quantitative and qualitative components of the study. The rationale for selecting consecutive and convenience sampling for the quantitative components and purposive sampling for the qualitative components of the study, were discussed.

From a data collection perspective, a web survey design for quantitative data collection and semi-structured interviews for the collection of qualitative data were utilised and the rationale, strengths, and limitations of the selected methods were discussed.

Data analysis methods for the quantitative component of the study will be discussed in Chapters 3, 4 and 6 of the thesis. The rationale for utilising reflexive thematic analysis as the qualitative method of data analysis, was discussed.

Finally, the regulatory approvals, subsequent amendments to the study protocol and the ethical considerations in terms of risk, confidentiality, and recruitment of both groups of study participants were discussed.

Chapter 3 of this thesis will report the findings of the systematic review and meta-analysis of the diagnostic accuracy of existing screening questionnaires for OSA in adults in different clinical cohorts.

3

Diagnostic Accuracy of Screening Questionnaires for Obstructive Sleep Apnoea in Adults in different Clinical Cohorts: A Systematic Review and Meta-analysis

3.1 Introduction

To support risk stratification, a simple and reliable screening tool may help triage patients at risk of OSA, for consideration of referral to specialist services for appropriate management (Abrishami, Khajehdehi & Chung, 2010; Costa *et al.*, 2015). Clinical prediction formulae have been developed but are limited by complexity and the requirement for a computer or mathematical calculations (Rowley, Aboussouan & Badr, 2000). In contrast, OSA screening questionnaires are less complicated and may be a viable alternative to clinical prediction formulae in specific settings.

To date, there have been four systematic reviews exploring the accuracy of OSA screening tools in adults (Abrishami, Khajehdehi & Chung, 2010; Ross *et al.*, 2000; Ramachandran & Josephs, 2009; Chiu *et al.*, 2017). One of the first systematic reviews and meta-analyses to explore the accuracy of screening tools for OSA identified four screening questionnaires; however, due to heterogeneity pertaining to the questionnaire, OSA definition and threshold, meta-analysis was not performed (Ross *et al.*, 2000). Ramachandran and Josephs (2009) reported that clinical prediction models performed better than the eight questionnaires studied to predict OSA in pre-operative cohorts. Abrishami, Khajehdehi and Chung (2010) focused on a 'sleep disorder' cohort

and a cohort 'without a history of sleep disorders. It was concluded that questionnaires were useful for early detection of OSA, especially in the surgical population. Despite finding it difficult to draw a definite conclusion about questionnaire accuracy, the STOP and STOP-Bang questionnaires were recommended for screening in a surgical population (Abrishami, Khajehdehi & Chung, 2010). Recently, Chiu *et al.* (2017) compared the diagnostic accuracy of the Berlin, STOP-Bang, STOP and ESS. In-line with Abrishami, Khajehdehi and Chung (2010), they reported the STOP-Bang questionnaire to have the highest sensitivity in both the sleep clinic and surgical populations.

Since the publication of previous systematic reviews, new OSA screening questionnaires have emerged, further validation studies conducted, and different clinical settings and patient cohorts considered. As test performance often varies across clinical cohorts, it is recommended that tools are evaluated in clinically relevant cohorts (Mulherin & Miller, 2002).

3.2 Aim

The aim of this chapter is to describe the systematic review and meta-analysis that evaluated and compared the accuracy and clinical utility of existing screening questionnaires for the identification of OSA in different clinical cohorts.

3.3 Methods

The protocol was registered at the International Prospective Register of Systematic Reviews (PROSPERO) (CRD42018104018) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Page *et al.*, 2020).

The review protocol was amended to include the following changes:

1. Addition of the Brazil team,
2. Addition of LILACS database,
3. Addition of Spanish and Portuguese languages to accommodate the search of the LILACS database, and

4. It was not possible to calculate pooled positive predictive values (PPV) and negative predictive values (NPV) due to variation in disease prevalence across studies and high heterogeneity amongst PPV and NPV.

3.3.1 Types of studies

Observational studies that met the following eligibility criteria were included:

Inclusion criteria:

1. Prospective studies measuring the diagnostic value of screening questionnaires for OSA,
2. Studies in adults (>18 years of age),
3. Studies in which the accuracy of the questionnaire was validated by level one or two PSG,
4. OSA was defined as AHI or Respiratory Disturbance Index (RDI) ≥5,
5. Data allowed for construction of 2 x 2 contingency tables, and
6. Publication in English, Spanish or Portuguese.

Exclusion criteria:

1. Studies measuring the diagnostic value of clinical scales, scores, and prediction equations as screening tools for OSA.
2. Conference proceedings, reviews, or case reports.
3. Insufficient data for analysis after several attempts to contact the author.
4. Studies in children (<18yrs of age).
5. Levels three and four portable studies were used as the reference standard.
6. Studies conducted in in-patient settings.
7. Publication language is other than English, Spanish, or Portuguese.

3.3.2 Index test

The test under evaluation was only OSA screening questionnaires (self-reported or clinician completed).

3.3.3 Target conditions

The target condition was OSA, defined as AHI or RDI:

AHI/RDI ≥5 – diagnostic cut-off for OSA

AHI/RDI ≥15 – diagnostic cut-off for moderate to severe OSA

AHI/RDI ≥ 30 – diagnostic cut-off for severe OSA

3.3.4 Reference standard

The reference standard was a level one (attended cardiorespiratory PSG with at least 7 channels) or two (unattended cardiorespiratory PSG at home with at least 7 channels) PSG.

3.3.5 Search methods for identification of studies

Comprehensive literature searches in CINAHL PLUS, Scopus, PubMed, Web of Science and the Latin American and Caribbean Health Sciences Literature (LILACS) database were conducted from inception to 18 December 2020. Detailed individual search strategies, with appropriate truncation and word combinations, were developed for each database (**Table 7**). Additional records were identified from grey literature sources comprising ETHos, OpenGrey, Google Scholar, ProQuest, and New York Grey Literature Report. The reference lists from the final articles for analysis and related review articles were manually searched for references that could have been omitted during the electronic database searches.

Table 7 Database Search Strategies

CINAHL Plus, Scopus Web of Sciences, PubMed	LILACS
(“obstructive sleep apnea” OR “obstructive sleep apnoea” OR “OSA” OR “sleep disordered breathing” OR “sleep-disordered breathing” OR “SDB” OR “sleep related respiratory disorder” OR “OSAHS” OR “obstructive sleep apnea hypopnea syndrome” OR “obstructive sleep apnoea hypopnoea syndrome”) **AND** (“question*” OR “screen*” OR “survey*” OR “score” OR “risk” OR “tool”) **AND** (“polysomnography” OR “polysomnographies” OR “PSG”) **AND** (“accuracy” OR “validity” OR “sensitivity” OR “specificity” OR “accuracies” OR “PPV” OR “positive predictive value*” OR “NPV” OR “negative predictive value*” OR “validity and reliability” OR “utility”)	("polysomnography" **or** "polisomnografía" **or** "polissonografia") **AND** ("sleep apnea syndromes" **or** "síndromes de la apnea del sueño" **or** "síndromes da apneia do sono" **or** "apnea" **or** "apnea" **or** "apneia") **AND** ("Surveys and Questionnaires" **or** "Encuestas y Cuestionarios" **or** "Inquéritos e Questionários")

3.3.6 Data collection and analysis

3.3.6.1 Study selection

Two reviewers (LB, EB) screened the titles and abstracts of the electronic search results independently to identify studies eligible for inclusion in the review. Records classified as “excluded” by both reviewers were excluded. The full text of any study about which there was disagreement or uncertainty was assessed independently against the selection criteria and resolved through discussion and consultation with a third reviewer (IS or NR). Duplicates were identified and excluded before recording the selection process in sufficient detail to complete the PRISMA flow diagram and tables describing the characteristics of the excluded studies (Page *et al.,* 2020) **(Appendix 6**).

3.3.6.2 Data extraction and management

Two reviewers (LB, EB) independently conducted data extraction on all studies included and extracted the data required to reconstruct the 2x2 contingency tables, including true positive (TP), false positive (FP), true negative (TN) and false negative (FN) values. A data collection form tailored to the research question and fulfilling the data entry requirements of MetaDTA (Diagnostic Test Accuracy Meta-Analysis v1.43) was utilised (Freeman *et al.,* 2019).

HP and JR extracted the study characteristics, and demographic data for all included studies and LB and EB entered the data into Review Manager 5.3.

No studies with inconclusive results were identified.

3.3.6.3 Assessment of methodological quality

The quality of studies included was appraised independently by the reviewers (LB, EB) utilising the Quality Assessment for Diagnostic Accuracy Studies tool (QUADAS-2). The four main areas of the QUADAS-2 tool, including patient selection, index test, reference standard and flow and timing domains, were categorised as low, high, or unclear risk of bias. Disagreements were resolved through consultation with a third reviewer (IS or NR) (Whiting *et al.*, 2011).

3.3.6.4 Statistical Analysis and Data Synthesis

Statistical analysis was performed according to Chapter 10 of the *Cochrane Handbook for Systematic Review of Diagnostic Test Accuracy* (Macaskill *et al.,* 2010).

Questionnaire screening was considered positive for OSA if the questionnaire score was above the defined threshold specified in the primary study and negative if the questionnaire score was below the defined threshold. The TP, FP, TN, and FN results were produced by cross classifying the questionnaire results with those of the PSG results. These were based on the ability of screening questionnaires to classify and detect OSA correctly.

The sensitivity and specificity of individual studies were calculated using 2x2 contingency tables and presented as forest plots. The meta-analysis was conducted using MetaDTA version 1.43, which models sensitivity and specificity by fitting the random effects bivariate binomial model of Chu and Cole (Reitsma *et al.,* 2005; Chu & Cole, 2006). The summary receiver operating characteristic (SROC) plot was drawn using the hierarchical SROC parameters, which are estimated from the bivariate model parameters using the equivalence equations of Harbord *et al.* (2007). Following guidance from the *Cochrane Handbook for Systematic Review of Diagnostic Test Accuracy* (Macaskill *et al.,* 2010) the positive and negative predictive values were not pooled due to the prevalence of OSA varying across studies.

As per the Cochrane DTA handbook, heterogeneity was investigated by plotting the observed study results and SROC curve in the ROC space alongside the 95% confidence region (Macaskill *et al.,* 2010).

A meta-regression was conducted to investigate differences in sensitivity and specificity among questionnaires, including the type of questionnaire as a covariate. Meta-regression was conducted in R version 4.0.1 using the lme4 package (Bates *et al.,* 2015).

To assess the robustness of the meta-analysis, sensitivity analyses were conducted by excluding studies based on their QUADAS-2 assessment score

(Whiting et al., 2011). Those identified as high risk in any QUADAS-2 domain or as unclear in four domains were excluded.

Different AASM scoring criteria and desaturation (and arousal) thresholds were applied to the included studies. Therefore, additional sensitivity analyses were conducted by analysing studies that applied the ≥3% desaturation scoring criteria together and those that applied the ≥4% desaturation scoring criteria.

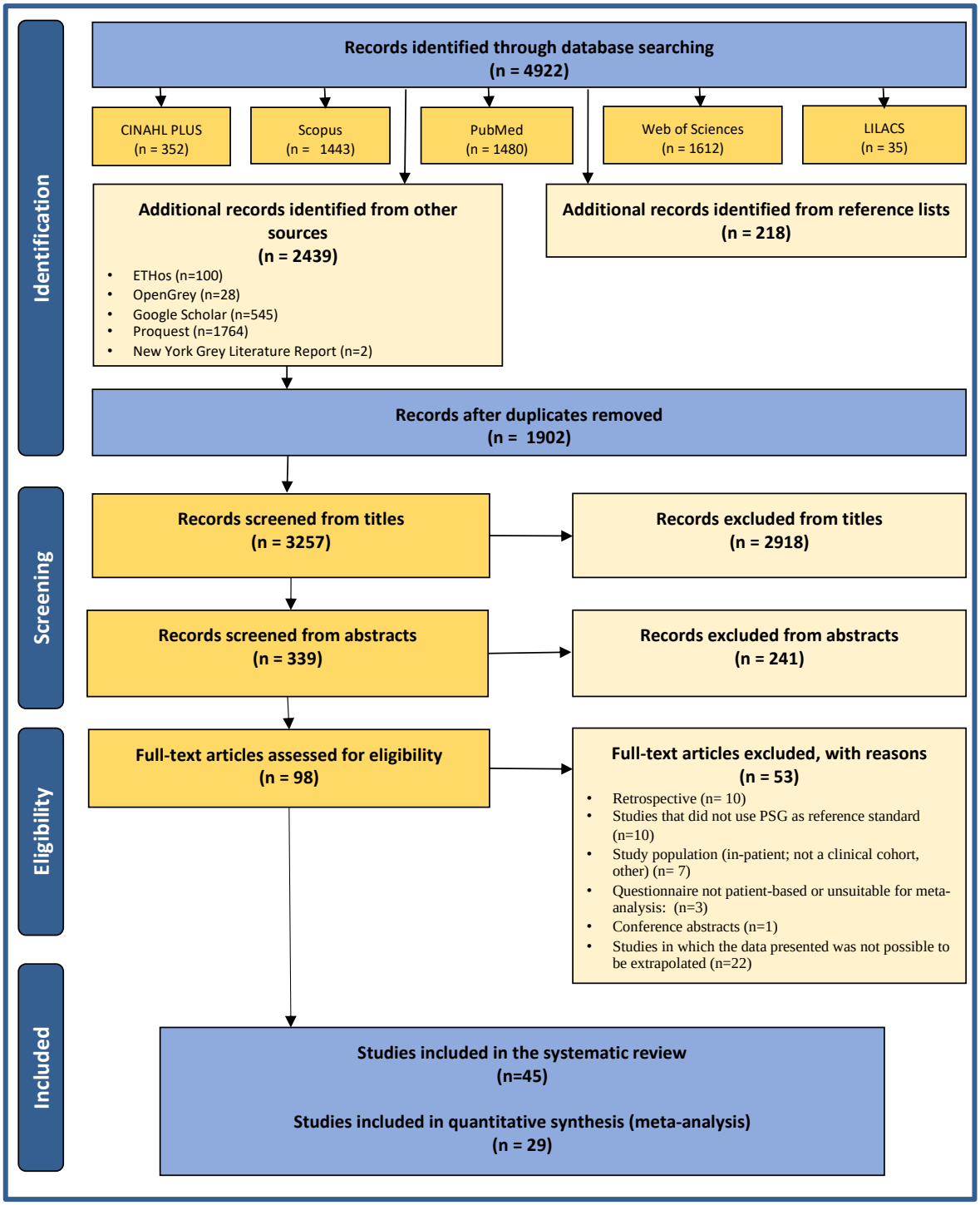
Neither reporting bias nor publication bias were assessed due to the uncertainty about the determinants of publication bias for diagnostic accuracy studies, and the inadequacy of tests for detecting funnel plot asymmetry (Deeks, Macaskill & Irwig, 2005).

3.4 Results

3.4.1 Results of the search

Search results are summarised in **Figure 8.**

Of 45 studies, 29 were included for meta-analysis in the sleep clinic population (n=10 951), 7 were included for meta-analysis in the surgical population (n=2275), and 2 were included in the resistant hypertension population (n=541). The remaining 7 studies were excluded from the meta-analysis due to heterogeneity of included populations. Study characteristics and demographic data were summarised for all included studies **(Appendices 7 and 8)**. Overall, 10 clinical settings were identified, of which the sleep clinic, surgical, and resistant hypertension cohorts had sufficient studies for inclusion in the meta-analysis.



PSG: polysomnography

Figure 8 Flow Chart

3.4.2 Methodological quality of included studies

Results of the QUADAS-2 assessment are summarised in **Figure 9 and Appendix 9).**

In the patient selection domain, 3 studies were rated as high risk of bias due to the case-control study design. For both the index test and reference standard domains, 18 studies were rated as unclear risk of bias due to inadequate information related to blinding; it was unclear if the index test and reference standard findings were interpreted without the knowledge of the other. Thirty-four studies were rated as unclear risk of bias in the flow and timing domain due to lack of reporting on the time interval between the index test and the reference standard. Applicability was rated as low risk in all 45 studies.

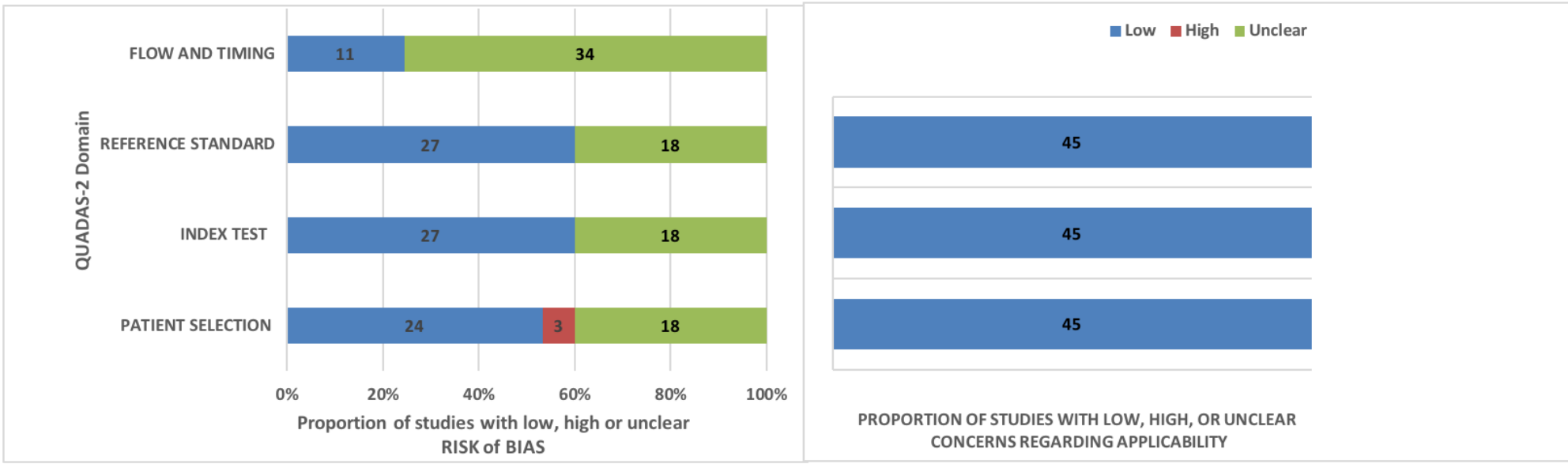
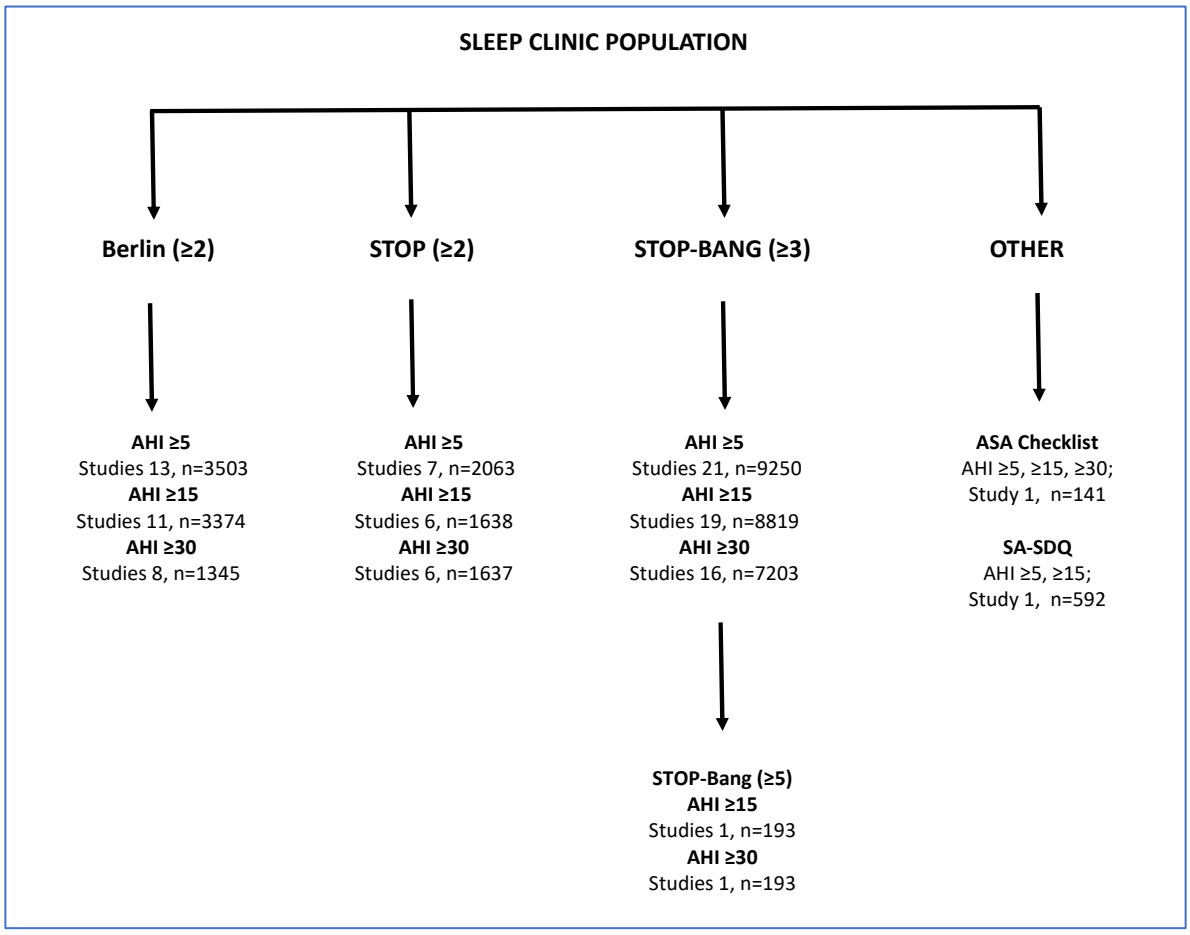


Figure 9 Risk of Bias Summary using the QUADAS-2 Tool

3.4.3 Findings

3.4.3.1 Sleep Clinic Population

In the sleep clinic population (N=10 951) (**Figure 10**), the Berlin (score cut-off ≥2) (Netzer *et al.,* 1999), STOP (score cut-off ≥2) and STOP-Bang (score cut-off ≥3)(Chung *et al.,* 2013) questionnaires were included in the meta-analysis. The American Society of Anaesthesiology (ASA) checklist, Sleep Apnea Scale for the Sleep Disorders Questionnaire (SA-SDQ) and STOP-Bang (cut-off ≥5) questionnaires were excluded due to insufficient studies.

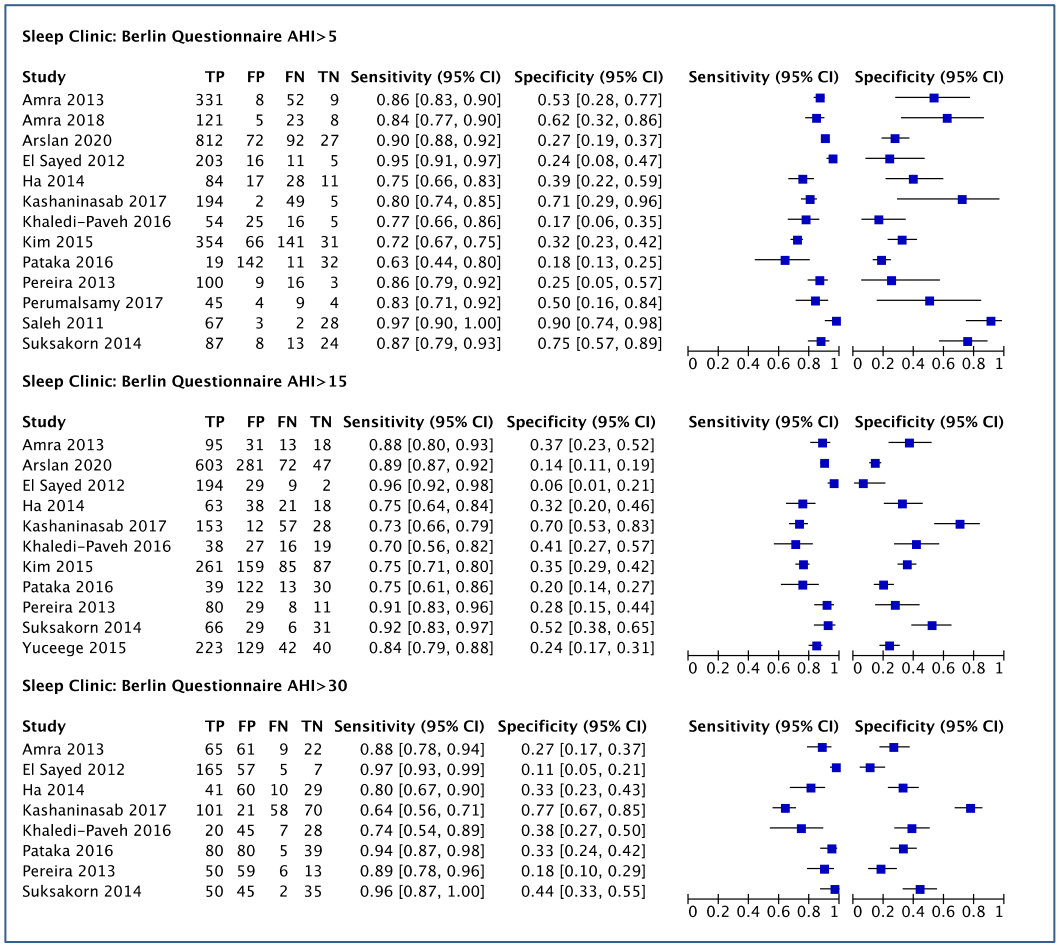


AHI: apnoea hypopnoea index; ASA: American Society of Anesthesiology; SA-SDQ: Sleep Apnea Scale for Sleep Disorders Questionnaire

Figure 10 Questionnaire Validation Studies in Sleep Clinic Population

3.4.3.1.1 Predictive parameters of the Berlin Questionnaire (score cut-off ≥2)

The prevalence of AHI ≥5 (All OSA), AHI ≥15 (moderate to severe) and AHI ≥30 (severe) OSA was 84%, 64% and 50% respectively. The pooled sensitivity of the Berlin questionnaire to predict all OSA, moderate-severe and severe OSA was 85% (95% confidence interval (CI): 79%, 89%), 84% (95% CI: 79%, 89%) and 89% (95% CI: 80%, 94%) respectively. Pooled sensitivity remained consistent across OSA severity. Pooled specificity was 43% (95% CI: 30%, 58%), 30% (95% CI: 20%, 41%) and 33% (95% CI: 21%, 46%) respectively. The corresponding diagnostic odds ratio (DOR) were 4.3 (95% CI: 0.7,7.8), 2.3 (95% CI: 1.3, 3.3) and 3.9 (95% CI: 2.1, 5.7) **(Figure 11 and Table 8)**.

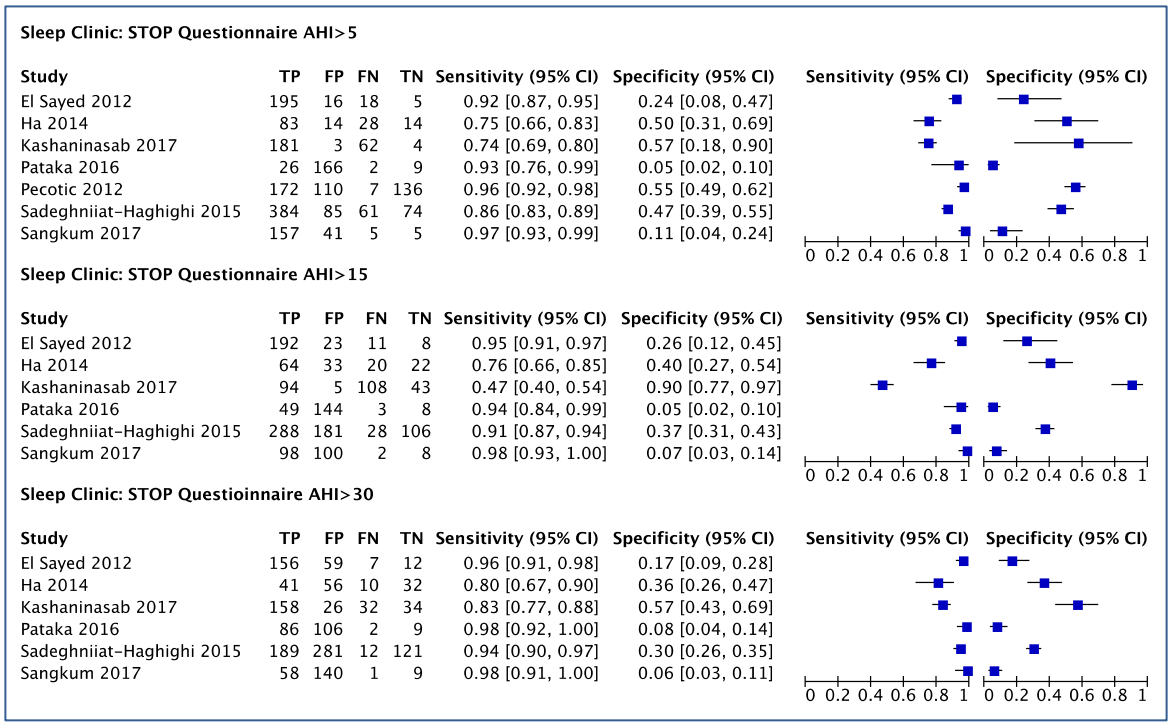


AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

Figure 11 Forest Plots for Berlin Questionnaire in Sleep Clinic Population

3.4.3.1.2 Predictive parameters of the STOP Questionnaire (score cut-off ≥2)

The prevalence of AHI ≥5 (All OSA), AHI ≥15 (moderate to severe) and AHI ≥30 (severe) OSA was 67%, 58% and 46% respectively. The pooled sensitivity of the STOP questionnaire to predict all OSA, moderate-severe and severe OSA was 90% (95% CI: 82%, 95%), 90% (95% CI: 75%, 97%) and 95% (95% CI: 88%, 98%) respectively. The pooled specificity was 31% (95% CI: 15%, 53%), 29% (95% CI: 10%, 61%) and 21% (95% CI: 10%, 39%) respectively. The corresponding DOR were 4.2 (95% CI: 0.8, 7.6), 3.8 (95% CI: 1.7, 5.9) and 4.7 (95% CI: 2.6, 6.8) respectively (**Figure 12 and Table 8**). Greater uncertainty and variability in specificity was noted in the CI width and scatter of individual study estimates.



AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

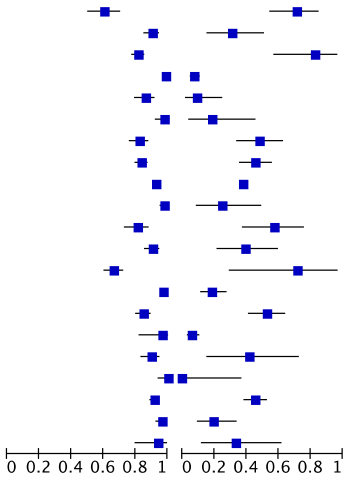
Figure 12 Forest Plots for STOP Questionnaire in Sleep Clinic Population

3.4.3.1.3 Predictive parameters of the STOP-Bang Questionnaire (score cut-off ≥3)

The prevalence of AHI ≥5 (All OSA), AHI ≥15 (moderate to severe) and AHI ≥30 (severe) OSA was 80%, 59% and 39%, respectively. The pooled sensitivity of the STOP-Bang questionnaire to predict all OSA, moderate-severe and severe OSA was 92% (95% CI: 87%, 95%), 95% (95% CI: 92%, 96%) and 96% (95% CI: 93%, 98%) respectively. The pooled specificity was 35% (95% CI: 25%, 46%), 27% (95% CI: 18%, 34%) and 28% (95% CI: 20%, 38%) respectively. The corresponding DOR were 6.0 (95% CI: 4.4, 7.6), 6.4 (95% CI: 3.3, 9.5) and 9.2 (95% CI: 5.9, 12.4) respectively **(Figure 13 and Table 8)**. Greater uncertainty and variability in specificity was noted in the CI width and scatter of individual trial estimates, particularly for AHI ≥5.

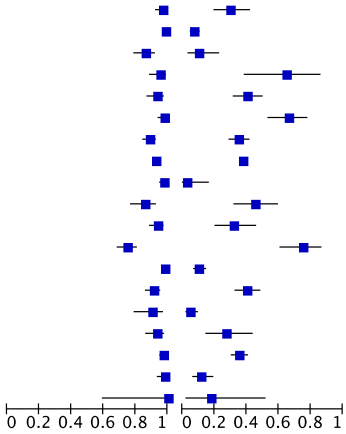
Sleep Clinic: STOP-Bang Questionnaire AHI>5

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Abdullah 2017	58	11	38	27	0.60 [0.50, 0.70]	0.71 [0.54, 0.85]
Alhouqani 2015	148	20	16	9	0.90 [0.85, 0.94]	0.31 [0.15, 0.51]
Amra 2018	312	3	71	14	0.81 [0.77, 0.85]	0.82 [0.57, 0.96]
Arslan 2020	665	303	10	25	0.99 [0.97, 0.99]	0.08 [0.05, 0.11]
Avincsal 2017	111	29	18	3	0.86 [0.79, 0.92]	0.09 [0.02, 0.25]
BaHammam 2015	82	13	2	3	0.98 [0.92, 1.00]	0.19 [0.04, 0.46]
Boynton 2013	139	26	30	24	0.82 [0.76, 0.88]	0.48 [0.34, 0.63]
Duarte 2017	298	54	59	45	0.83 [0.79, 0.87]	0.45 [0.35, 0.56]
Duarte 2020	1902	963	154	587	0.93 [0.91, 0.94]	0.38 [0.35, 0.40]
El Sayed 2012	209	15	5	5	0.98 [0.95, 0.99]	0.25 [0.09, 0.49]
Ha 2014	90	12	21	16	0.81 [0.73, 0.88]	0.57 [0.37, 0.76]
Hu 2019	152	17	16	11	0.90 [0.85, 0.94]	0.39 [0.22, 0.59]
Kashaninasab 2017	161	2	82	5	0.66 [0.60, 0.72]	0.71 [0.29, 0.96]
Kim 2015	480	79	15	18	0.97 [0.95, 0.98]	0.19 [0.11, 0.28]
Ong 2010	200	37	36	41	0.85 [0.80, 0.89]	0.53 [0.41, 0.64]
Pataka 2016	27	165	1	11	0.96 [0.82, 1.00]	0.06 [0.03, 0.11]
Pereira 2013	105	7	12	5	0.90 [0.83, 0.95]	0.42 [0.15, 0.72]
Perumalsamy 2017	54	8	0	0	1.00 [0.93, 1.00]	0.00 [0.00, 0.37]
Sadeghniiat-Haghighi 2015	376	105	35	87	0.91 [0.88, 0.94]	0.45 [0.38, 0.53]
Sangkum 2017	156	37	6	9	0.96 [0.92, 0.99]	0.20 [0.09, 0.34]
Vana 2013	30	10	2	5	0.94 [0.79, 0.99]	0.33 [0.12, 0.62]



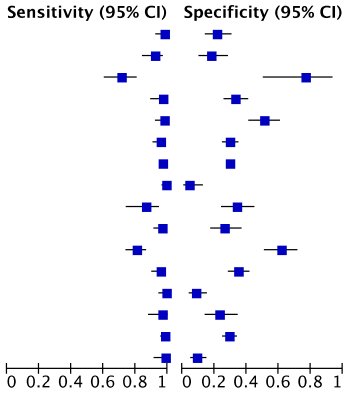
Sleep Clinic: STOP-Bang Questionnaire AHI>15

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alhouqani 2015	119	49	4	21	0.97 [0.92, 0.99]	0.30 [0.20, 0.42]
Arslan 2020	665	303	10	25	0.99 [0.97, 0.99]	0.08 [0.05, 0.11]
Avincsal 2017	99	42	16	5	0.86 [0.78, 0.92]	0.11 [0.04, 0.23]
BaHammam 2015	79	6	4	11	0.95 [0.88, 0.99]	0.65 [0.38, 0.86]
Boynton 2013	96	69	7	47	0.93 [0.86, 0.97]	0.41 [0.32, 0.50]
Delgado Vargas 2020	128	21	3	41	0.98 [0.93, 1.00]	0.66 [0.53, 0.78]
Duarte 2017	211	142	27	77	0.89 [0.84, 0.92]	0.35 [0.29, 0.42]
Duarte 2020	1902	963	154	587	0.93 [0.91, 0.94]	0.38 [0.35, 0.40]
El Sayed 2012	198	30	5	1	0.98 [0.94, 0.99]	0.03 [0.00, 0.17]
Ha 2014	72	30	12	25	0.86 [0.76, 0.92]	0.45 [0.32, 0.59]
Hu 2019	131	38	9	18	0.94 [0.88, 0.97]	0.32 [0.20, 0.46]
Kashaninasab 2017	151	12	51	36	0.75 [0.68, 0.81]	0.75 [0.60, 0.86]
Kim 2015	339	220	7	26	0.98 [0.96, 0.99]	0.11 [0.07, 0.15]
Ong 2010	144	93	14	63	0.91 [0.86, 0.95]	0.40 [0.33, 0.49]
Pataka 2016	46	145	5	8	0.90 [0.79, 0.97]	0.05 [0.02, 0.10]
Pereira 2013	82	29	6	11	0.93 [0.86, 0.97]	0.28 [0.15, 0.44]
Sadeghniiat-Haghighi 2015	274	207	8	114	0.97 [0.94, 0.99]	0.36 [0.30, 0.41]
Sangkum 2017	97	96	2	13	0.98 [0.93, 1.00]	0.12 [0.07, 0.20]
Vana 2013	7	9	0	2	1.00 [0.59, 1.00]	0.18 [0.02, 0.52]



Sleep Clinic: STOP-Bang Questionnaire AHI>30

Study	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)
Alhouqani 2015	85	83	2	23	0.98 [0.92, 1.00]	0.22 [0.14, 0.31]
Avincsal 2017	78	63	7	14	0.92 [0.84, 0.97]	0.18 [0.10, 0.29]
BaHammam 2015	59	4	24	13	0.71 [0.60, 0.81]	0.76 [0.50, 0.93]
Boynton 2013	60	105	2	52	0.97 [0.89, 1.00]	0.33 [0.26, 0.41]
Delgado Vargas 2020	83	53	2	55	0.98 [0.92, 1.00]	0.51 [0.41, 0.61]
Duarte 2017	124	229	6	97	0.95 [0.90, 0.98]	0.30 [0.25, 0.35]
Duarte 2020	1247	1627	44	688	0.97 [0.95, 0.98]	0.30 [0.28, 0.32]
El Sayed 2012	167	61	2	3	0.99 [0.96, 1.00]	0.05 [0.01, 0.13]
Ha 2014	44	58	7	30	0.86 [0.74, 0.94]	0.34 [0.24, 0.45]
Hu 2019	105	64	4	23	0.96 [0.91, 0.99]	0.26 [0.18, 0.37]
Khaledi-Paveh 2016	128	35	31	56	0.81 [0.73, 0.86]	0.62 [0.51, 0.72]
Ong 2010	103	134	5	72	0.95 [0.90, 0.98]	0.35 [0.28, 0.42]
Pataka 2016	88	104	1	10	0.99 [0.94, 1.00]	0.09 [0.04, 0.16]
Pereira 2013	53	56	2	17	0.96 [0.87, 1.00]	0.23 [0.14, 0.35]
Sadeghniiat-Haghighi 2015	201	281	4	117	0.98 [0.95, 0.99]	0.29 [0.25, 0.34]
Sangkum 2017	58	135	1	14	0.98 [0.91, 1.00]	0.09 [0.05, 0.15]



AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

Figure 13 Forest Plots for STOP-Bang Questionnaire in Sleep Clinic Population

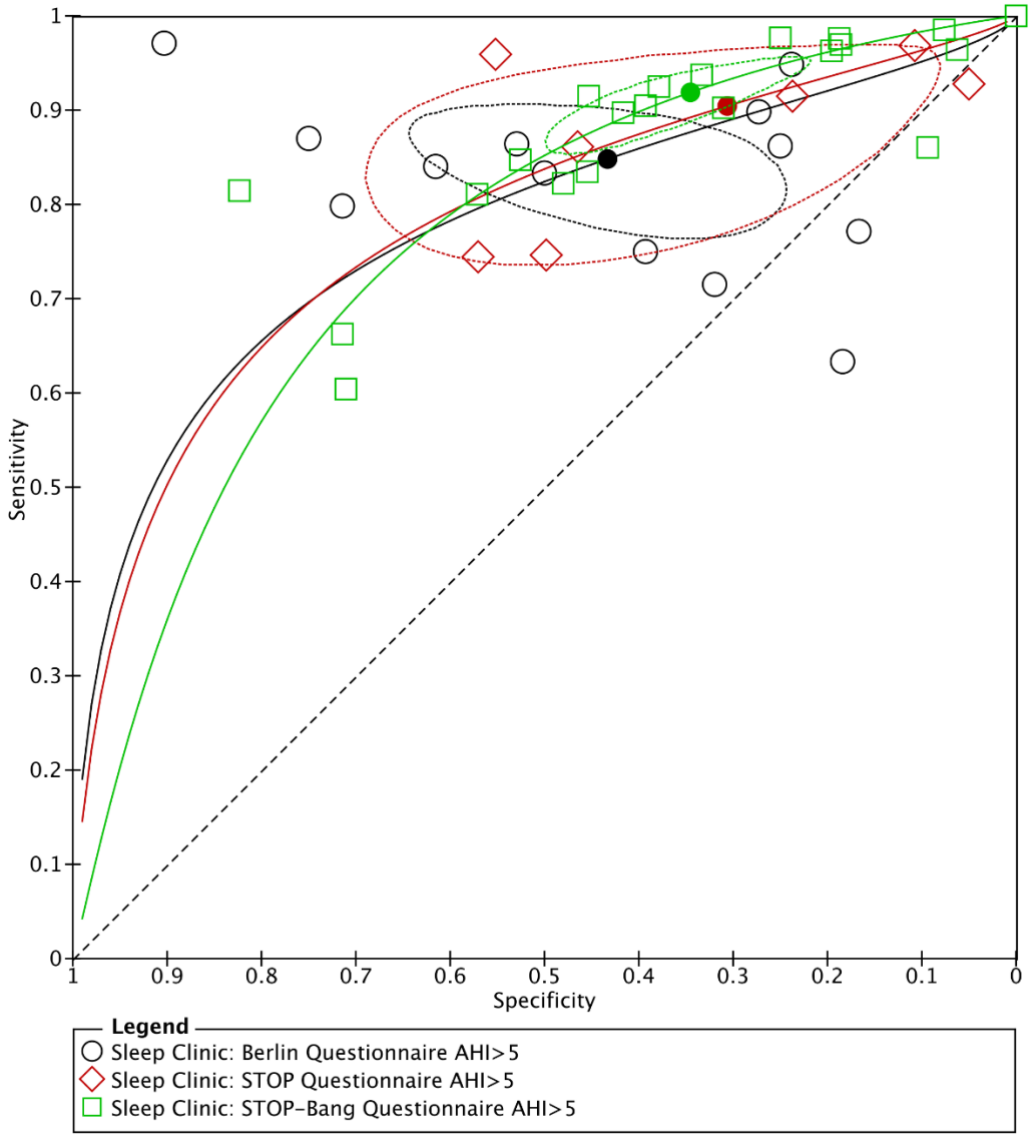
Table 8 Summary statistics for Berlin, STOP and STOP-Bang Questionnaire (Sleep Clinic)

Predictive Parameters	Berlin AHI≥5	STOP AHI≥5	STOPB AHI≥5	Berlin AHI≥15	STOP AHI≥15	STOPB AHI≥15	Berlin AHI≥30	STOP AHI≥30	STOPB AHI≥30
	13 Studies; n= 3503	7 Studies; n=2063	21 Studies; n=9250	11 Studies; n=3374	6 Studies; n=1638	19 Studies; n=8819	8 Studies; n=1345	6 Studies; n=1637	16 Studies; n=7203
Prevalence (% and range)	83.8 (14.71-97.2)	66.94 (13.79-97.20)	79.98 (13.73-97.20)	64 (25.49-86.72)	58.42 (25.49-86.75)	58.78 (25.00-86.75)	50.11 (27.0-72.65)	45.94 (28.37-76.00)	39.25 (28.31-83.0)
Sensitivity (95% CI)	0.848 (0.79,0.891)	0.904 (0.824,0.95)	0.919 (0.874,0.949)	0.843 (0.785,0.887)	0.903 (0.754,0.966)	0.945 (0.920,0.963)	0.886 (0.804,0.936)	0.945 (0.883,0.975)	0.959 (0.930,0.976)
Specificity (95% CI)	0.433 (0.296,0.582)	0.306 (0.148,0.528)	0.345 (0.248,0.457)	0.298 (0.204,0.413)	0.29 (0.098,0.606)	0.271 (0.181,0.384)	0.334 (0.211,0.458)	0.214 (0.104,0.391)	0.282 (0.199,0.384)
False Positive Rate	0.567 (0.418,0.704)	0.694 (0.472,0.852)	0.655 (0.543,0.752)	0.702 (0.587,0.796)	0.71 (0.394,0.902)	0.729 (0.616,0.819)	0.666 (0.515,0.789)	0.786 (0.609,0.896)	0.718 (0.616,0.801)
Log LR +ve (95% CI)	1.497 (1.066,1.927)	1.304 (0.970,1.637)	1. 403 (1.232,1.598)	1.201 (1.049,1.353)	1.273 (0.904,1.642)	1.296 (1.125,1.466)	1.330 (0.110,1.550)	1.203 (1.027,1.279)	1.336 (1.184,1.488)
Log LR -ve (95% CI)	0.350 (0.155,0.546)	0.312 (0.118-0.506)	0.235 (0.183,0.301)	0.527 (0.361,0.693)	0.333 (0.194,0.472)	0.203 (0.123,0.466)	0.343 (0.210,0.475)	0.256 (0.154,0.357)	0.146 (0.095,0.196)

Predictive Parameters	Berlin AHI≥5	STOP AHI≥5	STOPB AHI≥5	Berlin AHI≥15	STOP AHI≥15	STOPB AHI≥15	Berlin AHI≥30	STOP AHI≥30	STOPB AHI≥30
	13 Studies; n= 3503	**7 Studies; n=2063**	**21 Studies; n=9250**	**11 Studies; n=3374**	**6 Studies; n=1638**	**19 Studies; n=8819**	**8 Studies; n=1345**	**6 Studies; n=1637**	**16 Studies; n=7203**
DOR (95% CI)	4.270 (0.718,7.822)	4.174 (0.767,7.581)	5.969 (4.410,7.529)	2.279 (1.309,3.249)	3.825 (1.7,5.949)	6.383 (3.255,9.511)	3.882 (2.06,5.704)	4.704 (2.615,6.794)	9.168 (5.932,12.405)

AHI: apnoea hypopnoea index; STOPB: STOP-Bang; CI: confidence interval; DOR: diagnostic odds ratio LR: likelihood ratio; +: positive; -: negative

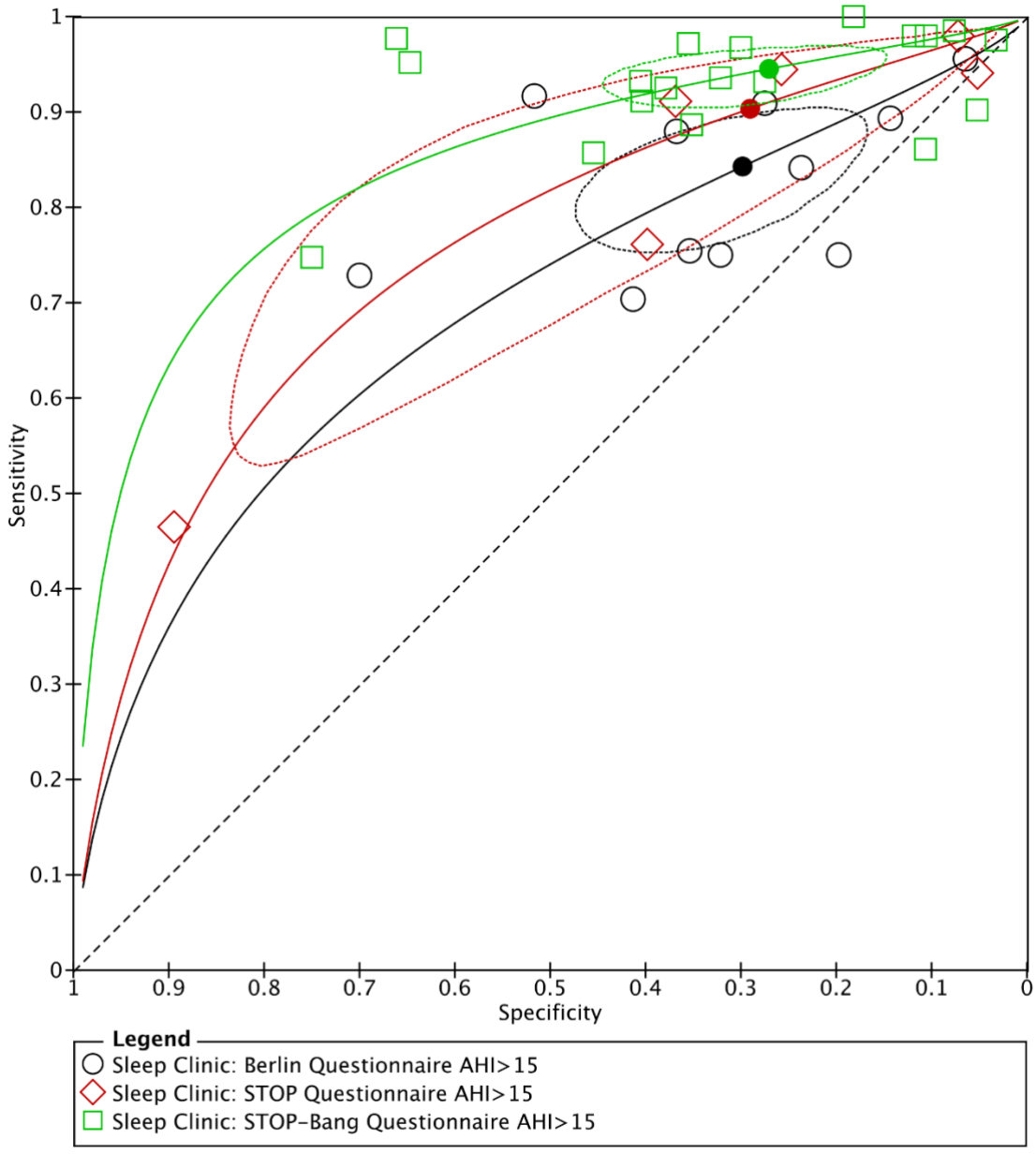
SROC plots were used to display the results of individual questionnaires in the ROC space, plotting each questionnaire as a single sensitivity-specificity point (Macaskill *et al.,* 2010). When the SROC were plotted for all three questionnaires on the same axes, the confidence regions of the Berlin, STOP and STOP-Bang questionnaires, for all OSA (AHI ≥5) (**Figure 14**) and severe OSA (AHI ≥30) (**Figure 16**) overlapped, suggesting that there was no statistically significant difference in sensitivity among the 3 questionnaires.



AHI: apnoea hypopnoea index

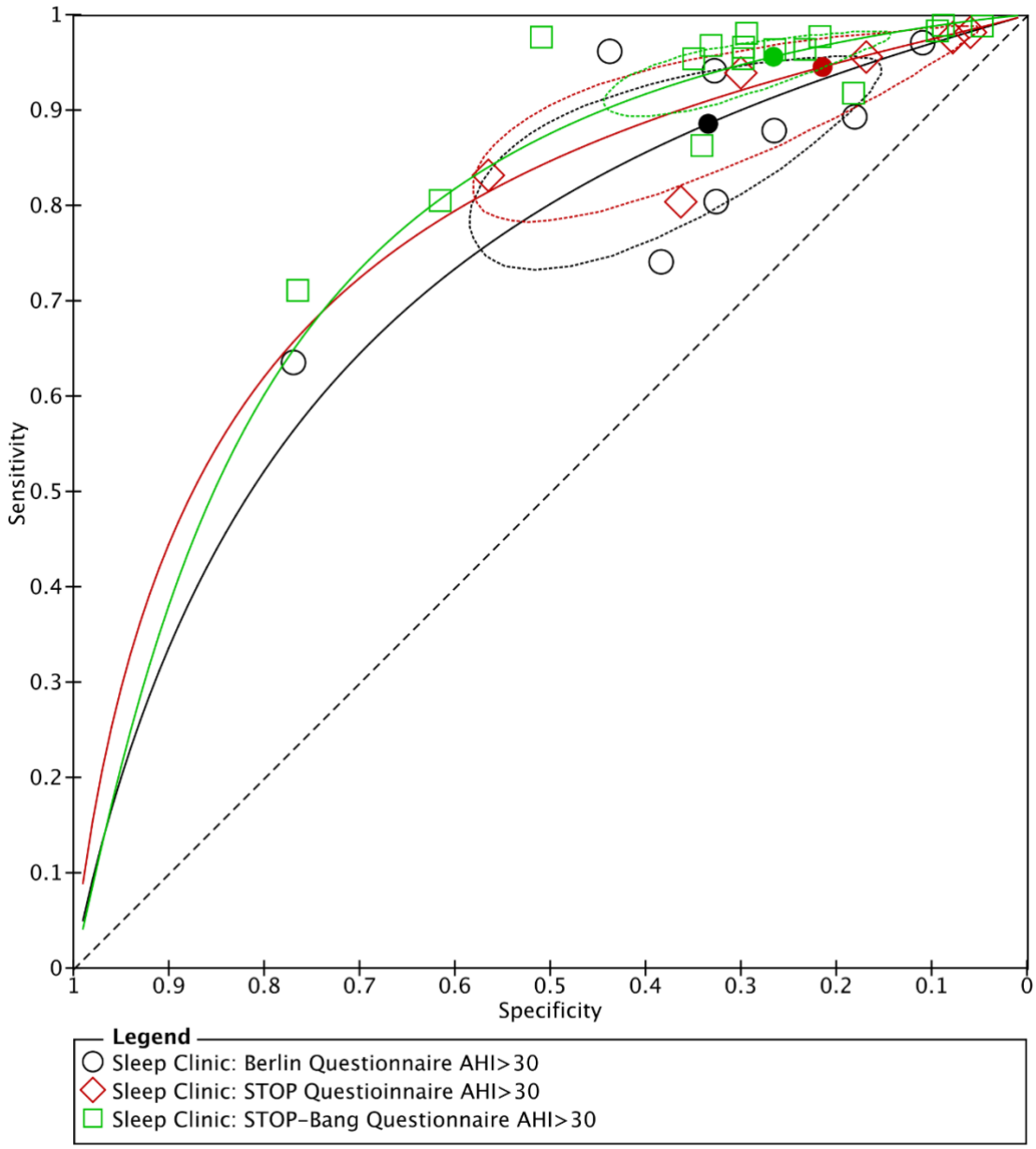
Figure 14 SROC Plot for Berlin, STOP and STOP-Bang Questionnaire AHI≥5

Figure 15 shows no overlap of the confidence regions for the Berlin and STOP-Bang questionnaires, suggesting a possible difference in sensitivity between the two questionnaires. A meta-regression model assuming equal variances for logit sensitivity and logit specificity suggested that the expected sensitivity or specificity differed between the two tests (chi-square=14.1, 2df, p=0.0008).



AHI: apnoea hypopnoea index

Figure 15 SROC Plot for Berlin, STOP and STOP-Bang Questionnaire AHI ≥15



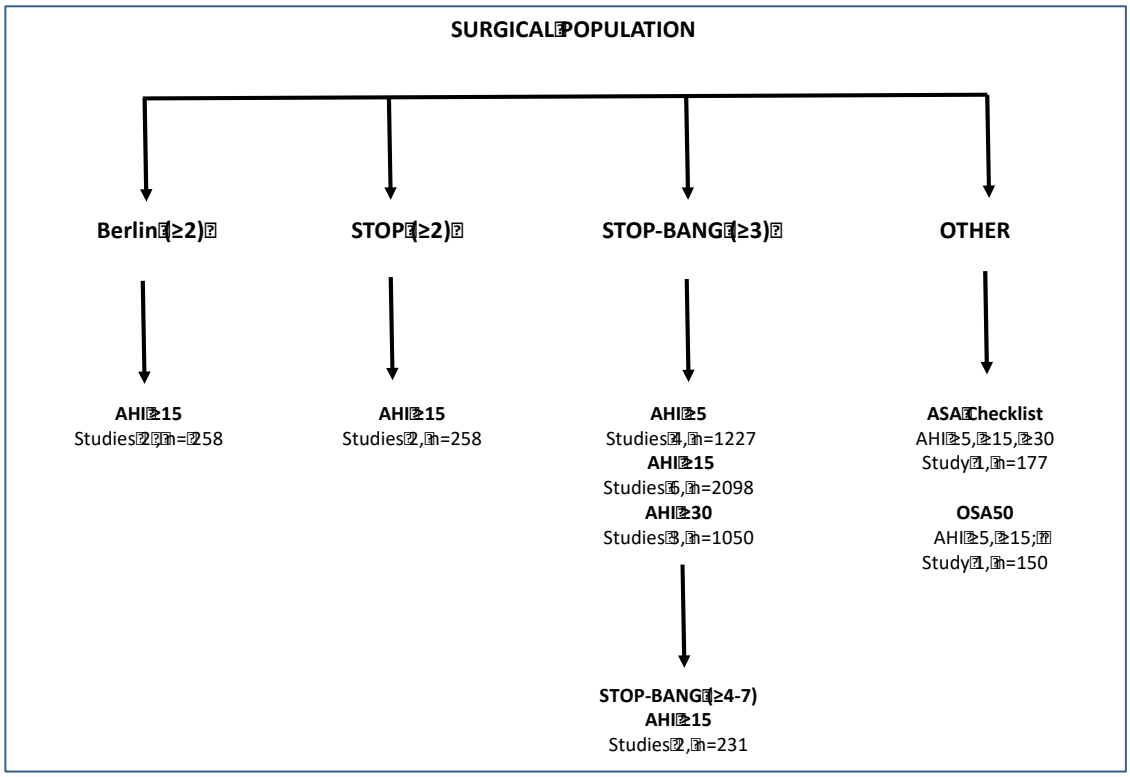
AHI: apnoea hypopnoea index

Figure 16 SROC Plot for Berlin, STOP and STOP-Bang Questionnaire AHI≥30

3.4.3.2 Surgical Population

In the surgical population (n=2710) (**Figure 17**), the Berlin, STOP and STOP-Bang questionnaires were identified for inclusion in the meta-analysis. The ASA checklist and OSA50 questionnaires were excluded from meta-analysis due to an insufficient number of studies. Nunes *et al.* (2015) included two surgical

cohorts, abdominal and coronary artery bypass grafting (CABG), which were entered as separate cohorts.



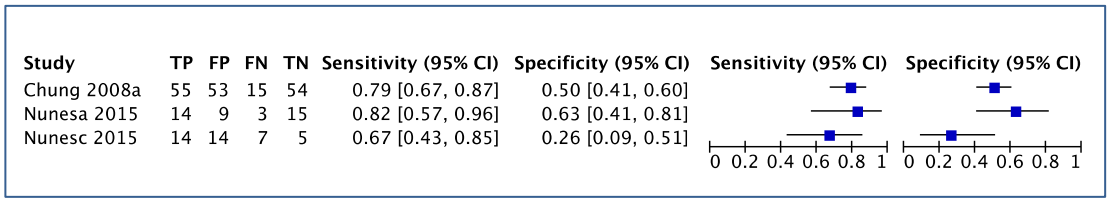
AHI: apnoea hypopnoea index; ASA: American Society of Anesthesiology; OSA50: obstructive sleep apnoea 50

Figure 17 Questionnaire Validation Studies in Surgical Population

3.4.3.2.1 Predictive parameters of the Berlin Questionnaire (score cut-off ≥2)

Two studies were included in the meta-analysis of the Berlin Questionnaire for moderate to severe OSA (AHI≥15) **(Figure 18).** Due to insufficient data, it was not possible to conduct a meta-analysis for all (AHI≥5) and severe OSA (AHI≥30).

The prevalence of moderate to severe OSA or AHI of ≥15 was 42%. The pooled sensitivity of the Berlin questionnaire to predict moderate to severe OSA (AHI ≥15) was 76% (95%CI: 66%, 84%), and the pooled specificity was 47% (95%CI: 32%, 62%). The DOR was 2.9 (95% CI: 0.2, 5.5) (**Table 9**).

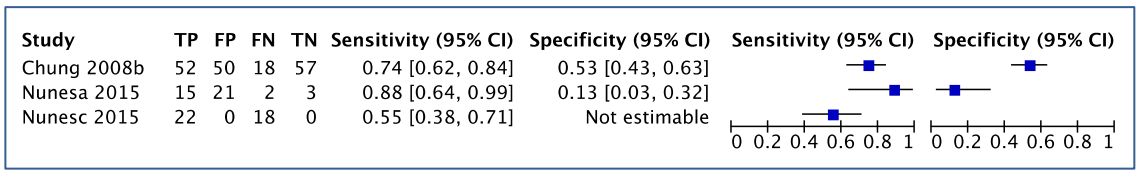


AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

Figure 18 Forest Plot for Berlin Questionnaire in Surgical Population for AHI≥15

3.4.3.2.2 Predictive parameters of the STOP Questionnaire (score cut-off ≥2)

Two studies were eligible for inclusion in the STOP Questionnaire meta-analysis for moderate to severe OSA (AHI ≥15). However, due to insufficient studies and large heterogeneity around the specificity, the STOP questionnaire was excluded from the meta-analysis (**Figure 19**).



AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

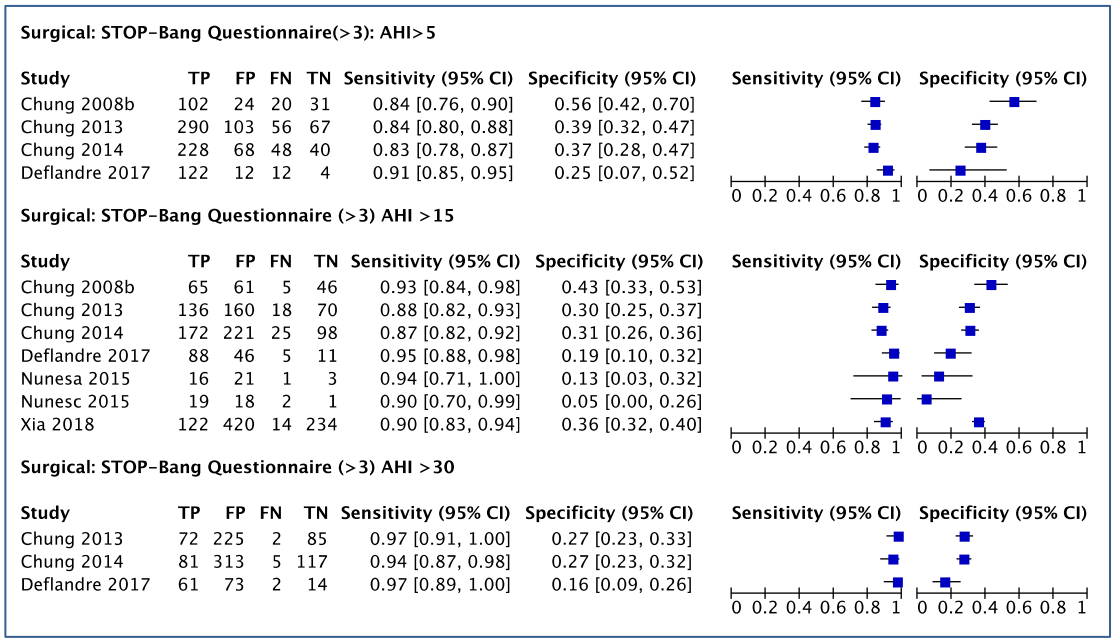
Figure 19 Forest Plot for STOP Questionnaire in Surgical Population for AHI≥15

3.4.3.2.3 Predictive parameters of the STOP-Bang Questionnaire (score cut-off ≥3)

Six studies were included in the meta-analysis of the STOP-Questionnaire for moderate to severe OSA (AHI≥15) (**Figure 20**).

The prevalence of AHI ≥5 (all OSA), AHI ≥15 (moderate to severe) and AHI ≥30 (severe) OSA was 72%, 33% and 21%, respectively. The pooled sensitivity of the STOP-Bang questionnaire to predict all OSA, moderate-severe and severe OSA was 85% (95% CI: 81%, 88%), 90% (95% CI: 87%, 93%) and 96% (95% CI: 92%, 98%) respectively. The pooled specificity was 40% (95% CI: 30%,

50%), 27% (95% CI: 19%, 37%) and 26% (95% CI: 21%, 46%). The corresponding DOR were 3.6 (95% CI: 2.3, 4.8), 3.4 (95% CI: 1.9, 4.9) and 8.4 (95% CI: 2.7, 14.2), respectively **(Table 9).** Compared to the Berlin and STOP questionnaire, individual trial estimates of sensitivity appeared to be more homogeneous for the STOP-Bang questionnaire (**Figures 18, 19 & 20**).



AHI: apnoea hypopnoea index; TP: True positive; FP: False positive; FN: False negative; TN: True negative; CI: confidence interval

Figure 20 Forest Plots for STOP-Bang Questionnaire for AHI ≥5; ≥15; ≥30

Table 9 Pooled Predictive Parameters of Berlin & STOP-Bang Questionnaires for AHI≥15 (Surgical)

Parameter (95%CI)	Berlin AHI ≥15	STOP-BANG AHI >5	STOP-BANG AHI ≥15	STOP-BANG AHI ≥30
	2 Studies n=258	4 Studies n=1227	6 Studies; n=2098	3 Studies n=1050
Prevalence (% and range)	41.86 (39.55-52.50)	71.56 (67.05-89.33)	32.79 (17.22-62.00)	21.24 (16.67-42.00)
Sensitivity (95% CI)	0.764 (0.661, 0.843)	0.846 (0.811, 0.876)	0.903 (0.871, 0.927)	0.96 (0.924, 0.979)
Specificity (95% CI)	0.468 (0.320, 0.623)	0.394 (0.298, 0.498)	0.269 (0.189, 0.367)	0.261 (0.232, 0.292)
False Positive Rate (95% CI)	0.532 (0.377, 0.680)	0.606 (0.502, 0.702)	0.731 (0.633, 0.811)	0.739 (0.708, 0.768)
Log LR +ve (95% CI)	1.437 (0.929, 1.945)	1.395 (1.187, 1.603)	1.235 (1.093, 1.377)	1.299 (1.236, 1.362)
Log LR -ve (95% CI)	0.504 (0.206, 0.802)	0.391 (0.304, 0.479)	0.361 (0.235, 0.487)	3.169 (2.502, 3.836)
DOR (95% CI)	2.849 (0.194, 5.505)	3.564 (2.311, 4.817)	3.421 (1.892, 4.949)	8.406 (2.65, 14.162)

AHI: apnoea hypopnoea index; CI: confidence interval; LR: likelihood ratio; DOR: diagnostic odds ratio; +: positive; -: negative

3.4.3.2.4 Predictive performance of STOP-Bang at various scores

In the surgical population, two of six studies reported data at multiple cut-off points for the STOP-BANG questionnaire for moderate-to-severe OSA (AHI≥15) (Nunes *et al.*, 2015; Deflandre *et al.*, 2017). Increasing the questionnaire threshold from 4 to 7 increased specificity from 31% (95% CI: 0.2, 0.4) to 96% (95% CI: 0.89, 0.99), and was greatest at cut-off values ≥6 and ≥7 (**Table 10**). However, increase in specificity was at the expense of a reduction in sensitivity.

Table 10 STOP-Bang at different questionnaire cut-offs for AHI≥15 (Surgical)

Predictive Parameters	SBQ≥4 AHI≥15	SBQ≥5 AHI≥15	SBQ≥6 AHI≥15	SBQ≥7 AHI≥15
	2 Studies; n=231			
Prevalence (% and range)	56.71 (41.46-62)			
Sensitivity (95% CI)	0.893 (0.828, 0.936)	0.640 (0.480, 0.774)	0.372 (0.211, 0.567)	0.120 (0.033, 0.353)
Specificity (95% CI)	0.310 (0.227, 0.407)	0.575 (0.458, 0.684)	0.807 (0.676, 0.894)	0.958 (0.889, 0.985)
False Positive Rate (95% CI)	0.690 (0.593, 0.773)	0.425 (0.316, 0.542)	0.193 (0.106, 0.324)	0.042 (0.015,0.111)
Log LR +ve (95% CI)	1.294 (1.108, 1.481)	1.505 (1.052, 1.958)	1.930 (0.859, 3.000)	2.875 (-2.580,7.647)
Log LR -ve (95% CI)	0.345 (0.147, 0.543)	0.627 (0.372, 0.881)	2.481 (0.547, 4.414)	0.918 (0.756,1.080)
DOR (95% CI)	3.755 (1.135, 6.374)	2.402 (0.763, 4.041)	8.406 (2.650, 14.162)	3.131 (-2.580,8.841)

AHI: apnoea hypopnoea index; CI: confidence interval; LR: likelihood ratio; DOR: diagnostic odds ratio; +: positive; -: negative

3.4.3.3 Resistant Hypertension Population

Two studies (n=517) were included in the meta-analysis of the Berlin Questionnaire (cut-off ≥2) for All OSA (AHI of ≥5) (Margallo *et al.,* 2014; Giampá *et al.*, 2018) (**Table 11**). Due to insufficient study data, it was not possible to conduct a meta-analysis for moderate-severe (AHI≥15) and severe OSA (AHI≥30).

The prevalence of all OSA or an AHI of ≥5 was 80%. The Berlin questionnaire's pooled sensitivity to predict All OSA or AHI of ≥5 was 80% (95%CI: 60%, 92%), and the pooled specificity was 36% (95%CI: 21%,55%). The DOR was 2.2 (95% CI: 0.7, 3.8).

Table 11 Pooled Predictive Parameters of Berlin Questionnaire for AHI ≥5 (Resistant Hypertension)

Predictive Parameters	All OSA AHI≥5
	2 Studies; n=517
Prevalence (% and range)	80.08 (71.58-81.99)
Sensitivity (95% CI)	0.801 (0.596, 0.917)
Specificity (95% CI)	0.358 (0.206, 0.545)
False Positive Rate (95% CI)	0.642 (0.455, 0.794)
Log LR +ve (95% CI)	1.248 (1.010, 1.486)
Log LR -ve (95% CI)	0.555 (0.242, 0.869)
DOR (95% CI)	2.248 (0.679, 3.817)

CI: confidence interval; LR: likelihood ratio; DOR: diagnostic odds ratio; +: positive; -: negative

3.4.3.4 Other Cohorts not included in Meta-analysis

Asthma, community clinic, highway bus drivers, neurology clinic, primary care, respiratory and snoring clinic cohorts were identified but were excluded from the meta-analysis due to having only one study per cohort.

3.4.3.5 Sensitivity analyses

3.4.3.5.1 Risk of Bias

No studies were evaluated as high risk in the surgical and resistant hypertension populations; therefore, no sensitivity analyses were conducted.

In the Sleep Clinic Population, sensitivity analyses were conducted for the Berlin **(Appendix 10)**, STOP-Bang **(Appendix 11)** and the STOP questionnaires for AHI>5, AHI≥15 and AHI≥30 (**Appendix 12**) excluding studies identified as high risk in any QUADAS-2 domain, unclear in four domains or outliers.

One study was excluded for the STOP questionnaire for AHI≥5 (Pecotic *et al.,* 2016), AHI≥15 (Kashaninasab *et al.*, 2015), AHI ≥30 (Kashaninasab *et al.*, 2015).

For the STOP-Bang questionnaire, five studies were excluded for AHI≥5 (Abdullah *et al.*, 2018; Alhouqani *et al.,* 2015; Amra *et al.*, 2013; Avincsal *et al.*, 2017; Boynton *et al.,* 2013), four studies for AHI≥15 (Alhouqani *et al.,* 2015; BaHammam *et al.,* 2015; Delgado-Vargas *et al.,* 2020; Kashaninasab *et al.*, 2017) and AHI ≥30 (Alhouqani *et al.*, 2015; BaHammam *et al.,* 2015; Delgado-Vargas *et al.*, 2020; Kashaninasab *et al.*, 2017).

For the Berlin questionnaire AHI≥5 (Khaledi-Paveh *et al.,* 2015; Kim *et al.,* 2015; Saleh, Ahmad & Awadalla; 2011; Suksakorn *et al.,* 2014) and AHI≥15 (Khaledi-Paveh *et al.,* 2015; Kim *et al.,* 2015; Saleh, Ahmad & Awadalla; 2011; Suksakorn *et al.,* 2014) four studies were excluded, and for an AHI≥30 (Kashaninasab *et al.*, 2015; Khaledi-Paveh *et al.,* 2015; Suksakorn *et al.,* 2014), three studies were excluded.

Across all three questionnaires, exclusion of studies was associated with stable or slightly increased sensitivity. In contrast, exclusion of studies was associated with reduced specificity. The STOP-Bang questionnaire remained the most effective questionnaire with the highest sensitivity compared to the Berlin and STOP questionnaires. Specificity among all three questionnaires remained low.

3.4.3.5.2 Desaturation and Arousal Criteria

Study selection for sensitivity analyses based on the desaturation criteria are summarised in **Appendix 13**. Due to an insufficient number of studies, no sensitivity analysis was conducted in the resistant hypertension population.

In the surgical population, the Berlin and STOP questionnaire studies utilised the ≥3% desaturation scoring criteria; therefore, no sensitivity analyses were conducted. For the STOP-Bang questionnaire, studies applied either ≥ 3% or ≥4% desaturation criteria. When the ≥3% desaturation criteria were applied to the STOP-Bang questionnaire, one study was excluded for AHI>5 (Chung *et al.,* 2013), two studies for AHI≥15 (Chung *et al.,* 2013; Xia *et al.,* 2018) and one study for AHI≥30 (Chung et al., 2013). In turn, when ≥4% desaturation criteria were applied, four studies were excluded for AHI≥15 (Chung *et al.,* 2008; Chung *et al.,* 2014; Deflandre *et al.,* 2017; Nunes *et al.,* 2015). Across the three AHI thresholds, sensitivity remained stable, compared to a stable or slightly decreased sensitivity with application of the ≥3% desaturation criteria. For AHI≥15, application of the ≥4% desaturation criterion was associated with a slight reduction in sensitivity and an increase in specificity **(Appendix 14).**

A sensitivity analysis was conducted in the Sleep Clinic Population for the Berlin, STOP and STOP-Bang questionnaires, applying both the ≥3% and ≥4% desaturation criteria respectively. Studies were excluded based on high risk of bias, scoring criteria not specified and desaturation criteria (≥3% or ≥4%) (**Appendices 15, 16, 17**)

Across all three questionnaires in the sleep clinic population, exclusion of studies was associated with stable sensitivity and reduced specificity, particularly when applying the ≥ 4% desaturation criterion. Overall, the STOP-Bang questionnaire remained the most effective questionnaire with the highest sensitivity compared to the Berlin and STOP questionnaires. Specificity among all three questionnaires remained low.

3.5 Discussion

This systematic review and meta-analysis investigated questionnaires' accuracy and clinical utility as screening tools for OSA in adults in different clinical cohorts.

Consistent with previous studies, study findings showed that the STOP-Bang questionnaire (score cut-off ≥3) suggested the highest sensitivity to detect OSA and the highest diagnostic odds ratio in both the sleep clinic and surgical populations (Abrishami, Khajehdehi & Chung, 2010; Chiu *et al.,* 2017; Nagappa *et al.*, 2015). However, the STOP-Bang questionnaire was limited by consistently low specificity across all AHI thresholds, resulting in high false-positive rates. The Berlin questionnaire (score cut-off≥2) appeared to be the least useful, demonstrating overall low sensitivity and low specificity across all three cohorts (Abrishami, Khajehdehi & Chung, 2010; Chiu *et al.,* 2017; Senaratna *et al.,* 2017). Although there was no comparison with other questionnaires in the resistant hypertension cohort, findings were comparable with the sleep clinic and surgical cohorts.

OSA screening questionnaires are intended to provide the information required to identify patients most likely to benefit from downstream management decisions, such as onward referral for objective sleep testing and possible treatment following a positive full diagnostic test. The potential utility of OSA screening questionnaires in risk stratification of patients has been demonstrated in several cohorts. Not only has OSA been associated with risk of peri-operative complications and consequent longer length of hospital stay, but it has also been linked to poor clinical outcomes including higher rates of post CABG AF (Kaw *et al.,* 2006; Liao *et al.,* 2009; Van Oosten *et al.,* 2014). In the context of the ongoing Coronavirus Disease 2019 (Covid-19) pandemic, a recent study reported worse clinical outcomes in patients with Covid-19 classified by the Berlin questionnaire as high risk, compared to those at low risk, of OSA (Peker *et al.,* 2021). The study also highlighted the challenges with objective assessment of OSA with PSG during the Covid-19 pandemic, emphasizing the need for alternative approaches beyond PSG, such as validated screening

questionnaires. In this context, assessment, and validation of OSA screening questionnaires are encouraged, particularly the STOP-Bang questionnaire, as screening tools for risk stratification appropriate clinical settings, with the aim of improving outcomes for patients.

Although sensitivity and specificity provide the necessary information to discern between the available screening questionnaires, the clinical value and application of the screening questionnaires are demonstrated by means of the positive and negative predictive values which are dependent on the prevalence of the disease in the given clinical population. Although pooling of the predictive values of individual questionnaires was not possible due to variation in prevalence across studies, the point estimates of PPV and NPV for the STOP-Bang questionnaire in both the sleep clinic and surgical population demonstrated an increase in NPV as OSA severity increases (**Appendix 18**). The combination of high sensitivity and NPV of the STOP-Bang questionnaire is therefore useful to help clinicians exclude patients with low risk of clinically significant OSA.

At the same time, the low specificity of the STOP-Bang questionnaire (and therefore its relative inability to correctly identify patients without OSA) leads to a high rate of false positive findings; this may have emotional and cognitive implications for individual patients with added consequences for clinical services, not least cost (Bossuyt *et al.,* 2012).

This systematic review's main strength lies in the comprehensive literature search with stringent eligibility criteria to identify all relevant studies reporting on the accuracy and clinical utility of existing OSA screening questionnaires that were validated against the gold standard PSG. Inclusion of the LILACS database expanded the search to include Latin America and the Caribbean studies. Of previous reports, the review by Ramachandran and Josephs (2009) was limited to a search of two databases, English publications only and omitted any grey literature sources in their search strategy. Additionally, it was unclear if Ross *et al.* (2000) and Abrishami, Khajehdehi and Chung (2010) included any grey literature sources in their searches.

Two independent reviewers completed data extraction, and the QUADAS-2 tool was used to assess rigorously all included studies for risk of bias. To evaluate the robustness of the meta-analysis, sensitivity analyses were conducted to investigate the potential influence on the findings from studies at high, or unclear, risk of bias. Although this study did not explore source differences from an ethnicity or geographical perspective, a further sensitivity analysis was conducted to evaluate the impact of varying scoring criteria on the study findings. The utilisation of different AASM scoring criteria and desaturation (and arousal) thresholds across studies created a source of variability (AASM, 1999; Iber *et al.*, 2007; Berry *et al.*, 2012). Although the definition for apnoeas remained stable, there has been much controversy about the definition of hypopnoeas, specific to flow reduction, oxygen desaturation and the presence or absence of arousal. Varying definitions of hypopnoea not only impacts on prevalence estimates but is likely to underestimate OSA in patients who may benefit from treatment (Shamim-Uzzaman, Singh & Chowdhuri, 2018). A study by Guilleminault *et al.* (2009) showed that by using the 30% flow reduction and 4% desaturation without arousal criteria would have missed 40% of patients who were identified using the criteria with arousal and who were responsive to CPAP therapy with reduction in AHI and symptomatic improvement.

On this background, this review is based on a larger number of studies than prior analyses (Ross *et al.*, 2000; Ramachandran & Josephs, 2009; Abrishami, Khajehdehi & Chung, 2010). Although the review by Chiu *et al.* (2017) encompassed a larger dataset, that report carried a greater risk of bias due to the inclusion of retrospective studies and studies that used PSG and portable monitoring as the reference standard.

Furthermore, this review considered all existing OSA screening questionnaires for inclusion. In contrast, Chiu *et al.* (2017) preselected four questionnaires, including the ESS, which was not developed as a screening questionnaire, but as a measure of daytime sleepiness.

Similar to Abrishami, Khajehdehi and Chung (2010) and Chiu *et al.* (2017), this review focused on questionnaires only, in contrast to Ross *et al.* (2000) and

Ramachandran and Josephs (2009) who also included portable monitoring and clinical prediction tools, respectively.

There are several limitations to this work. The findings are influenced by the limitations of the included studies. In several, the true risk of bias was unclear in several of the QUADAS-2 domains due to underreporting in the Index Test, Reference Standard and Flow and Timing domains. Similarly, it was often unclear if the results of the index test and the reference standard were interpreted independently. Very few studies provided adequate information to determine if the time interval between the index test and the reference standard was appropriate.

The decision to exclude seven additional clinical cohorts may be considered a limitation; however, in the context of unclear, and possibly substantial, differences among these studies in the patient spectrum and disease prevalence, it was felt appropriate not to include these in the meta-analysis. Because the accuracy of screening tools varies according to the spectrum of disease, this further reiterates the need for validation studies in similar clinical cohorts.

There was a high degree of heterogeneity amongst included studies with the possibility of selection bias, especially in the sleep clinic population. Consequently, reported sensitivity estimates will be higher than lower-risk populations, making it difficult to extrapolate the true utility of the questionnaire in clinical practice.

3.6 Conclusion

This systematic review meta-analysis investigated the accuracy and clinical utility of existing OSA screening questionnaires in different clinical cohorts. While the STOP-Bang questionnaire had a high sensitivity to detect OSA in both the sleep clinic and surgical cohorts, it lacked adequate specificity.

This review did not identify any studies that were validated in a stable CHF cohort. Pooled results from the validation studies in the sleep clinic population, are unlikely to be generalisable to a stable CHF population due to possible

selection bias, spectrum effect and higher prevalence than expected in a stable CHF population. Therefore, findings from this review reiterate the need for diagnostic validation studies in clinically similar cohorts to enable the extrapolation of the true accuracy and clinical utility of existing OSA screening questionnaires.

Chapter 4 of this thesis, will evaluate and describe the diagnostic accuracy of the STOP-Bang questionnaire in a sleep clinic cohort with co-existing stable CHF.

4

Diagnostic Accuracy of the STOP-Bang Questionnaire in a Sleep Clinic Population with co-existing Heart Failure

4.1 Introduction

Due to the high prevalence of OSA in patients with CHF and associated sequelae, a validated screening questionnaire could support risk stratification of patients who may require formal investigation for OSA, however, no screening questionnaires have been validated in patients with CHF.

Chapter 3 of this thesis investigated the accuracy and clinical utility of existing OSA screening questionnaires in different clinical cohorts. Although specificity was low across all questionnaires, findings from this systematic review and meta-analysis reported the STOP-Bang questionnaire to be the most useful questionnaire due to its ease of use, methodological quality of validation studies and high sensitivity in both the sleep clinic and surgical population, compared to the Berlin and the STOP questionnaires. There were no validation studies identified or included in a CHF cohort.

Therefore, the objective of this study was to prospectively evaluate the ability of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of stable CHF. The primary outcome measure for this study was the sensitivity of the STOP-Bang questionnaire to detect OSA.

4.2 Aim

The aim of this chapter is to evaluate and describe the diagnostic accuracy of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of CHF.

4.3 Materials and Methods

4.3.1 Study Design

A prospective, cross-sectional study was conducted between January 2018 and December 2019 in the Sleep Disorders Service at the University Hospitals of Leicester NHS Trust in Leicester, UK.

4.3.2 Participants

Twenty-five consecutive patients, referred to the Sleep Disorders Service for the investigation of suspected OSA and who met the eligibility criteria, were enrolled in the study. Selection criteria are summarised in **Table 12**.

Table 12 Selection Criteria for Diagnostic Validation Study

Inclusion Criteria	Exclusion Criteria
• Referred for assessment of OSA and attending for a sleep study at the Sleep Disorders Service, • ≥18 years of age, • CHF (≥ 12 weeks since diagnosis) according to European Society of Cardiology guidelines, • NYHA I-III at time of visit as scored by the Chief Investigator at the time of assessment, • Left ventricular systolic dysfunction (LVEF ≤ 49% by imaging method such as echocardiography/cardiac magnetic resonance imaging) in the last 24 months, • No hospitalization for CHF in the 4 weeks prior to enrolment,	• <18 years of age, • NYHA IV • Cardiac surgery, PCI, myocardial infarction, or unstable angina within the last 6 months, • CRT implantation scheduled/performed within 6 months prior to enrolment • Predominantly CSA (with ≥ 50% central events), • Transient ischemic attack within 3 months, • Haemodynamically significant uncorrected primary valvular heart disease, • Acute pericarditis/myocarditis within the previous 6 months,

Inclusion Criteria	Exclusion Criteria
• Taking maximum tolerated doses of appropriate evidence-based therapy. No change in loop diuretic therapy for 4 weeks prior to enrolment. • Predominantly OSA (apnoea-hypopnoea index (AHI)>15 events/hr with ≥50% obstructive events, derived from respiratory polygraphy), • Willing and able to give informed consent, and • Read, write, and communicate confidently in English.	• Untreated or therapy-refractory restless legs syndrome, • Current CPAP/bilevel therapy at the time of recruitment, • Contra-indication to the use of CPAP therapy, • Those either unwilling or unable to give consent, and • Unable to read, write or communicate confidently in English.

PCI: percutaneous coronary intervention; CPAP: continuous positive airway pressure; NYHA: New York Heart Association; CHF: chronic heart failure; CRT: cardiac resynchronisation therapy; LVEF: left ventricular ejection fraction; CSA: central sleep apnoea; OSA: obstructive sleep apnoea.

4.3.3 Procedure

4.3.3.1 Regulatory Approval, NIHR Clinical Research Network Portfolio and Ethical Considerations

The study protocol was approved by the Health Research Authority (HRA) and the East Midlands-Leicester South Ethics committee (REC reference: 17/EM/0400) and adopted onto the NIHR Clinical Research Network (CRN) portfolio. Full details of regulatory approval and ethical considerations were discussed in Chapter 2 of this thesis.

4.3.3.2 Recruitment

Consecutive patients who attended the Sleep Disorders Service at the Leicester General Hospital for the assessment of suspected OSA were considered for participation in the study. Referrals were screened and assessed for study eligibility by a team of Sleep Medicine Consultants. Prior to the patient's appointment at the sleep laboratory or sleep clinic, a letter of invitation **(Appendix 19**) and participant information sheet (**Appendix 20**) were sent by post to the patient.

On the day of appointment, it was confirmed that the patient had received the letter of invitation and participant information sheet and that they had read the

information. A full explanation of the study was given, and patients had the opportunity to ask questions. Completion of the STOP-Bang Questionnaire and study related activities were undertaken once the informed consent was received.

All participants were offered a minimum of 24 hours to consider the information, and the opportunity to question the Investigator, their general practitioner, or other independent parties prior to making the decision to participate in the study.

Written and verbal versions of the participant information and informed consent were presented to all participants detailing no less than:

- the exact nature of the study,
- the implications and constraints of the protocol, and
- the known side effects and any risks involved in taking part.

Participants were free to withdraw from the study at any time for any reason without prejudice to future care, and with no obligation to give the reason for withdrawal.

Written, informed consent was received by the investigator prior to participants undertaking any study related activities. Participants personally signed and dated the latest approved version of the informed consent form **(Appendix 21).** The original signed form was retained at the study site within the Trial Master File.

4.3.3.3 Study Procedures

4.3.3.3.1 Medical History

A detailed history of disease or surgical interventions were obtained from participants and their medical records, including a sleep and cardiac history.

4.3.3.3.2 Anthropometric Measurements

The following anthropometric measurements were obtained and recorded:

- **Height** (cm): measured without shoes.
- **Weight** (kg): measured with light clothes and without any shoes.
- **BMI** was calculated using the following metric formula: $BMI = \frac{weight(kg)}{height(m^2)}$

- **Neck circumference** (cm): measured in the midway of the neck, using a non-stretchable plastic tape with the participants standing upright. In men with a laryngeal prominence or Adam's apple, the measurement was taken just below the prominence.
- **Waist circumference** (cm): measured at the level of the belly button and top of the hipbone.

4.3.3.3.3 Epworth Sleepiness Scale

All participants completed the ESS at the time of their sleep study appointment. The ESS is a self-reported questionnaire to assess the propensity for daytime sleepiness. The questionnaire consists of 8 questions and for each ESS item, the participant allocates a score of 0-3. The normal reference range for ESS scores are 0-10 and scores of 11-24 are indicative of raised levels of EDS (Johns, 1992).

4.3.3.3.4 Index Test: STOP-Bang Questionnaire

Supported by the investigator, all participants completed the STOP-Bang questionnaire. This short, self-administered screening questionnaire for OSA can be completed with ease within 1-2 minutes. It consists of four questions related to snoring, tiredness, observed apnoeas and high blood pressure and four clinical attributes including BMI, age, neck circumference, and male gender.

All the questions are dichotomous (yes/no). A score of 1 is allocated for all "yes" responses and a score of 0 is allocated for all "no" responses. A score of 1 is also allocated for BMI>35; neck circumference >40cm; male gender and a BMI>35. The risk of OSA is scored from 0 to 8 and can be interpreted as low (0-2), intermediate (3-4) or high (5-8) risk (Chung *et al.*, 2008).

4.3.3.3.5 Reference Standard: Level 3 Home Sleep Apnoea Testing

Full in-lab PSG is considered the gold standard for the objective assessment of OSA. The test involves overnight monitoring of sleep in a sleep laboratory with ≥ 7 signals including electroencephalogram, electro-oculogram (EOG), chin electromyogram (EMG), electrocardiogram (ECG), airflow, respiratory effort, and oximetry. PSG is time-consuming, costly, requires specialist input and is

mostly reserved for cases where portable monitoring or HSAT is inadequate to establish the diagnosis of OSA in those with a high pre-test probability (Collop *et al.*, 2005).

Due to limited resources, patients were offered level three RP as standard care, a technique that has been sufficiently validated for the diagnosis of OSA (El Shayeb *et al.*, 2014). Most participants were investigated with the Embletta® MPR Sleep System (Natus, 2020), a fourth-generation ambulatory sleep recorder that offers 7 channels of data including abdominal effort, thoracic effort and nasal pressure, nasal flow, snore, SpO_2 and pulse rate, ECG, and position.

Due to sleep study reporting backlog, an additional device, the WatchPAT™300 (Itamar Medical, 2020) system, was utilised for a short period of time. The WatchPAT™300 device was selected due to its ability to auto-score and reduce the sleep study reporting backlog.

The WatchPAT™300 system utilises the peripheral arterial tone signal (PAT) and measures up to 7 channels via 3 points of contact. These include the PAT signal, heart rate, oximetry, actigraphy, body position, snoring and chest motion. The device can differentiate between central and obstructive events and provides AHI, RDI and oxygen desaturation index data based upon sleep time and sleep staging (Itamar Medical, 2020). Furthermore, raw data can be downloaded and auto scored within 1 minute of study completion.

4.3.3.3.6 Diagnostic Criteria for OSA

Diagnostic criteria for OSA in adults are outlined by the International Classification of Sleep Disorders, 3rd edition (ICSD3) (Sateia, 2014).

Criteria include a combination of (A and B) or C:

The presence of one or more of the following criteria:

Complaints of sleepiness, nonrestorative sleep, fatigue, or insomnia;

Reports of breath holding, gasping, or choking;

Bed partner reports of habitual snoring, breathing interruptions or both during sleep;

Diagnosis of comorbidities, including hypertension, mood disorder, cognitive dysfunction, coronary heart disease, stroke, CHF, AF, or type 2 diabetes mellitus;

AND

PSG or out-of-centre sleep testing (home sleep study) demonstrates:

≥5 obstructive respiratory events (obstructive or mixed apnoeas, hypopnoeas or respiratory effort-related arousals) per hour sleep during PSG or OCST.

OR

PSG or OCST demonstrates:

≥15 obstructive respiratory events per hour of sleep during PSG or per hour of monitoring.

4.3.3.3.7 OSA Severity Criteria

The severity of OSA was determined by the frequency of respiratory events during sleep, also known as the AHI.

$$AHI = \frac{number\ of\ apnoeas\ and\ hypopoeas}{number\ of\ hours\ sleep}$$

OSA severity is classified as normal (AHI<5), mild (AHI 5-14), moderate (≥15) and severe (AHI≥30) (Kryger, Roth & Dement, 2017). An apnoea is characterised by a drop in the peak signal excursion by ≥90% from baseline lasting for ≥10 seconds. The AASM Rules for scoring respiratory events in sleep (2012), describe an apnoea as a drop in airflow of ≥ 90% from baseline, lasting ≥10 seconds and a hypopnoea as a 30% drop in nasal pressure excursion for ≥10 seconds associated with ≥3% desaturation or arousal (Berry *et al.,* 2012).

4.3.3.3.8 Interpretation of Index Test

The STOP-Bang questionnaire (index test) was completed by participants with support of the investigator prior to undertaking the sleep study. Participant data were anonymised and entered in an electronic database. Patient clinical data/medical records were not available at the time of completing the STOP-Bang questionnaire. Medical history was obtained from the patient following

completion of STOP-Bang questionnaire. Sleep technologists did not have access to the STOP-Bang questionnaire results and were therefore blinded to the results of the index test. The STOP-Bang questionnaire was completed on the same day and prior to the home sleep study.

4.3.3.3.9 Interpretation of the Reference Standard

The home sleep study (reference standard) set-up was conducted by two assistant practitioners and scored by a sleep medicine technologist. Utilising a small number of technologists potentially reduced inter observer variability and scoring of three sleep studies were reviewed by a senior sleep medicine technologist to assess for inter observer variability. The sleep medicine technologists did not have access to the medical records at the time of sleep study scoring, however, the referral letter was available to them. The final sleep study report was reviewed by a Sleep Medicine Consultant during the patient's clinic visit with access to the patient's medical records. All the sleep medicine technologists and clinicians were blinded to the STOP-Bang questionnaire results.

Due to significant pressure on the sleep disorders service and reporting backlog, it was not possible to have sleep studies rescored by a second sleep medicine technologist.

4.4 Analysis

4.4.1 Sample size calculation

For the sample size calculation, the function power.diagnostic.test in R was used, assuming a significance level of 0.05 and power of 80%.

For a prevalence of 50%, assuming a significance level of 0.10 for an estimated sensitivity of 0.8, the sample size required was 188 (94 cases + 94 controls). This sample calculation has been selected based on feasibility. Sample sizes were calculated and considered for an unselected HF population in primary care, however it was not feasible due to large sample size requirements.

As data became available and the prevalence of OSA notably higher, the sample size was recalculated. For a prevalence of 90%, assuming a significance level of 0.10 and estimated sensitivity of 0.8, the required sample

size was 105 patients (94 positive cases with OSA + 11 negatives cases without OSA).

4.4.2 Methods for estimating or comparing measures of diagnostic accuracy

Baseline participant characteristics were summarised using descriptive statistics. Data were assessed for normality. Categorical variables were reported as percentages and continuous variables were reported as median and interquartile range as data was not normally distributed.

The estimated OSA risk, as assessed by the STOP-Bang questionnaire were compared to the diagnosis of all OSA (AHI ≥5), moderate-severe (AHI ≥15) and severe OSA (AHI ≥30) as determined by RP or WatchPAT testing. The ability of the STOP-Bang questionnaire to detect all, moderate-severe and severe OSA (AHI ≥5, ≥15 and ≥30) was assessed by evaluating the sensitivity, specificity, PPV, NPV, positive likelihood and negative likelihood ratios. These values were calculated using multiple 2 x 2 contingency tables. The exact Clopper-Pearson confidence intervals were calculated for sensitivity, specificity, PPV and NPV using Stata version 16 (STATA Statistical Software: Release 16. College Station, TX: StataCorp LLC. StataCorp.).

4.4.3 Indeterminate index test or reference standard results

Indeterminate test results were not expected for either the index test or the reference standard. Pre-selected criteria categorised the patient as low, intermediate, or high risk (index test) or as all, moderate-severe, or severe OSA (reference standard). In the event of indeterminate results, a conservative or worst-case scenario approach would have been utilised. All indeterminate results from the index test would be considered as false-negative in those with the target condition or false-positive in those without the condition (Cohen *et al.,* 2016).

4.4.4 Missing Data

Participants with missing data from the index test or reference standard were excluded from the analysis.

4.5 Results

4.5.1 Participant Screening

Figure 21 demonstrates the flow of participants through the study.

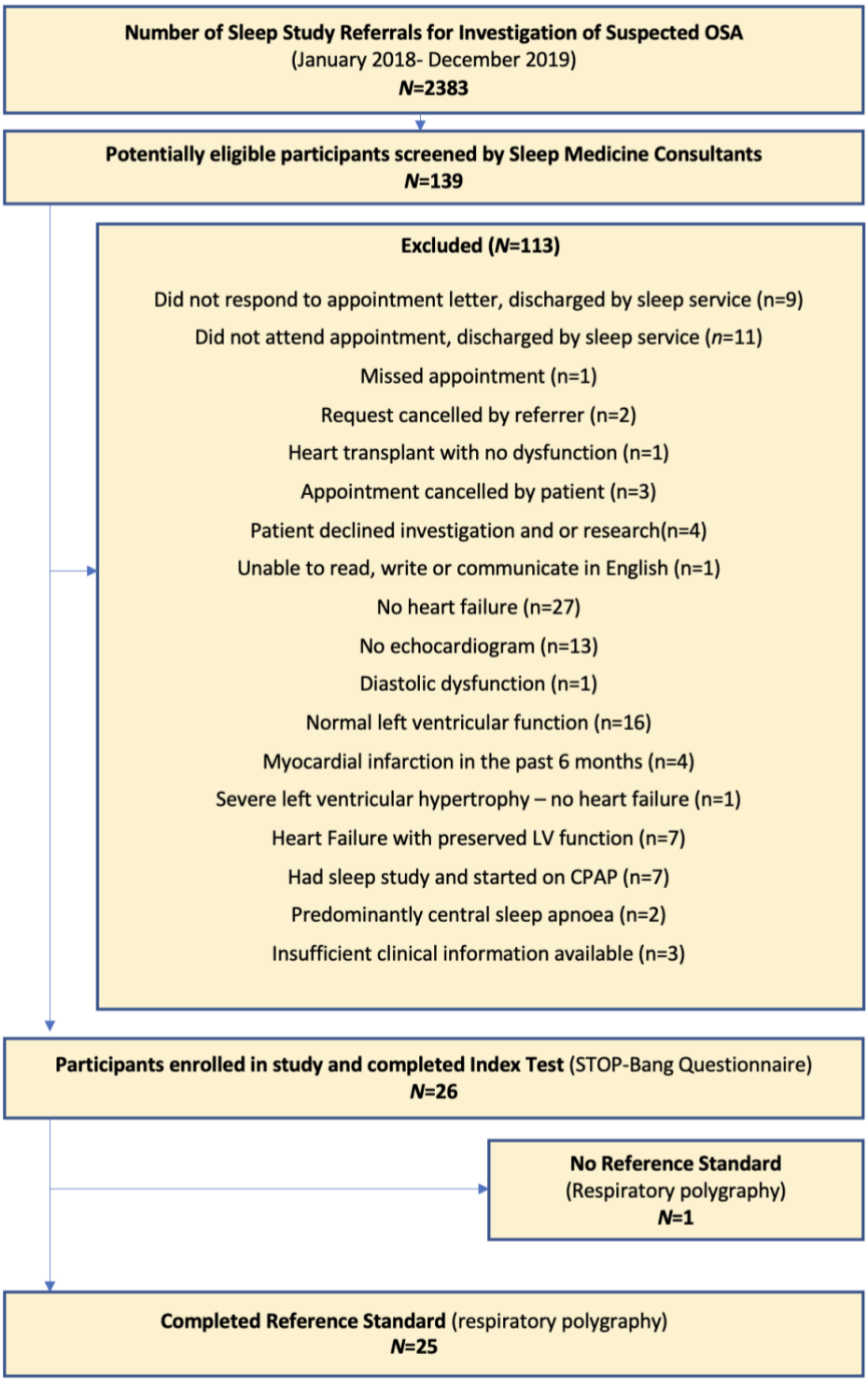


Figure 21 Flow Chart of Participant Screening

Between January 2018 and December 2019, the Sleep Service at the Leicester General Hospital received 2383 sleep study referrals for the investigation of suspected OSA. After initial screening by the sleep medicine consultant team, 139 potentially eligible participants were identified. Of the 139, 26 participants met the eligibility criteria, consented to participate in the study and completed the STOP-Bang questionnaire. One participant declined RP, therefore data from 25 participants were included in the analysis. Reasons for non-eligibility are summarised in **Figure 21.**

4.5.2 Participant Characteristics

Of the 25 participants enrolled in the study, 20 (80%) were male and largely white British. The median age of participants was 70 years (range 40-87).

The predominant comorbidity was AF (*N*=15), followed by hypertension and diabetes. Notably, of those with a history of AF, 10 (67%) participants were in the moderate to severe OSA group (AHI≥15), compared to 4 (40%) participants with mild OSA (AHI<15). Participant characteristics are summarised in **Table 13**.

Table 13 Participant Characteristics

Characteristic	Criteria	All *N* (%)	AHI<15 *N* (%)	AHI≥15 *N* (%)
Gender	Male, n (%) Female n (%)	20 (80%) 5 (20%)	10 (100%) 0 (0%)	10 (66.7%) 5 (33.3%)
Age	Age, year	70 (IQR 59-75)	73 (IQR 59-75)	68 (IQR 59-76)
Ethnicity	White British Mixed White and Black Caribbean	24 (96%) 1 (4%)	9 (90%) 1 (10%)	15 (100%) 0 (0%)
Cigarette Smoking, n (%)	Never Ex-smoker Current	11 (44%) 13 (52%) 1 (4%)	0 (0%) 7 (70%) 3 (30%)	1 (7%) 6 (40%) 8 (53%)
Alcohol drinking, n (%)	No Yes	13 (52%) 12 (48%)	5 (50%) 5 (50%)	7 (47%) 8 (53%)
Comorbidities	Myocardial Infarction PCI CABG Atrial Fibrillation Hypertension Diabetes Heart Failure Valve disease	9 (36%) 4 (16%) 4 (16%) 14 (56%) 11 (44%) 8 (32%) 25 (100%) 1 (4%)	6 (60%) 3 (30%) 4 (40%) 4 (40%) 5 (50%) 4 (40%) 10 (40%) 0 (0%)	3 (20%) 1 (7%) 0 (0%) 10 (67%) 6 (40%) 4 (27%) 15 (60%) 1 (7%)

AHI: apnoea hypopnoea index; PCI-percutaneous coronary intervention; CABG-coronary artery bypass graft

4.5.3 Heart Failure Characteristics

Over half of participants had a non-ischaemic origin of their CHF with predominantly moderate to severe left ventricular systolic dysfunction (LVSD). Overall, participants reported stable CHF symptoms classified as NYHA II or III. Of the 25 participants, 23 (92%) were established on ACE-inhibitors and beta blockers, whilst 16 (64%) were on aldosterone antagonists and 15 (60%) on a loop diuretic. HF characteristics are summarised in **Table 14**.

Table 14 Heart Failure Characteristics

Characteristics	Criteria	Frequency (*N*=25)
Aetiology	Non-ischaemic	14 (56%)
	Ischaemic	11 (44%)
LVSD	Mild	4 (16%)
	Mild-moderate	3 (12%)
	Moderate	8 (32%)
	Moderate-severe	1 (4%)
	Severe	9 (36%)
Device	ICD/CRT	7 (28%)
Signs and Symptoms	Orthopnoea	6 (24%)
	PND	0 (0%)
	Oedema	3 (12%)
	Dizziness	7 (28%)
	Palpitations	5 (20%)
	Fatigue	4 (16%)
	Chest Pain	3 (12%)
	Cough	3 (12%)
NYHA Class	I	5 (20%)
	II	12 (48%)
	III	8 (32%)
Evidence-Based Medication	Sacubitril Valsartan	1 (4%)
	ACEi/ARB	23 (92%)
	Beta Blockers	23 (92%)
	Aldosterone Antagonists	16 (64%)
	Loop Diuretics	15 (60%)

LVSD-left ventricular systolic dysfunction; ICD-implantable cardioverter defibrillator; CRT-cardiac resynchronisation therapy; PND: paroxysmal nocturnal dyspnoea; NYHA: New York Heart Association; ACEi-angiotensin converting enzyme inhibitor; ARB-angiotensin receptor blocker

4.5.4 Anthropometric Measurements

Data were assessed for normality. Distribution of neck circumference, waist circumference and BMI did not fit normal distribution and are reported as median and interquartile range **(Table 15)**. Neck circumference measurements were similar in both mild (AHI<15) and moderate to severe (AHI≥15) OSA groups, however, waist circumference and BMI measurements were higher for participants in the moderate-severe OSA group, compared to those in the mild OSA group.

Table 15 Anthropometric Measurements

Anthropometric Measurements	Criteria	Median (IQR)	Minimum	Maximum
Neck Circumference	All (cm) AHI<15 AHI≥15	44 (41-46) 44 (41-46) 44 (41-46)	38 39 38	50 49 50
Waist Circumference	All (cm) AHI<15 AHI≥15	118.5 (106-127) 113.75 (100.8-122) 120.5 (106.8-129.8)	78 81 78	155 132 155
BMI	All (kg/m2) AHI<15 AHI≥15	35 (28.5-40) 32 (29-37.5) 36 (27-43)	22 27 22	52 41 52

IQR: interquartile range; BMI: body mass index

4.5.5 Sleep Assessment

Sleep assessment results are summarised in **Table 16**. Twenty-one (84%) participants reported a history of snoring and 17 (68%) reported episodes of breath holding during sleep. Whilst 17 (68%) reported a dry mouth when they wake up, only 3 (12%) participants reported waking with a headache. More than 70% of participants reported nocturia.

The median ESS score for all participants was 10 (IQR 6-15), with 13 (52%) participants reporting a score >10.

Table 16 Sleep Assessment

Assessment	Criteria	Frequency (n=25)
Sleep Assessment (% of "Yes" answers)	Do you snore?	21 (84%)
	Has your snoring ever bothered other people?	19 (76%)
	Has anyone observed you stop breathing during sleep?	17 (68%)
	Do you often wake up with a headache?	3 (12%)
	Do you often wake up with a dry mouth?	17 (68%)
	Do you often wake during the night to use the toilet?	18 (72%)
Epworth Sleepiness Scale	Score below 10	11 (44%)
	0	1 (4%)
	2	1 (4%)
	3	2 (8%)
	5	1 (4%)
	6	1 (4%)
	7	3 (13%)
	8	2 (8%)
	Score 10 or above	13 (52%)
	10	5 (21%)
	11	1 (4%)
	15	2 (8%)
	16	1 (4%)
	19	1 (4%)
	20	1 (4%)
	22	1 (4%)
	23	1 (4%)
	Not reported	1 (4%)

4.5.6 STOP-Bang Questionnaire

Of the 25 participants, the STOP-Bang questionnaire categorised 22 (88%) participants as high risk. High scoring criteria included snoring, tiredness, age, male

gender, and neck circumference. Eleven (44%) participants reported a history of hypertension and 13 (52%) a BMI of >35 **(Table 17)**.

The STOP-Bang questionnaire was completed on the day of, and prior to undertaking, the home sleep study. Therefore, with a short time interval, there were no clinical interventions between the index test and reference standard. No adverse events were reported from performing RP, WatchPAT or from completing the STOP-Bang questionnaire.

Table 17 STOP-Bang Questionnaire

STOP-Bang Questionnaire	Criteria	% of "yes" answers
Criteria	Snoring (loudly)	20 (80%)
	Tiredness, sleepiness, fatigue	20 (80%)
	Observed Apnoea	17 (68%)
	Pressure	11 (44%)
	BMI (>35)	13 (52%)
	Age (>50)	24 (96%)
	Neck circumference	22 (88%)
	Gender (male)	20 (80%)
STOP-Bang Score	Low risk (score 0-2)	1 (4%)
	Intermediate risk (score 3-4)	2 (8%)
	High risk (score 5-8)	22 (88%)

BMI: body mass index

4.5.7 Home Sleep Study

Twenty-five participants completed a home sleep study of which 23 (92%) were investigated with the Embletta® MPR Sleep System (RP) and two (8%) with the WatchPAT™300 system (peripheral arterial tone signal). One participant was classified as "no OSA", 9 (36%) were classified as mild OSA (AHI<15) compared to 7 (28%) as moderate-severe (AHI≥15) and 8 (32%) as severe OSA (AHI≥30).

The reported median index time was 447 minutes (IQR 455-507) with a median AHI of 20.9 (IQR 11-33.8). Snore time ranged from 0 to 348.9 minutes with a median of

137 minutes (IQR 55-209) snoring episodes per recording. Oxygen saturation ranged from 86%-95% with 17.9 (IQR 11-34) desaturation events per hour **(Table 18)**.

One participant declined the home sleep study; therefore, his demographic data were not included in the analysis. The excluded participant was a 56-year-old male of white British background. His comorbidities include a history of AF, diabetes and LVSD of non-ischaemic cardiomyopathy origin and EF of 45%. This patient reported stable HF symptoms with NYHA I.

His anthropometric measurements were BMI of 35, waist circumference of 136 cm and neck circumference of 49.5cm. He reported a history of loud snoring, breath holding, nocturia and an ESS score of 15. His STOP-Bang score on assessment was 6.

When compared to the characteristics of the participants who completed the home sleep study, this patient is slightly younger with a greater waist and neck circumference, than the rest of the group.

Table 18 Home Sleep Study: Sleep Summary

Criteria	Median (IQR)	Minimum	Maximum	Outlier
Total Recording Time (minutes)	482 (IQR 455-507)	376	571	648
Index Time	447 (IQR 408-484)	375	587	230
AHI	20.9 (IQR 11-33.8)	0.2	33	66.4
Oxygen Saturation **Oxygen Desaturation Events** **Oxygen Desaturation Events/hr**	92 (IQR 89.8-93) 112 (IQR 74-245) 17.9 (IQR 11-34)	85.6 2 0.2	95.2 475 55.4	n/a n/a 70.3
Snore Time **Number of Snoring Episodes**	94 (IQR 27-168) 137 (IQR 55-209)	0 0	348.9 395	n/a n/a
Heart Rate Statistics	67 (IQR 59-72)	49	84	94, 95, 132

IQR: interquartile range; AHI: apnoea hypopnoea index

4.5.8 Predictive Parameters of the STOP-Bang questionnaire

Cross tabulation of the STOP-Bang questionnaire results by the results of the Sleep Study

The STOP-Bang score for questionnaire thresholds of ≥3 (intermediate risk) and ≥5 (high risk), and AHI were tabulated for each participant **(Appendix 22; Table 19)**. Of the 25 participants, the home sleep study classified 9 (36%) participants in the mild OSA category (AHI≥5), 7(28%) in the moderate to severe (AHI≥15) category and 8 (32%) in the severe (AHI≥30) category. The STOP-Bang questionnaire classified 1 (4%) participant as low risk, 2 (8%) as intermediate risk and 22 (88%) as high risk. STOP-Bang questionnaire scores ranged from 2 to 8.

Table 19 Relationship between the STOP-Bang Questionnaire and AHI

Sleep Study	STOP-Bang Questionnaire		
AHI/Hour	Low Risk (0-2)	Intermediate Risk (3-4)	High Risk (5-8)
<5 (normal)	0	0	1
≥5 (mild)	0	0	9
≥15 (moderate)	1	1	5
≥30 (severe)	0	1	7
Total	**1**	**2**	**22**

AHI: apnoea hypopnoea index

4.5.9 Estimates of diagnostic accuracy for all OSA (AHI ≥5)

Test characteristics of the STOP-Bang questionnaire (thresholds ≥3 and ≥5) and AHI threshold of ≥5 is shown in **Tables 20 & 21**. Prevalence of OSA for AHI≥5 was 96%. Due to a small sample size and the absence of negative sleep studies, it was not possible to calculate the specificity and NPV. The negative likelihood ratio was not estimable.

Sensitivity of the STOP-Bang questionnaire for threshold ≥3 and ≥5 was 0.958 (95% CI: 0.788; 0.999) and 0.875 (95% CI: 0.676; 0.973) respectively. PPV for the STOP-Bang questionnaire ≥3 and ≥5 was 0.958 (95% 0.788; 0.999) and 0.955 (95% CI: 0.772; 0.999) and the positive likelihoods ratio was 0.958 (95% CI: 0.882; 1.042) and 0.875 (95% CI: 0.752; 1.018) respectively (**Table 22**).

Table 20 2x2 Contingency Table for STOP-Bang threshold ≥3 and AHI ≥5

Index Test	*Reference Standard (sleep study)*		
	OSA +	**OSA -**	**Total**
STOP-Bang +	23	1	24 test positive
STOP-Bang -	1	0	1 test negative
Total	24 diseased	1 non-diseased	25

OSA: obstructive sleep apnoea

Table 21 2x2 Contingency Table for STOP-Bang threshold ≥5 and AHI ≥5

Index Test	*Reference Standard (Sleep Study)*		
	OSA +	**OSA -**	**Total**
STOP-Bang +	21	1	22 test positive
STOP-Bang -	3	0	3 test negative
Total	24 diseased	1 non-diseased	25

OSA: obstructive sleep apnoea

Table 22 Estimates of diagnostic accuracy of the STOP-Bang Questionnaire for AHI ≥5

Parameters	Formulae	Stop-Bang ≥3		Stop-Bang ≥5	
		Calculations	Results	Calculations	Results
Prevalence	$\frac{\boldsymbol{No\ of\ people\ with\ OSA}}{\boldsymbol{No\ of\ people\ assessed}}\ \boldsymbol{x\ 100}$	$\frac{24}{25}\ x\ 100$	96%	$\frac{24}{25}\ x\ 100$	96%
Sensitivity (95% CI)	$\frac{\boldsymbol{true\ positive}}{(\boldsymbol{true\ positive} + \boldsymbol{false\ negative})}\ \boldsymbol{x100}$	$\frac{23}{(23+1)}\ x100$	0.958 (0.788;0.999)	$\frac{21}{(21+3)x100}$	0.875 (0.676;0.973)
Specificity	$\frac{\boldsymbol{true\ negative}}{(\boldsymbol{false\ positive} + \boldsymbol{true\ negative})}\ \boldsymbol{x100}$	$\frac{0}{(1+0)}\ x\ 100$	0	$\frac{0}{(3+0)x100}$	0
PPV	$\frac{\boldsymbol{true\ positive}}{(\boldsymbol{true\ positive} + \boldsymbol{false\ positive})}\ \boldsymbol{x100}$	$\frac{23}{(23+1)}\ x\ 100$	0.958 (0.788;0.999)	$\frac{21}{(21+1)x100}$	0.955 (0.772;0.999)
NPV	$\frac{\boldsymbol{true\ negative}}{(\boldsymbol{false\ negative} + \boldsymbol{true\ negative})}\ \boldsymbol{x100}$	$\frac{0}{(1+0)}\ x\ 100$	0	$\frac{0}{(1+0)x100}$	0
LR+	$\frac{\boldsymbol{sensitivity}}{(\boldsymbol{100} - \boldsymbol{specificity})}$	$\frac{95.8}{(100-0)}$	0.958 (0.882;1.042)	$\frac{87.5}{(100-0)}$	0.875 (0.752;1.018)
LR-	$\frac{(\boldsymbol{100} - \boldsymbol{sensitivity})}{\boldsymbol{specificity}}$	$\frac{(100-96.8)}{0}$	NE	$\frac{(100-87.5)}{0}$	NE

PPV: positive predictive values; NPV: negative predictive values; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NE: not estimable

4.5.10 Estimates of diagnostic accuracy for moderate to severe OSA (AHI ≥15)

Test characteristics of the STOP-Bang questionnaire (threshold ≥3 and ≥5) and AHI threshold of ≥15, are shown in **Table 23 & 24**. Prevalence of OSA for AHI≥15 was 60%. Sensitivity of the STOP-Bang questionnaire (≥3 and ≥5) was 0.933 (95% CI: 0.680; 0.998) and 0.800 (95% CI:0.519; 0.957), whilst the PPV was 0.583 (95% CI:0.366; 0.779) and 0.545 (95% CI: 0.322; 0.756) respectively. Positive likelihood ratios for STOP-Bang questionnaire (threshold ≥3 and ≥5) were 0.933 (95% CI: 0.815; 1.069) and 0.8 (95% CI: 0.621; 1.030) respectively. Due to a small sample size and the absence of negative sleep studies, it was not possible to calculate the specificity and NPV. The negative likelihood ratio was not estimable (**Table 25**).

Table 23 2x2 Contingency Table for STOP-Bang threshold ≥3 and AHI ≥15

	Sleep Study		
	OSA +	**OSA -**	**Total**
STOP-Bang +	14	10	24 test positive
STOP-Bang -	1	0	1 test negative
Total	15 diseased	10 non-diseased	25

OSA: obstructive sleep apnoea

Table 24 2x2 Contingency Table for STOP-Bang threshold ≥5 and AHI ≥15

	Sleep Study		
	OSA +	**OSA -**	**Total**
STOP-Bang +	12	10	22 test positive
STOP-Bang -	3	0	3 test negative
Total	15 diseased	10 non-diseased	25

OSA: obstructive sleep apnoea

Table 25 Estimates of diagnostic accuracy for moderate to severe OSA (AHI ≥15)

Parameters	Formulae	Stop-Bang ≥3		Stop-Bang ≥5	
		Calculations	Results	Calculations	Results
Prevalence	$\frac{\textbf{No of people with OSA}}{\textbf{No of people assessed}}\ \textbf{x 100}$	$\frac{15}{25}\ x\ 100$	60%	$\frac{15}{25}\ x\ 100$	60%
Sensitivity	$\frac{\textbf{true positive}}{(\textbf{true positive} + \textbf{false negative})}\ \textbf{x100}$	$\frac{14}{(14+1)}\ x100$	0.933 (0.680; 0.998)	$\frac{12}{(12+3)x100}$	0.800 (0.519; 0.957)
Specificity	$\frac{\textbf{true negative}}{(\textbf{false positive} + \textbf{true negative})}\ \textbf{x100}$	$\frac{0}{(10+0)}\ x\ 100$	0	$\frac{0}{(10+0)x100}$	0
PPV	$\frac{\textbf{true positive}}{(\textbf{true positive} + \textbf{false positive})}\ \textbf{x100}$	$\frac{14}{(14+10)}\ x\ 100$	0.583 (0.366;0.779)	$\frac{12}{(12+10)x100}$	0.545 (0.322;0.756)
NPV	$\frac{\textbf{true negative}}{(\textbf{false negative} + \textbf{true negative})}\ \textbf{x100}$	$\frac{0}{(1+0)}\ x\ 100$	0	$\frac{0}{(3+0)x100}$	0
LR+	$\frac{\textbf{sensitivity}}{(\textbf{100} - \textbf{specificity})}$	$\frac{0.933}{(100-0)}$	0.933 (0.815;1.069)	$\frac{0.8}{(100-0)}$	0.800 (0.621;1.030)
LR-	$\frac{(\textbf{100} - \textbf{sensitivity})}{\textbf{specificity}}$	$\frac{(100-0.933)}{0}$	NE	$\frac{(100-0.8)}{0}$	NE

PPV: positive predictive values; NPV: negative predictive values; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NE: not estimable

4.5.11 Estimates of diagnostic accuracy for severe OSA (AHI ≥30)

Test characteristics of the STOP-Bang questionnaire (≥3 and ≥5) and AHI threshold of ≥30, are shown in **Tables 26 & 27**. Prevalence for AHI≥30 was 32%. Sensitivity of the STOP-Bang questionnaire (≥3 and ≥5) was 1.000 (95% CI: 0.631; 1.000) and 0.778 (95% CI: 0.400; 0.972) and the NPV was 1.000 (95% CI: 0.207; 1.000) and 0.333 (95% CI: 0.008; 0.906), respectively. Specificity of the STOP-Bang questionnaire (≥3 and ≥5) was 0.059 (95% CI: 0.002; 0.287) and 0.063 (95% CI: 0.002; 0.302) and the PPV was 0.333 (95% CI: 0.156; 0.553) and 0.318 (95% CI:0.139; 0.549) respectively (**Table 28 & 29**).

Table 26 2x2 Contingency Table for STOP-Bang ≥3 and AHI ≥30

	Sleep Study		
	OSA +	**OSA -**	**Total**
STOP-Bang +	8	16	24 test positive
STOP-Bang -	0	1	1 test negative
Total	8 diseased	17 non-diseased	25

OSA: obstructive sleep apnoea

Table 27 2x2 Contingency Table for STOP-Bang ≥5 and AHI ≥30

	Sleep Study		
	OSA +	**OSA -**	**Total**
STOP-Bang +	7	15	22 test positive
STOP-Bang -	1	2	3 test negative
Total	8 diseased	17 non-diseased	25

OSA: obstructive sleep apnoea

Table 28 Estimates of diagnostic accuracy for severe OSA (AHI ≥30)

Parameters	Formulae	Stop-Bang ≥3		Stop-Bang ≥5	
		Calculations	Results	Calculations	Results
Prevalence	$\frac{\boldsymbol{No\ of\ people\ with\ OSA}}{\boldsymbol{No\ of\ people\ assessed}}\ \boldsymbol{x\ 100}$	$\frac{8}{25}\ x\ 100$	32%	$\frac{8}{25}\ x\ 100$	32%
Sensitivity	$\frac{\boldsymbol{true\ positive}}{(\boldsymbol{true\ positive} + \boldsymbol{false\ negative})}\ \boldsymbol{x100}$	$\frac{8}{(8+0)}\ x100$	1.000 (0.631;1.000)	$\frac{7}{(7+1)x100}$	0.778 (0.400;0.972)
Specificity	$\frac{\boldsymbol{true\ negative}}{(\boldsymbol{false\ positive} + \boldsymbol{true\ negative})}\ \boldsymbol{x100}$	$\frac{1}{(16+1)}\ x\ 100$	0.059 (0.002;0.287)	$\frac{2}{(15+2)x100}$	0.063 (0.002;0.302)
PPV	$\frac{\boldsymbol{true\ positive}}{(\boldsymbol{true\ positive} + \boldsymbol{false\ positive})}\ \boldsymbol{x100}$	$\frac{8}{(8+16)}\ x\ 100$	0.333 (0.156;0.553)	$\frac{7}{(7+15)x100}$	0.318 (0.139;0.549
NPV	$\frac{\boldsymbol{true\ negative}}{(\boldsymbol{false\ negative} + \boldsymbol{true\ negative})}\ \boldsymbol{x100}$	$\frac{1}{(0+1)}\ x\ 100$	1.000 (0.207; 1.000)	$\frac{2}{(1+2)x100}$	0.333 (0.008;0.906)
LR+	$\frac{\boldsymbol{sensitivity}}{(\boldsymbol{100} - \boldsymbol{specificity})}$	$\frac{1.0}{(100-0.059)}$	1.063 (0.943;1.197)	$\frac{0.778}{(100-0.063)}$	0.830 (0.572;1.203)
LR-	$\frac{(\boldsymbol{100} - \boldsymbol{sensitivity})}{\boldsymbol{specificity}}$	$\frac{(100-1.0)}{0.059}$	0	$\frac{(100-0.778)}{0.063}$	3.556 (0.372;33.980)

PPV: positive predictive values; NPV: negative predictive values; LR+: positive likelihood ratio; LR-: negative likelihood ratio

Table 29 Summary of Predictive values of STOP-Bang (≥3 and ≥5) and AHI ≥5, 15 & 30

	STOP-Bang Threshold ≥3			STOP-Bang Threshold ≥5		
Criteria	**AHI≥5**	**AHI≥15**	**AHI≥30**	**AHI≥5**	**AHI≥15**	**AHI≥30**
Prevalence	96%	60%	32%	96%	60%	32%
Sensitivity	0.958 (0.788; 0.999)	0.933 (0.680; 0.998)	1.000 (0.631;1)	0.875 (0.676; 0.973)	0.800 (0.519; 0.957)	0.778 (0.400;0.972)
Specificity	0	0	0.059 (0.002;0.287)	0	0	0.063 (0.002;0.302)
PPV	0.958 (0.788; 0.999)	0.583 (0.366;0.779)	0.333 (0.156;0.553)	0.955 (0.772; 0.999)	0.545 (0.322;0.756)	0.318 (0.139;0.549
NPV	0	0	1.000 (0.207; 1)	0	0	0.333 (0.008;0.906)
LR+	0.958 (0.882; 1.042)	0.933 (0.815;1.069)	1.063 (0.943;1.197)	0.875 (0.752; 1.018)	0.800 (0.621;1.030)	0.830 (0.572;1.203)
LR-	NE	NE	0	NE	NE	3.556 (0.372;33.980)

PPV: positive predictive values; NPV: negative predictive values; LR+: positive likelihood ratio; LR-: negative likelihood ratio; NE: not estimable

4.6 Discussion

The objective of this study was to evaluate prospectively the ability of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of stable CHF.

Findings from this study demonstrated a high prevalence of OSA (AHI>5) in this study population. For a STOP-Bang questionnaire threshold of ≥3, sensitivity was ≥93.3%, whilst for a questionnaire threshold of ≥5, sensitivity was >77.8%. A decline in PPV was noted as disease severity increased. Consistent with findings from the systematic review and meta-analysis described in Chapter 3, an increase in questionnaire threshold was associated with a reduction in questionnaire sensitivity.

Due to a small sample size and absence of negative sleep studies, it was not possible to determine the questionnaire specificity or negative predictive values. Although a high sensitivity resonates with previous validation studies and systematic reviews of the STOP-Bang questionnaire (Abrishami, Khajehdehi & Chung, 2010; Chiu *et al.,* 2017; Nagappa *et al.*, 2015), a small sample size with possible impact on confidence intervals and precision of the findings, limits any firm conclusion from the study results.

Findings from this study are unlikely to be generalisable to a stable HF population in an outpatient or primary care set-up where the use of OSA screening questionnaires is likely to be useful. Firstly, prevalence in a sleep clinic cohort is expected to be higher than in an unselected CHF cohort, due to clinical screening and high pre-test probability. Prevalence of OSA (AHI≥15) in the study population was 60%, whilst prevalence of OSA (AHI≥15) in CHF reported from the SchlaHF registry was 46% (Artz *et al*., 2016). Consequently, predictive values which are dependent on prevalence, will not be generalisable to any other population outside of the sleep clinic population, further strengthening the need for validation of screening questionnaires in clinically similar cohorts. Secondly, due to pre-screening by clinical teams, there is likely to be a degree of selection bias in this sleep clinic cohort. Interestingly, a lack of negative sleep studies in the study population, suggests that HF clinicians are referring appropriate at-risk patients for further investigation and treatment.

Additionally, it is likely that high pre-test probability resulted in patients with more severe OSA being referred and investigated and less so those with milder forms of OSA, therefore introducing a spectrum effect.

In an ideal situation, to determine the true accuracy of the STOP-Bang questionnaire in the CHF population, the diagnostic validation should be completed in an unselected, stable CHF population utilising modern validation methodology. Predictive values calculated for an unselected CHF population will give a far more accurate indication of how the questionnaire will perform in clinical practice. Due to a large sample size requirement in an unselected CHF population, resource implications and a significant impact on scoring and reporting capacity in an already overstretched local sleep service, it was not feasible to conduct the validation of the STOP-Bang questionnaire in an unselected CHF population.

There were several strengths and limitations associated with this study.

Recruitment proved challenging from the outset of the study due to low referral of CHF patients who met the study selection criteria. It is likely that referral numbers were influenced by clinical lack of awareness, low clinical priority, or perceived lack of prognostic benefit due to lack of outcome data for the treatment of OSA in CHF. Recruitment challenges impacted on the sample size and in conjunction with the absence of negative sleep studies, it was not possible to calculate the specificity, NPV and negative likelihood ratio for most of the AHI thresholds.

In response to the low recruitment, eligibility criteria were reviewed and adapted. Whilst still ensuring stability from a CHF perspective, the period for imaging was increased from 12 months to 24 months.

While the Sleep Disorders Service is the main department for the investigation of SDB and other sleep related disorders, the Respiratory Physiology Unit provides a limited service for the investigation of SDB. However, due to differences in local clinical practice associated with scoring criteria and pre-screening with pulse oximetry, it was not possible to expand recruitment to this service.

The original sample size calculation was based on an estimated prevalence of 50%. On review, it appeared that the prevalence of OSA in the study population was >90%. Recalculation of the sample size with a prevalence of 90% adjusted the required sample to 105 participants (94 with OSA and 11 without OSA). Despite the measures to improve recruitment, it was not possible to achieve the target sample size with possible impact on confidence intervals and precision of the findings.

Study quality and risk of bias were assessed in the patient selection, index text, reference standard and flow and timing domains.

In the patient selection domain, this study utilised a consecutive sample of participants that met the eligibility criteria. Although no inappropriate exclusions were planned, it was not possible to include participants who did not communicate confidently in English. High pre-test probability and pre-screening by clinical teams have likely introduced a degree of selection bias and spectrum effect. Therefore, there was relatively high risk of bias in the patient selection domain.

Risk of bias in the index test domain was low. The STOP-Bang questionnaire (index test) was completed prior to the patient undertaking the home sleep study (reference standard) and was interpreted by the researcher without the knowledge of the home sleep study. The STOP-Bang questionnaire thresholds (low risk 0-2; intermediate risk 3-4 and high risk 5-8) were specified prior to conducting the study. In addition, there were no concerns about the conduct or interpretation of the index text in relation to the review question.

The reference standard selected for this study was level 3 RP, the standard method used in the Sleep Disorders Service. Because the index text was completed by the researcher, the sleep medicine technicians were blinded to the index test at the time of sleep study scoring and analyses, reducing the risk of observer bias. The target condition (OSA) as defined by the RP matched the study question, therefore there were no concerns with regards to applicability. In addition, the threshold for the diagnosis of OSA was pre-determined as outlined by the international Classification of Sleep Disorders, 3rd edition (ICSD3) (Sateia, 2014).

Furthermore, the sleep studies were scored by a small number of technologists, potentially reducing inter observer variability. Three sleep studies were reviewed by a senior sleep medicine technologist. Due to reporting backlog and clinical pressure, it was not possible to re-score some of the sleep studies to adequately assess interobserver variability in scoring. Due to reporting back log, two participants were tested using the WatchPAT™300 system. Using two devices as the reference standard may introduce verification bias and the possibility of misclassification and overestimation of sensitivity and specificity.

There was low risk of bias in the flow and timing domain. The index test was completed on the day, prior to the home sleep study. The short time interval between the index test and reference standard did not allow time for any clinical interventions between the index test and the reference standard.

4.7 Conclusion

Findings from this study indicated a high sensitivity of the STOP-Bang questionnaire to detect OSA in a sleep clinic population with co-existing CHF, however, precision of these findings were limited by a small sample size. Due to differences in prevalence, risk of selection bias and spectrum effect, validation in a sleep clinic population is unlikely to reflect the true performance of the STOP-Bang questionnaire in a stable CHF population. Therefore, to determine the true utility and accuracy of the STOP-Bang questionnaire, diagnostic validation is required in an unselected, stable CHF population.

Chapter 5 of this thesis will explore barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives.

5

Perceived Barriers to and enablers of the Diagnosis and Treatment of Obstructive Sleep Apnoea in Chronic Heart Failure: Qualitative Analysis of Patients' and Clinicians' Interviews

5.1 Introduction

Multiple, multi-faceted barriers to the diagnosis and treatment of OSA have been associated with both clinicians and patients. External barriers are often embedded in the larger health care context, with many of these barriers understood to exist within the belief systems and behaviour of the health care clinician.

Although health care improvement can be facilitated at different levels of the health care system and through the modification of clinical behaviour, many earlier studies investigating barriers to, and enablers of evidence-based practice or clinical quality interventions were limited by the lack of theoretically informed solutions to the barriers (Rothman, 2004; French e*t al.,* 2012; Cane *et al.,* 2012). In response to these limitations, theoretical frameworks such as the Theoretical Domain Framework (TDF), can be utilised to investigate barriers and enablers. Informed by psychological and organisational theory, the TDF consists of 14 domains and 84 constructs specifically developed to address difficulties enacting behaviour change in a variety of settings. Designed to be

utilised by any discipline which needs to identity barriers and enablers to support behaviour change, this integrative framework can be employed to help apply theoretical approaches to interventions aimed at facilitating behavioural change (Lipworth, Taylor & Braithwaite, 2013; Phillips *et al.,* 2015).

In this thesis, the TDF was selected to inform the investigation of barriers to, and enablers associated with, the diagnosis and treatment of OSA in CHF because of its broad perspective and theoretical underpinning. It provides a systematic method by which to identify the most significant barriers and enablers associated with the diagnosis and treatment of OSA.

Exploration of both clinicians and patients' perceptions of and attitudes towards various clinical quality initiatives have been captured within a substantial body of qualitative literature within the sphere of a growing implementation science. Malaweera (2015) investigated potential barriers to the diagnosis and treatment of SDB in hospital care and in primary care. Key barriers reported by hospital clinicians included lack of awareness of SDB, lack of effective screening tools, low clinical priority, time burden, limited access to sleep studies, and limited availability of resources. Furthermore, lack or responsibility for patients with SDB, and poor patient compliance with CPAP treatment were further reported. Survey data from GPs reported GP beliefs, patient factors and poor access to services as barriers, whilst patient data reported patient expectations and healthcare factors as key barriers.

Further studies have sought to capture issues with implementation. Luyster *et al.* (2016) explored barriers and motivators to the use of CPAP from patient and partner perspectives. Findings reported discomfort associated with mask use and inconvenience of travelling as key barriers, whilst symptomatic improvement and partner support as key motivators. This is echoed by Bakhai *et al.* (2017), reporting a lack of clinician knowledge of guidelines, lack of reminders to use the screening tool, the time burden associated with using a screening tool and discussing findings with patients. Patient barriers included lack of knowledge, lack of transport and cost of sleep studies.

More recently Ye *et al.* (2021) reported key barriers to the diagnosis of OSA as lack of attention to symptoms, negative framing of diagnosis and subsequent treatment, and poor organisation of health services. The study reported that the partners role in care seeking, patients own role in care seeking and clinicians recognising the risk of OSA, as the key facilitators to the diagnosis and treatment of OSA.

Barriers are often exacerbated by a lack of a strong evidence base or lack of effective implementation of existing evidence (Lipworth, Taylor & Braithwaite, 2013). The use of CPAP for the treatment of clinically significant OSA in the general population has been clearly established and supported by clinical guidelines (NICE 2008; NICE, 2021). Due to differences between the CHF population and the general population, particularly in relation to EDS, current evidence from the SAVE trial has not shown CV hospitalisation or mortality benefit when treating OSA with CPAP in CHF. However, it did show an improvement in quality of life, reduction in depression and improvement in workplace productivity (McEvoy *et al.,* 2016).

There is an ongoing need to understand the barriers associated with the delivery of optimal patient care (Baker *et al.,* 2010). Therefore, to explore and understand the factors associated with the diagnosis and treatment of OSA in CHF from clinicians' and patients' perspectives, the objective of the qualitative component of this study was to identify barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives.

5.2 Aim

The aim of this chapter is to present the methods, analysis, and findings of the qualitative component of this thesis. CHF patients' and clinicians' perceptions of the barriers and enablers associated with the diagnosis and treatment of OSA in CHF were explored through emergent themes developed through thematic analysis of the interview data.

5.3 Methods

5.3.1 Study Design and Setting

A qualitative study design was utilised to elicit and describe perceived barriers and enablers associated with the diagnosis and treatment of OSA in CHF from both patients' and clinicians' accounts. Designed as two studies, both studies utilised semi-structured interviews for data collection, and thematic analysis for data analysis. Full details of regulatory approval and ethical considerations were discussed in Chapter 3 of this thesis.

5.3.2 Sampling

For the patient interview study, consecutive patients referred to the sleep disorders service for the assessment of possible OSA, and who met the selection criteria (see section 5.3.2)**,** were invited to participate in the diagnostic validation study and the patient interview study. Of the 25 patients who consented to participate in the diagnostic validation study, 10 patients opted-in and consented to participate in the patient interview study.

For the clinician interview study, purposive sampling was utilised to recruit 20 participants consisting of doctors, nurses and pharmacists with an interest and expertise in the active management of patients with CHF in England, Scotland, and Wales.

Key characteristics of the sample were:

- Clinicians who actively manage patients with CHF, and
- Employed by an NHS organisation.

To allow variability across the data set, clinicians were included from

- both primary and secondary care,
- different clinical professions (doctors, nurses, and pharmacists) and
- different geographical regions.

5.3.3 Sample Size and Saturation

The proposed sample sizes for the patient and clinician interview studies were between 20-30 participants respectively, however, recruitment would continue until data saturation was achieved.

The quality and trustworthiness of a qualitative study is often reflected in the size and composition of the study sample (Spencer *et al.,* 2003). However, to support the depth of the analysis, samples in qualitative research tend to be relatively small, but should be large enough to create a rich understanding of the issues whilst still small enough to allow in-depth analysis of the data (Sandelowski, 1996; Baker & Edwards, 2012).

Dependent on the study nature, study design, and data quality, it was understood that the richer data each participant provides, the fewer participants were required (Morse, 2000). However, there were differing views on the number of participants required for a qualitative study. Britten (1995) and Ritchie, Lewis, and Elam (2003) proposed between 50-60 participant interviews for larger studies. In contrast, Green and Thorogood (2004) considered that participant numbers which exceeded 20 participants, were likely to yield limited new information. Not specifying a specific sample size, Lincoln, and Guba (1985) suggested that recruitment should continue until no new themes emerged from the data. In addition, Malterud, Siersma and Guassora (2015) proposed that the greater the quality of the sample provided, the smaller the sample could be.

With origins in grounded theory, saturation is a concept that refers to the threshold where no new data or new themes emerge from the data (Glaser & Straus, 1967; Fusch & Ness, 2015). Based on two main principles it firstly suggests that an *a priori* initial analysis sample should be specified and secondly, a stopping criterion should be specified (Vasileiou *et al.,* 2018). Interviews analysed by Guest, Bunce, and Johnson (2006) found that saturation of themes were reached by the 12th interview, whilst Francis *et al.* (2010) reported data saturation at the 17th interview. Furthermore, Hennink, Kaser and

Marconi (2017) showed that code saturation is achieved after 9 interviews, however, it was suggested that for studies with more heterogeneous samples, a larger sample would be required to achieve saturation.

5.3.4 Procedure

5.3.4.1 Patient Interview Study

Consecutive patients who attended the Sleep Disorders Service at the Leicester General Hospital for the assessment of suspected OSA and who met the selection criteria, were invited to participate in the study. Participants were offered the option to opt-in or opt-out of the Interview Study.

A letter of invitation and patient information leaflet were sent to the patient with their appointment letter **(Appendix 19 & Appendix 20**). Informed consent was received by the chief investigator prior to participants undertaking any study related activities **(Appendix 21).** Consent to participate in the study and for interviews to be audio recorded were reaffirmed prior to conducting the interview. Interviews were conducted in a quiet, private room at the Leicester General Hospital or via telephone and lasted roughly 30-45 minutes. Although virtual telephone interviews are sometimes viewed as a 'poor substitute' for face-to-face interviews, it provided a practical alternative and optimal use of resources (time).

Interviews were scheduled at the convenience of the participants and a debriefing session was offered following the interview in the format of a general discussion, allowing the participant the chance to ask questions pertaining to the research **(Appendix 23).** A password-protected, digital audio voice recorder (Philips VoiceTracer Audio Recorder DVT 2710) was used to record the interviews. All interviews were transcribed verbatim by transcription experts, Armstrong Transcription.

Screening, eligibility assessment and informed consent of participants were discussed in Chapter 4.

5.3.4.2 Clinician Interview Study

A purposively selected group of doctors, nurses and pharmacists with an interest and expertise in the active management of patients with CHF in England, Scotland and Wales were invited to participate in the study. Our approach was pragmatic, influenced by time limits relating to completing the study and the number of HF clinicians who agreed to participate in the study.

Study participants who met the eligibility criteria, were invited to participate via e-mail communication. The invitation e-mail (**Appendix 24)** gave the rationale for the study, the required time commitment, and assurances that all responses would be anonymised. The participant information sheet **(Appendix 25)** and a reply slip **(Appendix 26)** were attached to the e-email.

Participants were required to give consent prior to the interview process. Written and verbal versions of the participant information and informed consent **(Appendix 27)** were presented to the participants detailing no less than

- the exact nature of the study,
- the implications and constraints of the protocol,
- any risks involved in taking part.

It clearly stated that the participant is free to withdraw from the study at any time, with no obligation to give the reason for withdrawal.

Participants were allowed a minimum of 24 hours to consider the study information, and the opportunity to question the Investigator or other independent parties to decide whether they want to participate in the study. Each participant personally signed and dated the latest approved version of the informed consent form before the interview was conducted. On completion of the interview, a debriefing session was offered in the format of a general discussion and allowing the participant the chance to ask questions pertaining to the research **(Appendix 28)**.

Informed consent was received by the Chief Investigator as detailed in the study protocol. The original signed form was retained at the study site within the

Trial Master File (TMF) and a copy of the signed Informed Consent was given to participants. All participants who consented to participate in the study, were interviewed.

Similarly, clinician interviews were carried out in a quiet, private room at the participant's usual place of work or via telephone and lasted no more than 45 minutes. Utilisation of telephone interviews provided a practical alternative to face-to-face interviews and allowed the researcher to interview participants in various geographical areas of the UK, without the requirement to travel.

The interviews were recorded using a password-protected, digital audio voice recorder (Philips VoiceTracer Audio Recorder DVT 2710) and all interviews were transcribed verbatim by transcription experts, Armstrong Transcription. Once transcribed, all interviews were listened to and check for accuracy.

5.3.5 Data Collection

To explore participant experiences and perspectives on the barriers and enablers associated with the diagnosis and treatment of OSA in CHF, semi-structured interviews were utilised as the primary method of data collection in both the patient and clinician interview studies. Interview schedules were developed and utilised to guide the semi-structured interviews. Due to the contextual nature of the interview questions, the researcher had the flexibility to adapt the wording and the order of questions during the interview, therefore giving participants the opportunity to discuss issues that was not represented in the interview schedule (Braun & Clarke, 2006).

The patient interview schedule focused on patients' perceptions and knowledge of OSA, their referral and treatment experience **(Appendix 29).** Informed by literature and developed in conjunction with academic supervisors, the patient interview guide consisted mostly of open-ended questions (for example: *What do you understand about OSA?)*

To identify barriers and enablers relevant to the diagnosis and treatment of OSA in CHF, the TDF informed the development of the clinician interview

schedule and were used to frame the analysis and interpretation of the study findings (Michie *et al*. 2005). (**Appendix 30**). The relevant TDF domains, definitions, constructs, and example interview questions are summarised in **Appendix 31**.

5.3.6 Data Analysis

Thematic analysis was utilised to analyse the interview transcripts guided by the six steps outlined by Braun and Clarke (2006) (**Table 30**). Interview data were organised in a systematic and meaningful manner through open coding which meant that codes were developed from the data and modified as the coding process progressed, rather than using pre-set codes. Following initial coding of interview transcripts, common features were categorised together to form preliminary themes. Because several codes might have been relevant to the same preliminary theme, these were collated into the same preliminary theme. The preliminary themes were then organised into broader themes which formed the subordinate themes. Commonalities in the subordinate themes were categorised together to elicit the overarching superordinate themes. QRS International's NVivo 12 qualitative data analysis software were utilised to facilitate data analysis.

Table 30 Step wise approach to Thematic Analysis

Phase	Actions
Familiarising yourself with the data	Following transcription of data, all anonymised transcripts were read and re-read. Initial ideas were noted.
Generating initial codes	Interesting features of the data were coded, and data were collated, relevant to each code. The TDF formed the initial coding structure for the clinician interviews.
Searching for themes	It was checked that the themes work in relation to the coded extracts. A thematic map of analysis was generated. Belief statements were generated.
Reviewing themes	Themes were checked and thematic map updated.
Defining and naming themes	Ongoing analysis supported the refinement of each theme. Definitions and names of each theme were generated.
Producing a report	Final analysis and report completed.

5.3.7 Reflexivity

As a HF specialist nurse with extensive experience in CV nursing and an interest in SDB in this context, my clinical experience and interest provided me with extensive knowledge of the clinical area under investigation. My clinical role as a HF specialist nurse positioned me in the role as an 'insider' providing me with specific advantages as highlighted by Kacen and Chaitin (2006) and Padgett (2008). Firstly, because the research topic is familiar to me, I could rely on prior knowledge with an understanding of participant responses and reactions. My role as HF specialist nurse facilitated recruitment of patient and clinician participants whilst helping me to gain trust and achieve rapport with participants.

Furthermore, my clinical experience and prior knowledge of CHF and OSA affected both the data collection and data analysis of the interview studies when approaching the study with some knowledge and as such having some intuition and insight about the topic under investigation. As a result of my position as an 'insider', I had to constantly focus and reflect on the impact of my presence and how it shaped the conversation with participants.

Despite the benefits of my positionality and familiarity with the area under investigation and my dual role as researcher and HF specialist nurse, there was a risk of blurred boundaries and imposing my own values, beliefs and perceptions as a researcher and projection of my personal biases. Furthermore, my familiarity with the topic area may have run the risk of participants withholding information because they assumed that it may have been obvious to me.

To ensure quality and rigour in the qualitative component of this thesis, I employed reflexivity as the key strategy for quality control in both the patient and clinician interview studies. Reflexivity was used through a process of ongoing internal dialogue and self-evaluation of my positionality, requiring an active acknowledgement and recognition of how my position may affect the various steps in the research process and subsequent outcome. Because of the

active role of the researcher in all aspects of the qualitative research process, I had to consider my social position, personal experiences, and beliefs, which may have an impact on various aspects of the research process and therefore requiring specific strategies to maximise the benefits of my familiarity with the area of research, whilst minimising potential negative impact (Berger, 2013).

Reflexivity was crucial throughout all stages of the research process. For example, being reflexive during the interview process helped me identify which questions or content I might emphasise or shy away from whilst developing an awareness of my own reactions, thoughts, and emotions I experienced in response to the interviews. During the analysis stage, I was conscious of the possibility of 'unconscious editing' in response to my own sensitivities or beliefs related to the possible barriers to the diagnosis and treatment of OSA in CHF which allowed stronger engagement with the data and subsequent analysis.

5.4 Results of Patient Interview Study

5.4.1 Participant characteristics

Ten CHF patients consented to participate in the patient interview study. All participants were White-British of whom 7 were male and 3 were female. Half of the participants were older than 70 years of age (range 40-77 years). Patient characteristics are summarised in **Table 31**.

Table 31 Participant characteristics (Patients)

Participant	Gender	Age	Ethnicity
1	Male	77	White-British
2	Female	71	White-British
3	Male	40	White-British
4	Female	57	White-British
5	Male	76	White-British
6	Male	72	White-British
7	Male	70	White-British
8	Male	55	White-British
9	Female	60	White-British
10	Male	55	White-British

5.4.2 Findings

Based on the qualitative data provided by patients, two superordinate and six subordinate themes were identified (**Table 32**). The superordinate themes included "incomplete understanding of OSA and intolerance to treatment" and "poor access to sleep services ".

Table 32 Overview of Themes

Superordinate Themes	Sub-ordinate themes	*n*=10
Theme 1 **Incomplete understanding of OSA and tolerance of treatment** *(Internal Domain)*	Poor recognition of symptoms	8
	Lack of understanding	8
	Insufficient information provided by HCP	10
	Treatment poorly tolerated	10
Theme 2 **Poor access to sleep services** *(External Domain)*	Long waiting times	9
	Perceived lack of resources	4

HCP: health care professional

5.4.2.1 Theme 1: Incomplete understanding of OSA and tolerance to treatment

5.4.2.1.1 Poor recognition of symptoms

Participants reported absence of typical OSA symptoms as a key barrier. Apart from a single report of EDS, the most frequently reported symptom was fatigue. Participants stated that despite a perceived good night's sleep, they wake up feeling tired in the morning or just feeling tired all the time.

I told the community heart nurse that although I seemed to sleep all the way through the night, I was still very tired in the morning. It was very hard to get up and I'd fall asleep during the day. [Patient 10, male]

Symptoms wise, before all the trouble, I was going to the toilet in the night, three and four times, two, three or four times, you know, each night, waking up. Well, since I've had this mask which has been seven or eight weeks, if I've got up twice that's all there is to it really, I'm getting a good night's sleep. [Patient 7, male]

Less frequently reported symptoms were headaches, forgetfulness, nocturia, poor sleep and altered mood. Nocturia is commonly reported in patients with CHF due to their clinical condition and diuretic therapy. Due to an overlap of symptoms between CHF and OSA, nocturia is rarely recognised as a symptom of OSA in patients with co-existing CHF. Furthermore, many symptoms are perceived as part of the patient's CHF symptom burden, rather than a separate condition, making the recognition of OSA challenging. As such, many participants reported that they thought their symptoms were related to CHF.

> But it's just lately that I'm getting more and more tired. I just thought it was my heart. I just thought it was a condition that I'm living with. [Patient 2, female]

Reports of breath holding and gasping for air were often the only symptoms reported by patients' partners during clinical consultation, therefore emphasizing the importance of partners in the detection and reporting of OSA symptoms.

> *Then my husband started telling me that I wasn't breathing for a considerable amount of time.*
> *[Patient 4, female]*

> *It all started, probably last Christmas, my wife kept waking up and couldn't hear me breathing. She sort of said I was holding my breath then all of a sudden I'd come out with a gasp.*
> *[Patient 7, male]*

However, one participant reported that her partner's input and report was still dismissed by her doctor due to the participant 'not fitting the criteria' for referral, despite a report of significant episodes of breath holding at night, resulting in a delay in the diagnosis and treatment of OSA.

> *Because I'd been to the doctor a couple of times with it, and because I wasn't fitting the criteria, he didn't seem to think I should be referred on. That's why my husband ended up doing a recording of it, so that we could go to the doctor and say, "Listen to this. She has got it." I think they need to listen to the partners more than you, to be honest, because they are the ones that hear it. [Patient 4, female]*

Despite the symptoms described above, most participants did not make the connection between their symptoms and a sleep disorder. They did not perceive that they were dealing with another health condition or that there was "a problem" in the first place.

> *I've got none of the symptoms other than the fact that the wife reported that I was not breathing, I was stopping breathing in the night," and that's pretty much it from there. [Patient 8, male]*
>
> *I didn't realise there was actually a problem. Until yesterday, well yesterday confirmed it, but certainly until the heart nurse went through the questionnaire, I didn't realise it was a problem at all. [Patient 10, male]*

Negative framing of OSA as a clinical condition and the perception of stigma related to OSA due to its association with obesity, were reported by participants. Consequent embarrassment or denial may delay reporting, diagnosis, and treatment.

> *Embarrassed that I'd got it. And I think because I'd put some weight on I think pushing that to the back of my mind, but also thinking back to when my husband started to say it, I wasn't that big. The past couple of years I have gained the weight. I wasn't as big as I am now, so I actually to think it wasn't necessarily the weight, whether it's genetic or not I don't know. [Patient 4, female]*
>
> *I thought it was just for people who were overweight because that's all they keep telling you all the time. [Patient 9, female]*

A dearth of typical OSA symptoms, overlap of symptoms, and negative framing of OSA were reported by patient participants as barriers to the detection of OSA and timely seeking of care. The role and input of partners were a strong enabler to the reporting of symptoms and detection of OSA.

5.4.2.1.2 Lack of understanding

A further barrier to the diagnosis of OSA was a reported lack of understanding relating to OSA as a health condition, the investigation and CPAP treatment. Some participants stated that they have never heard of the condition OSA.

> *I had never heard of sleep apnoea and its consequence; I just went along with it. [Patient 5, male)*
>
> *So, I don't know how the machine works on that, I don't know – does it hold your tongue in place? [Patient 2, female]*

Lack of information and subsequent understanding about what the investigation for OSA entailed were described as anxiety and fear provoking with a possible impact on some participants' decisions to attend the sleep study appointment.

> *I had no idea. I didn't know what they did. I didn't even know – I thought they may be kept you in. I was dead scared. I thought, "Please don't tell me I've got to sleep in the lab." I had visions of being stuck in some room for the night. I was quite relieved when they gave me a machine. [Patient 2, female]*
>
> *"I think to be perfectly honest; I was in dark about what it was going to be. Yeah, I did not really, I don't know. If I had to be perfectly honest, I thought …. would I come? That cross my mind. And I don't know whether I realised the seriousness of the problem or anything like that, because it hasn't affected me for some time now." [Patient 1, male]*

Participants reported that their awareness of other individuals with OSA expanded their understanding of OSA and the relevant treatment.

> *I'd already come across somebody who had it. So, I knew what the potential was. [Patient 10, male]*
>
> *My sister has to wear a machine to go to bed, so I'd heard about it then. But to be honest that's probably the first time I took any notice of it. [Patient 4, female]*

Furthermore, some participants did not perceive OSA as a serious condition and therefore might consider OSA as a low priority compared to their diagnosis of CHF.

> *I'm still unclear at the moment, which in a way makes me think, "Well it's not threatening, it can't be life threatening, because if it was life threatening it would be a different story. So, it's just, we'll get to it when we get to it." [Patient 3, male)*

5.4.2.1.3 Insufficient information provided by the health care professional

In addition to participants' perceived lack of understanding of the risk, diagnosis and treatment of OSA, most participants reported insufficient information provided by their clinicians.

> *I didn't really know to be honest. I didn't really know because I've never been before. I've never seen it before. She just said that it monitors how you sleep, how you sleep, and she thought it might be a good idea to go to see if I did have it. I didn't even know – I thought they may be kept you in. [Patient 2, female]*

I think the information was very, very sparse. [Patient 8, male]

I had no idea what the situation was, what it was I was being referred for. As I said, I had never heard of sleep apnoea and its consequence, I just went along with it. [Patient 5, male]

Not only did participants report limited information at the time of referral, but also when they attended for the sleep study, which was often their first contact with the sleep disorders service.

Not really, even when I went down to the sleep disorder clinic, all they did was show me how to use the test equipment, so I still don't really know much about it. [Patient 3, male]

In contrast, once the investigation was completed and participants attended for their results at the sleep disorders clinic, most of the explanation and information were provided at the follow-up appointment. Participants stated that more detailed information provided at the time of referral would be helpful and is likely to influence their decision to proceed with the sleep service appointment and investigation with a resultant reduction of their anxiety and fear.

"A little bit more information at the beginning, but no, once you've had your test done with the sleep thing monitoring you and you go back to see them, you get all your information there." [Patient 4, female]

Despite a lack of understanding and information provided by their clinicians, most participants reported having confidence in their relevant HCPs.

Well, at the time I didn't know what it was for, and I had built up a relationship with the consultant in which I had and have absolute confidence in him and in consequence, when he said, "I ought to refer you to the Sleep Clinic," I wasn't of a mind to question why. I just thought, "Well, he's sent me for heart scans, he's sent me for kidney scans, I've had this, that and the other," and this was just another one. [Patient 5, male]

Participants' decisions to go ahead with the referral and investigation of suspected OSA were likely to be influenced by their expectations of treatment outcome. Participants reported that an impact on their CHF, longevity, reduced risk of developing other conditions and symptomatic improvement as their motivation to be investigated and treated.

I am going to try it, because as I understand it sleep apnoea is not a good thing with somebody with a heart condition, and this is the recommended way forward. All I can do is go on with this, be measured for it, and give it a go. [Patient 6, male]

It's better off being kept alive and it's the same as medication, you don't really want to take medication every day, but it's just going to be a part and parcel of the illnesses that I've accrued from this. [Patient 9, female]

It seems to me that sleep is interrupted, and for reasons that I do not know and probably wouldn't understand this can cause heart attacks or stroke or something and it generally not a good thing and something should be done about it. [Patient 6, male]

I'm hoping not be so tired. I'm hoping I'm going to wake up and feel not as wiped out. [Patient 2, female]

I feel a lot, as I've woke up this morning, like every, morning I feel a lot livelier than I did. [Patient 7, male]

Despite limited information reported at time of referral and during the first visit to the sleep service, participants felt that detailed explanations were given when they attended for their results. They felt that information earlier on in the process would have aided their understanding and facilitated an informed decision about the investigation and treatment. Key enablers to the diagnosis and treatment of OSA were reported as high confidence in their referring clinician and their perceived outcome expectancy.

5.4.2.1.4 Treatment poorly tolerated

Most participants reported that they did not look forward to the CPAP treatment. For some it was the physical discomfort of wearing it, whilst others reported fear, shock, feeling anxious and embarrassment about using the CPAP mask.

"The thought of going to bed wearing an oxygen mask is not very appealing. That would make me anxious, because even when I had the test, I had to wear all of that, that made me very anxious as well, knowing that I had to have six hours' worth of sleep, I was conscious of the six hours, so that's now in my mindset. But if I have got it this will progressively get worse, to go to bed and sleep every night with an oxygen mask is not very appealing. You just want to go to bed and be free." [Patient 3, male]

"You're going to have to be on your mask for the rest of your life." Well, it was a bit of a shock to be honest with you. [Patient 7, male]

"These are the different sorts of masks you can have." The full face one that looks like Darth Vader to a little mask over your nose and lips. It's not very glamorous." [Patient 9, female]

Participants reported physical discomfort and a feeling of claustrophobia when wearing the mask at night. Furthermore, the potential impact of OSA on their ability to drive, informing the DVLA and their ability to go on holiday, were further important considerations.

"I think it frightened me a little bit that I had to put this mask on for the rest of my life, the rest of my life and I suppose that was the thing that frightened me just a little bit which it did do. I didn't fancy it at the time but it was a bit of a – for the first three or four nights, I felt so claustrophobic, you know? I was laying there thinking, "Oh, this is not for me." [Patient 7, male]

To be honest, if he'd said to me that there was any possibility of my driving license coming into question, I simply wouldn't have gone. I'd have said, "No, I'm not interested." [Patient 5, male]

But this is a major feature of life, and the idea of taking this thing through security at Heathrow Airport is not a prospect I relish. [Patient 6, male]

Lack of support sleep disorders service support outside of hours, was reported as a further barrier to the adherence of CPAP treatment. The sleep service offers a drop-in service to support CPAP related issues, however, limited support was available outside of hours. This is particularly challenging over a weekend when patients must wait until Monday when the service resumes.

"Last night, not doing too well. Red face, air gushing out of it and so on. This morning – or yesterday in fact, I thought, "Any trained nurse will know what to do, this is a straightforward problem." I went to our local walk in Minor Injuries Unit, "No, no idea about that." Our GP, "Sorry, no, Hospital, no not us." [Patient 6, male]

Despite the reports of CPAP being poorly tolerated, participants reported that a combination of support from their partner, instruction booklet, sleep services team and self-troubleshooting of CPAP related issues, supported their adherence to treatment.

If I've gone to bed and read a book or something and look like I'm falling asleep, he kind of nudges me and says, "You need to put your mask on." [Patient 4, female]

Well, the instructional booklet says you can get sprays and things for it. [Patient 6, male]

I looked this morning on YouTube and there are all sorts of demonstrations, clips on how to do it, so I think I may have solved it. [Patient 6, male]

They don't make you feel like it's your fault. I felt like it was my fault, and they don't make you feel like that at all. And I've not had to ring the line. You can drop in and go and see them if you need to. [Patient 4, female].

5.4.2.2 Theme 2: Poor access to Sleep Services

5.4.2.2.1 Long Waiting Times

Long waiting times at different stages of the referral and diagnostic process were reported by participants. Initial delays occurred at the point of referral to the sleep service.

> *"Nothing was mentioned about that until last year, when the new heart specialist asked me to go and see somebody about it could be something to do with my breathing, sleep apnoea as well. But that was over a year ago. It took me six months even to get an appointment. It's been 18 months since he actually said." [Patient 9, female]*

If a patient had to reschedule their appointment due to competing commitments, a further delay was built into the process as one participant stated that rescheduling his appointment resulted in a 3-month delay.

> *"I had to cancel it because it clashed with my pre-assessment for the implantation of the device. And then basically they moved the appointment for about three months further on, so it was delayed a lot longer than perhaps it would have been had I been able to take up the first appointment." [Patient 10, male]*
>
> *I daren't change that appointment or have a problem with that appointment, because if I have a problem with that appointment, you don't know when the next one is going to be. [Patient 3, male]*

Long waiting times were reported not only from referral to receiving the appointment for the sleep study, but also in receiving the sleep study results which further delayed initiation of treatment.

> *"Vague and slow. It's now July and I mentioned this to the heart failure clinic probably in early February, late January. So, I can't remember when I had my meeting with them, but I think it was nearly two and a half months ago, three months ago, when I wore the device and it's only now, at the beginning of January that I have got a meeting to find the results." [Patient 3, male]*

5.4.2.2.2 Perceived lack or resources

Participants reported the impact of staffing challenges and perceived lack of time on their clinic appointments. Although one participant described the willingness of their doctor to sit and talk, another felt that doctors did not have the time to provide explanations to their patients.

> *"And then when I went back and I saw – well she was a consultant, and she was busy, you could tell. No staff turned up or something for a shift. And you know they're rushed off their feet, but she didn't make you feel like that. She didn't make you feel like you've got to be rushed out. She was quite willing to sit there and talk. Even though she was in a hurry, you could tell she wanted to crack on, which is fair. She's got somebody else waiting, hasn't she?" [Patient 2, female]*

> *"Now, I think that is the way it happens in the medical profession, that maybe doctors haven't got the time to explain problems to patients." [Patient 5, male]*

Furthermore, participants reported their frustration with lack of access to the service. Difficulty in contacting the sleep service and being unable to leave a message or speak to a member of staff limited access to the sleep service.

> *"I left four messages over a week, and nobody replied, and they didn't reply to emails. I got however through to the secretary, who obviously is not hands on at the clinic itself…… But then they say, "Oh, we're a bit short on the clerical side." Well, you know, it does seem rather pointless, I know you're not running the Hospital, but just for a word in the right ear, it seems ridiculous if they've got professionals dealing with patients, and then for the sake of hiring a temp who could just listen to the blooming voicemail. You know you have people sitting around and leaping up and down." [Patient 6, male]*

Participants recognised that staff were busy but expressed their desire to a shorter waiting time between investigation, receiving the results and initiating treatment.

> *I think that was quite a long time and I think that you just think that there's nothing wrong. So, I think maybe – and I know they're busy, aren't they? They've got so many people, every time you go there it's packed, you know? So, they've got so many people to see, and they've got to read the readings I suppose, when you've had the test haven't they? They've got all that data to do and what have you and put it in the system and that. So, I suppose there is a lot of work to do but I think maybe it would be nice if it was a bit shorter. [Patient 2, female].*

5.5 Results of Clinician Interview Study

5.5.1 Participants characteristics

Twenty HF clinicians from primary and secondary care settings were interviewed for the study. Of the 20 participants, 75% were female, 70% were

nurses and 65% were from primary care. Participant characteristics are summarised in **Table 33**.

Table 33 Participants Characteristic (Health Care Professionals)

ID	Gender	Years as HFC	Role	Type of Organisation	Geographical Location
N01	Female	3-10 years	HFSN	Primary Care	Leicestershire
N02	Female	>10 years	HFSN	Primary Care	Leicestershire
N03	Female	>10 years	ANP	Secondary Care	Leicestershire
N04	Female	>10 years	HFSN	Primary Care	Leicestershire
N05	Female	3-10 years	HFSN	Primary Care	Leicestershire
N06	Female	>10 years	HFSN	Primary Care	Leicestershire
N07	Female	3-10 years	HFSN	Primary Care	Leicestershire
N08	Female	3-10 years	HFSN	Primary Care	Leicestershire

ID	Gender	Years as HFC	Role	Type of Organisation	Geographical Location
N09	Female	3-10 years	HFSN	Primary Care	Leicestershire
N10	Female	3-10 years	HFSN	Primary Care	Leicestershire
N11	Female	>10 years	HFSN	Primary Care	Leicestershire
N12	Female	>10 years	HFSN	Primary Care	Leicestershire
N13	Female	>10 years	HFSN	Secondary Care	Hampshire
N14	Female	>10 years	NC	Secondary Care	Hertfordshire
R01	Male	3-10 years	Registrar	Secondary Care	Leicestershire
C01	Male	>10 years	Consultant	Secondary Care	Leicestershire

ID	Gender	Years as HFC	Role	Type of Organisation	Geographical Location
C02	Male	>10 years	Consultant	Secondary Care	Leicestershire
C03	Male	>10 years	Consultant	Secondary Care	Leicestershire
P01	Male	>10 years	Pharmacist	Primary Care	Glasgow
P02	Female	3-10 years	Pharmacist	Primary Care	Glasgow

ID: study identity; HFC: heart failure clinician; F: female; M: Male; N: nurse; R: registrar; C: consultant; P: pharmacist; HFSN: heart failure specialist nurse; ANP: advanced nurse practitioner; NC: nurse consultant; HCP: health care professional

5.5.2 Findings

Based on the qualitative data provided by HF clinicians, seven superordinate themes were identified which were representative of six domains of the TDF: knowledge, skills, professional role and identity, beliefs about capabilities, beliefs about consequences, and environmental context and resources **(Table 34).**

Table 34 Overview of Themes

Themes	Subordinate-themes	*n*=20	TDF Domains
Theme 1 **Variable awareness and knowledge of OSA**	Perceived lack of awareness, knowledge, and educational opportunities Lack of awareness of clinical guidelines and perceived lack of evidence	20 18	**Knowledge**
Theme 2 **Variable skills in assessment of OSA**	Incomplete assessment of OSA Variable use of screening questionnaires Insufficient information provided to patients	16 18 5	**Skills**
Theme 3 **Perceived professional boundaries**	Role of HCP	18	**Social/professional role and identity**

Themes	Subordinate-themes	*n*=20	TDF Domains
Theme 4 **Variable levels of perceived confidence**	Low confidence in ability to detect patients with OSA	11	**Beliefs about capabilities**
Theme 5 **Priority of OSA in clinical practice**	Perceived low priority of OSA in clinical practice Perceived outcome expectancy	9 15	**Beliefs about consequences**
Theme 6 **Variable access to sleep services and resources**	Variable access to sleep service Time burden	15 12	**Environmental context and resources**
Theme 7 **Patient specific factors**	Poor uptake and adherence to treatment Perceived low priority of OSA	15 9	

HCP: health care professional; OSA: obstructive sleep apnoea

5.5.2.1 Theme 1: Variable awareness and knowledge of OSA

Two subordinate themes relevant to the knowledge domain emerged from the interview data and included: perceived lack of awareness, knowledge and educational opportunities, and lack of awareness of clinical guidelines and perceived lack of evidence.

5.5.2.1.1 Perceived lack of awareness, knowledge, and educational opportunities

Participants reported a lack of awareness among HF clinicians as a barrier to the identification of patients at risk of OSA. With some recognition of the importance of sleep, OSA was perceived as a condition that is not frequently mentioned or discussed and therefore low priority in clinical practice.

> *I think lack of awareness among healthcare professionals would probably be the one thing that might improve identification of the patients if we were to change one thing. [Doctor, C3]*

> *I think a lack of awareness among health professionals about the implications of it long-term, that it's under - whatever the word is. I don't think people realise the long-term effect of it and it's not a minor thing; it does have a significant physiological effect. [Nurse, N08]*

> *Lack of awareness about what the signs and symptoms are of sleep apnoea, how to access sleep services and for patients to see cardiologists, GPs, and cardiac nurses. [Pharmacist, P2]*

Participants did not only report a lack of understanding and knowledge of OSA and the impact on patient care, but an additional lack of knowledge relating to their local referral pathways. It was felt that despite having some knowledge

about OSA, it was probably still insufficient to identify patients with comorbid OSA.

> *I think the other barriers from my perspective is not having enough understanding of sleep apnoea and the impact it has on patient care. Because if a patient's not sleeping and the importance of sleep, it is so vitally important because if the patient's not sleeping properly, it has a profound impact, not just on their cardiovascular system but also on their mental health. [Nurse, N06]*
>
> *It's knowledge of the referral pathway, knowledge of the condition as well could be improved. [Nurse, N05]*
>
> *Because I'm unsure when I would see it, what I'm supposed to do with it, where I'm supposed to send somebody. I'm not sure we've got a service locally that could patients even if we ringside them. [Pharmacist, P1]*

In conjunction with a lack of awareness and knowledge of OSA, participants reported a lack of information and training opportunities at study days, HF training courses and in general within the clinical speciality.

> *So, I don't recall a talk on sleep apnoea for a long, long time in cardiology. There was a little bit of hoo-ha about the central apnoea, do you remember that when the study was – I bet the registrar who did it was very depressed. [Doctor, C1]*
>
> *It's not taught really as a session in, sort of thinking back to some of things I've done, it's never been there. You get the stuff on AF, you get the COPD, you get the diabetes talks, you*

get, you know, renal failure until you're done to death. In actual fact, I've not attended anything on sleep disordered breathing. [Nurse, N13]

I've not long finished my heart failure module. It wasn't something that came up on that, so maybe that needs looking at but it's not being delivered in the kind of bedrock of the education process that we receive as heart failure nurses. [Nurse, N09]

A key enabler in the knowledge domain was reported as education. Participants emphasised the importance of education and the difference if would make to their knowledge and understanding of OSA.

Well, there are lots of forums and lots of opportunity for education. All the standard articles in journals and conferences are all the standard things. There's lots of opportunities now for things like live webinars and that kind of thing, which I think get to people a lot better, because not everybody can go to specialist conferences. Particularly these days there isn't funding, people can't be released from work time. [Nurse, 03]

We could start by educating undergraduate medical students, for a start. I think educating nurses, in particular cardiac specialist nurses, not just in heart failure. It's a long time since I was a medical student, and I don't know whether it is part of the undergraduate curriculum in most medical schools. I'd be surprised if it gets any real airtime. [Doctor, C3]

5.5.2.1.2 Lack of awareness of clinical guidelines and perceived lack of evidence for the treatment of OSA

Most participants stated that they were unaware of guidelines relating to the management of OSA. Furthermore, some scepticism surrounded the evidence for the treatment of OSA in CHF.

If I'm honest, I don't know any of the guidelines for the management of OSA, apart from I would refer to the experts for their guidance. [Nurse, N02]

I should be thinking about and other than hearing once in a blue moon talk on sleep apnoea, then nobody's every really whetted my appetite enough to know, to go looking for a NICE guideline in something that's out within my speciality. So, do they exist? I've no idea, probably, but do I know what they are? Absolutely not. [Pharmacist, P1]

If I were asked, "What is the relative value of CPAP compared to an ACE inhibitor in somebody with impaired LV function?" then I've got loads of evidence on the one side for the drugs and I've got not very much awareness on the other side for the other intervention. I think there is an immediate barrier there and therefore I am less able to take time to try and inform the patient. I think that is a huge issue. [Doctor, C3]

5.5.2.2 Theme 2: Variable skills in the assessment of OSA

Three subordinate themes emerged in relation to the skills domain: incomplete assessment of OSA, variable use of screening questionnaires and insufficient information provided to patients.

5.5.2.2.1 Incomplete assessment of OSA

Participants reported that they regularly ask their patients about their sleep, however, questions about sleep were often in relation to symptoms of orthopnoea and paroxysmal nocturnal dyspnoea, rather than focussed on the quality of sleep and sleep-related issues.

> *But I think in my head, by asking about that I'm thinking more about the breathlessness rather than actually sleep apnoea. [Nurse, N04]*

> *I always ask about sleep because I think that helps dig out if they're having Orthopnoea and PND. [Nurse, N09]*

Most participants relied on the stereotypical presentation of OSA to identify those patients who they perceived to be at risk of OSA and that warrant further investigation and treatment. Key physical characteristics included male gender, overweight, and a large neck circumference. Unless patients fitted this profile, they were less likely to be considered at risk of OSA.

> *I think the obvious ones are overweight, obesity, male gender, to an extent. [Doctor, C03]*

> *Diagnosing the patient, there's a particularly stereotypical type of patient such as an obese patient with a fat neck, they're the initial ones who trigger or spring to mind. [Nurse, N02]*

Several participants reported the partner's description of symptoms such as snoring and breath holding as a key enabler to the detection of patients at risk of OSA.

> *Also, it's a little bit difficult if they haven't got a partner who's prepared to say that they do snore or whatever. [Nurse, N01]*

> *By asking them questions, if they have pauses in their breathing at night, if their partners have ever told them they've got pauses in their breathing at night, or if the patient's ever been told that they're loud snorers; again, pauses and catnapping in the day if they don't have anyone to sleep with at night to monitor for any pauses or snoring in the breathing. [Nurse, N02]*

5.5.2.2.2 Variable use of screening questionnaires

Despite the availability of several validated screening questionnaires to aid risk stratification of patients who might benefit from further investigation, participants reported variable use of screening questionnaires in clinical practice. At least half of participants stated that they use a screening questionnaire to identify patients at risk of OSA.

> *There's a couple but it's the STOP-Bang that I've used and that I'm familiar with, I can't recall the others to mind. [Nurse, N09]*

> *So, we use STOP-Bang and Epworth. [Nurse, N03]*

> *If the patient was saying that they were having pauses in their breathing and were snoring, then I'd fill in the rest of the STOP-Bang Assessment Tool, which looks at the collar size, their weight. [Nurse, N02]*

However, fewer than half of participants stated that they did not use screening questionnaires in their clinical practice.

> *I couldn't name a, you know, a screening tool or measure of obstructive sleep apnoea. I mean, I can read things in the literature, you know, I can't remember, is it the Epworth Scale or something like that? I mean, do I know what it is, would I know how to measure it? No, I've no idea, so no. [Pharmacist, P1]*

Although several participants reported the use screening questionnaires in their clinical practice, some were sceptical about the accuracy of existing screening questionnaires.

> *My increasing understanding is that the screening questionnaires are not very good, therefore what would I be introducing to my practice by introducing a screening questionnaire, I don't know. Would I be sending a lot of people for unnecessary investigations? I don't know. [Doctor, C3]*
>
> *So, they're not very precise. Okay, for the score, the whole lot, yes, but if they're sort of vague, do you score it a yes or no? [Doctor, C1]*

5.5.2.2.3 Insufficient information provided to patients

Participants reported that they rely on the sleep service or respiratory team to provide patients with information about the condition, investigation, and treatment, whilst another reported that they don't know what information to provide to the patient.

> *I throw them through the respiratory guys. I say, "I think you've got sleep apnoea, go and see them, they'll tell you what it's about." [Doctor, C01]*

All I tell them is that I'm going to refer them to a sleep clinic and that somebody will be in touch with them and then it gets taken from there. [Nurse, N13]

5.5.2.3 Theme 3: Perceived Professional Boundaries

Participants felt that any condition that impacts on HF, such as OSA, was part of their job and responsibility. Although they did not feel that the management of the condition was part of their role, they reported that identifying patients at risk and referring them for investigation and management of OSA were perceived as part of their role.

I think that anything that impacts upon heart failure is part of our job, and as that does then, yes, I think identifying. Not necessarily managing it, but onward referral I think is an appropriate part of our job. [Nurse, N04]

If they're undiagnosed and untreated I feel that that possibly could have a big impact on their quality of life particularly. I think it is definitely part of our role and appropriate for our role to assessing that. [Nurse, N10]

In contrast to the doctors and nurses, pharmacists reported that their main goal was to up-titrate evidence-based medication and not necessarily view their role as diagnostic.

Our goal is there to up-titrate secondary prevention, so I probably don't see it as my role. Our role is more a prescribing role than a diagnostics role. [Pharmacist, P02]

It was reported that role modelling from medical consultants may influence nurses to identify patients who may be at risk and require further investigation.

> *I'd probably say perhaps I don't very often see it written in our heart failure consultant clinic consultations. Maybe if it was a bit more sort of top down, that it was more on the agenda at consultant end, that that might have a bigger influence on nurses. [Nurse, N09]*

Participants recognised that they were specialists in their clinical area of HF, however felt that they were not trained to fully manage comorbid conditions and therefore anything outside of their speciality might be 'neglected'. Participants reported that their patients are often managed by other members of the multi-disciplinary team and might therefore be reporting their symptoms to clinicians other than their specialist. This raises the question of the clinical responsibility. With diffusion of responsibility there is a need to specify someone to take responsibility for the identification of OSA and onward referral for further investigation. Furthermore, it was felt that trainees may be less aware of OSA compared to their consultant colleagues, whilst it was perceived that 'generalists' such as general practitioners, had a far greater awareness of OSA.

> *So, part of the problem is heart failure is such a common condition that it doesn't just come to heart failure specialists. So, while I might refer a lot of my patients for assessment of obstructive sleep apnoea, whether or not the same can be said for a registrar who doesn't have heart failure as their primary focus is another question [Doctor, C01]*

> *I think most generalists, I'm sure GPs are very well aware of OSA. I'm sure most cardiologists and respiratory doctors are aware of OSA, maybe neurologists as well probably, but other specialties, probably not. I think many of the patients with this condition may be reporting their symptoms to people other than*

their specialist, it's probably very easy to manage insomnia with temazepam. [Doctor, C03]

I've referred onto GPs and said I suspect this patient has got sleep apnoea and my suggestion wasn't taken forward. They weren't scored or referred. [Nurse, N09]

5.5.2.4 Theme 4: Variable levels of perceived confidence

Participants reported variable levels of perceived confidence in identifying patients at risk of OSA. Half of participants reported feeling confident in identifying those who were typically deemed at risk of OSA. Some reported the usefulness of having a screening tool.

I feel a lot more confident now over these recent years, because of having the assessment tool and because of the questions they're responding to, the answer they're responding to with an appropriate assessment tool that I'm using, I feel very confident in referring patients, rather than just having intuition. [Nurse, N02]

In contrast, some participants reported a lack in confidence.

I don't think I'm fantastic at it. I feel as thick as a brick about Obstructive Sleep Apnoea. [Nurse, N14]

But I would not normally, unless there were obvious signs, feel that I have enough knowledge to do a full assessment. [Nurse, N01]

5.5.2.5 Theme 5: Priority of OSA in clinical practice

Two subordinate themes emerged in relation to the 'beliefs about consequences' domain: 'perceived low priority in clinical practice' and 'perceived outcome expectancy'.

5.5.2.5.1 Perceived low priority in clinical practice

Participants reported that identifying patients at risk of OSA was not necessarily deemed as high priority. When clinicians were time pressured and their patients were symptomatic with CHF, the HF would take priority above other comorbid conditions as failure to address the CHF symptoms might be felt to be more catastrophic.

> *I think that's possibly a considering factor that when you are time pressured, you probably look at maybe on a scale of priorities and you may be looking at, "Oh well your fluid overloaded, let's deal with that and come back to it." Or, "Let's deal with whatever the priority seems to be," and I suppose it's not something that is or has been particularly high on our agenda of prioritising, so it may well get left, but equally before we were doing this study, I've referred onto GPs and said I suspect this patient has got sleep apnoea and my suggestion wasn't taken forward. [Nurse, N09]*

> *I suppose the first issue is it not being at the forefront of our management plan, really. [Nurse, N02]*

5.5.2.5.2 Perceived Outcome expectancy

Some participants did not feel that treatment of OSA has specific prognostic benefit for patients with CHF.

There's no prognostic benefit for those patients. Even with those who have severe sleep apnoea, the prognostic benefit is indirect, in the sense that I might check your blood pressure. [Doctor, C1]

In contrast, others felt that management of OSA could contribute to symptomatic improvement of symptoms such as fatigue and ultimate improvement in patients' quality of life.

I absolutely have patients treated for obstructive sleep apnoea who feel a great deal better and it makes their heart failure easier to manage. [Doctor, C02]

I think with regard to the problem of fatigue, which is a significant symptom, it massively increases it. I think these patients have a very poor quality of life due to the symptom burden. And this obviously has an additive effect that's lightly to contribute to the high instance of depressive disorder as well in heart failure. [Nurse, N05]

5.5.2.6 Theme 6: Variable access to sleep services, resources, and patient factors

Two subordinate themes emerged in the environmental context and resources domain: "variable access to sleep service" and "time burden".

5.5.2.6.1 Variable access to sleep service

Several perceived barriers to accessing sleep services were reported by participants. Some participants stated that they were unaware of the sleep disorder service in their locality.

Certainly, locally we have services available, so that's not a problem. I presume other areas might not have, or certainly when I've spoken to other teams, they don't have local sleep services and they don't have access to sleep testing. [Nurse, N03]

Yes, so I'm sure there are these services in my area, but am I aware of them? No. [Pharmacist, P01]

Furthermore, several participants reported that they were unaware of the referral process which was sometimes complicated by a lack of access to referral forms.

People don't know what to do with it, do I go back to the GP, do I refer them direct, I mean I think a lot of those issues have been ironed out because you are doing this. [Nurse, N11]

I look for forms. I asked the blooming nurse, "Where's…?" and they don't know, "Where, what form? This is a cardiology clinic, what form is this?" Several times, not once or twice, several times. I'm always wandering around looking for this stupid form and now they've got two different forms – three forms, one for lung function, one for sleep apnoea, one for oxygen, okay, and the nurses don't even know there are these three forms. [Doctor, C1]

The request card itself is very badly written so I never know quite which box to tick. I've got a box which I always tick but I've always got in the back of my mind, is that the right one to be ticking for the tests that I want to have done. It would be nice to just be able to tick for, please assess this patient for

obstructive sleep apnoea rather than partial polysomnography or whatever it is on the card. [Doctor, C02]

Waiting times and insufficient communication between departments were reported as additional barriers to accessing sleep disorder services.

From point of view of time from us or from others, if someone's been diagnosed as sleep apnoea, they might have to wait a while to be seen. [Nurse, N01]

We have to refer them on, we don't know whether they're complying with treatment or not. We don't follow them up or we don't have any means of communication, or we see if the form went through to the sleep apnoea clinic on how they're doing, how they're getting on with the CPAP? [Doctor, R01]

And I don't necessarily always get feedback from the clinics, although I might initiate the referral, the response would be sent back to the GP, which is becoming easier now because of the bulk of the GPs are now using SystmOne so we get to see all the communications. [Nurse, N02]

5.5.2.6.2 Time burden

Participants reported that they don't always have the time to focus on other conditions and that subsequent referral causes an additional time burden.

Onward referral is always another thing to do, it's a timely issue even though it's important. [Nurse, N04]

I think everybody's so busy. I think our caseloads are massive here and I think sometimes we don't have the time the luxury to

actually think about our patients and treat them as individuals. They are very much on the heart failure bandwagon of, "You need this, you need this, you need this," and I think it's about thinking outside the box and having the time and the experience to think what else could be going on with your patient, does that make sense? [Nurse, N11]

However, most of the nursing participants felt that a 'prompt' in the electronic holistic assessment template would be a helpful reminder to take into consideration.

It could be prompts when you're completing the weight, again in the electronic questionnaire. If you put in weight, if it's above a certain BMI, it could just flash up, "Consider sleep apnoea," or, "Risk of sleep apnoea," that would trigger that thought process, to go into a bit more further detail, further questioning of your patient. [Nurse, 04]

There isn't anything there that would trigger people. I'm thinking maybe of junior members of the team who may not think about asking about sleep apnoea. It could be an adjunct to the holistic assessment that we currently use, having it added it on one of the tabs. [Nurse, N02]

5.5.2.7 Theme 7: Patient specific factors

5.5.2.7.1 Poor uptake and adherence to treatment

Participants reported that poorly tolerated CPAP treatment was a key barrier to the uptake and adherence to CPAP treatment.

There are always issues with patients' willingness to come back for tests and their tolerability of the CPAP equipment so

that sometimes they have had negative experiences with that in the past and they're not prepared to consider being reinvestigated for it. [Doctor, C2]

I've had a couple that I've said that I'm going to refer, and they've basically said, "Don't bother, I've been referred, and they gave me a machine and I didn't like it so I'm not using it." [Nurse, N13]

Participants reported that perceived implications for driving further affected patients' uptake of treatment.

Some of them will then say, "Oh, I've heard about this, I don't want to be tested because then you can't drive." [Nurse, N03]

They don't want another hospital appointment and some have declined the referral because of things that they've heard that they'd have to stop driving with regards to if you've got sleep apnoea, you have an increased risk of falling asleep at the wheel and they take your driving licence off you. [Nurse, N02]

Furthermore, participants reported that many of their patients did not feel that there was anything wrong with them which is further impacted by the overlap of symptoms between OSA and CHF.

My major problem has been trying to persuade patients they actually might have a problem. [Nurse, N01]

Now, that might be because patients just don't recognise it - so they don't actually bring it to our attention. [Nurse, N13]

It was reported that cultural differences and language barriers might also affect the uptake and adherence to CPAP treatment.

> *I certainly have quite a few South Asian patients who have severe sleep apnoea and just do not wear their treatment at all. I've tried to talk to them about it, I've had interpreters in and things. I'm not sure what the barriers are there, but they just won't wear it and are very symptomatic …… [Nurse, N03]*

5.5.2.7.2 Perceived low priority

Participants reported that patients did not perceive OSA as a high priority in comparison to the perceived seriousness of their diagnosis of CHF.

> *But a lot of them feel that having been told they've got a heart condition, they can put down all of this problem of not sleeping properly, being tired all the time, is actually due to that. And they don't seem to want to deal with another problem. [Nurse, 01]*

> *Generally, it's one more thing to deal with. So, if they're not finding it particularly problematic from their perspective and it's the partners that are sort of more worried about it, you kind of get a feeling that it's one more thing to deal with but, you know, that's a minority. [Nurse, N13]*

Mapped against the different steps in the diagnostic pathway, a summary of both the patients' and clinicians' barriers and enablers were summarised in **Figure 22** (Adapted from Ye et al., 2021). The diagnostic pathway was subdivided into three key domains and 8 steps:

1. Patient care seeking (domain 1): this stage consists of 3 steps, including patient awareness of symptoms, patient decision to seek care and patient presentation presenting to their clinician.
2. Clinical recognition (domain 2): this stage consists of 2 steps including clinical recognition and clinical referral.
3. Investigation, diagnosis, and treatment (domain 3): this stage consists of three steps including investigation, diagnosis, and treatment.

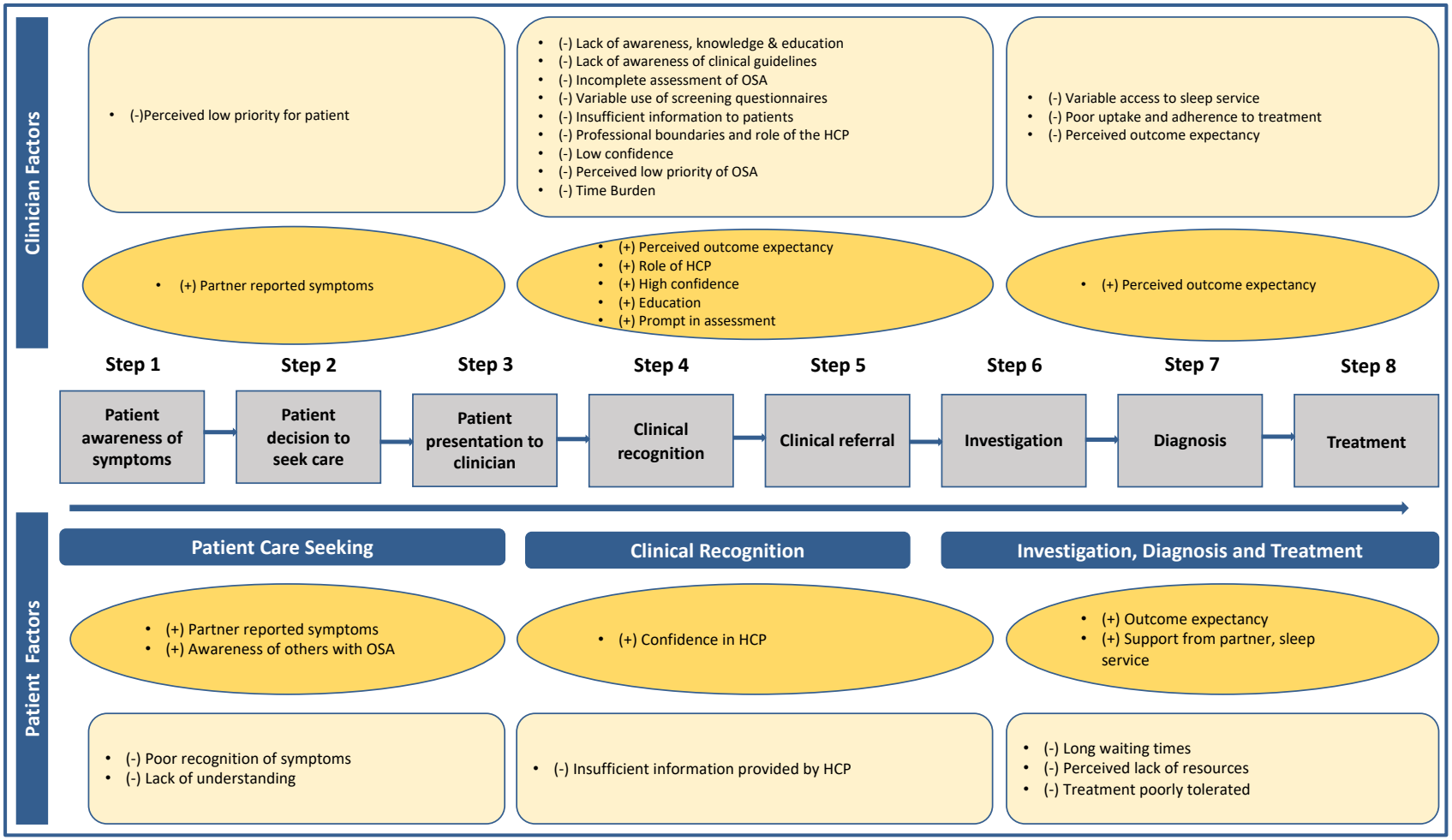


Figure 22 Barriers to and Enablers of the Diagnosis and Treatment of OSA in CHF

5.6 Discussion

The objective of the qualitative component of this thesis was to identify barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives.

5.6.1 Summary of Findings from Patient Study

Findings from patients' interview data reported barriers and enablers at various stages of the diagnostic pathway, including the 'patient care seeking', 'clinical recognition' and during the 'investigation, diagnosis and treatment' stages.

Consistent with findings from Ye *et al*. (2021), key barriers in the 'patient care seeking' stage were reported as poor recognition of symptoms and lack of patient understanding. Typically reported symptoms, such as EDS, were rarely reported by participants, mainly because individuals with comorbid CV disease are less likely to present with typical symptoms of OSA. Analysis of the Icelandic Sleep Cohort identified three distinct clusters classified as the 'disturbed sleep group', 'minimally symptomatic group' and 'EDS group'. Individuals in the 'minimally symptomatic group' had the highest probability of comorbid hypertension and CV disease, compared to the 'EDS group'. Therefore, awareness of heterogeneity in the clinical presentation of OSA is paramount to the detection of OSA (Ye et al., 2014).

Although fatigue was reported as a key symptom, most participants perceived fatigue as part of the CHF symptom burden rather than a manifestation of a different condition. Both conditions share nocturnal and diurnal symptoms, making it difficult to differentiate between the two conditions or establish whether they are comorbid. As such, overlap of symptoms such as fatigue, nocturia, paroxysmal dyspnoea further challenged the detection of OSA.

Key enablers in the 'patient care seeking' stage was an awareness of others with OSA, and partner reported symptoms. In this study, reports of breath holding by patient partners were often the only suspicion of OSA and indication that the patient may require formal investigation. The importance of engaging partners in the detection, diagnosis, and treatment of OSA has been

emphasised by Ye *et al.* (2021) and recommended in the latest European Society of Cardiology HF guidelines (2021) and NICE guidelines (2021) for OSAHS and obesity hypoventilation syndrome in over 16s.

One of the three female participants in this study reported a delay in her diagnosis and treatment of OSA, because her doctor felt that she 'did not fit the criteria' for referral, despite her husband providing a recording of significant breathing pauses at night. Although OSA has been historically described as a condition that primarily affects men, it has been recognised that OSA is far more prevalent in women than previously believed, making it an important problem in women (Ye, Pien & Weaver, 2009). Under diagnosis of OSA in women raised the possibility that women might present differently to men, which in turn may contribute to the misinterpretation of symptoms by clinicians. Under diagnosis of OSA is further exacerbated by unconscious bias about female presentation and the stereotypical belief that OSA is a male disease (Kapsimalis & Kryger, 2002). Women are often underrepresented and 'invisible' in scientific data, exposing a gender data gap and when they present in different or unusual ways, their diagnosis and treatment are likely to be poorer (Criado Perez, 2019). Therefore, to facilitate early detection of OSA, consideration of different patterns in clinical presentation and gender specific differences, are essential.

Insufficient information provided by the HCP at time of referral was a key barrier in the 'clinical recognition' stage. Lack of patient understanding was likely to be impacted by a lack of information provided by their clinicians at the time of referral. Lack of understanding and subsequent insufficient information provided by the HCP at the 'clinical recognition' stage was reported as anxiety and fear provoking with a potential impact on the patients' decision to attend for their appointments at the sleep disorder service. Without receiving adequate information about OSA, the investigation and possible treatment options, patients are unlikely to fully engage with informed or shared decision-making, therefore withholding from patients the ability and opportunity to make informed decisions or to align their preferences with the suggested investigation or

treatment (Long & Curtis, 2015). Confidence in their HCP was identified as a key enabler.

Consistent with previous findings, poor tolerance of CPAP treatment, long waiting times and lack of resources were reported as barriers in the 'investigation, diagnosis and treatment' stage (Broström *et al.*, 2010, Malaweera, 2015, Luyster *et al.* 2016). Poor tolerance of CPAP treatment was a key barrier with likely significant impact on clinical outcomes (Perger *et al.,* 2019)

Support from partners and outcome expectancy were key enablers to the uptake and adherence of CPAP treatment. Consistent with previous findings, the negative psychological impact of CPAP, practical problems with the CPAP mask such as feeling claustrophobic and aesthetic issues with the mask, were key barriers (Sawyer *et al.* 2010; Luyster *et al.,* 2016). Outcome expectancy and support from partners were identified as key enablers at this stage.

Consistent with previous studies, findings from the patient interview data reported long waiting times for the diagnosis and treatment of OSA (Flemons, 2004; Malaweera, 2015; Thornton *et al.,* 2020; Ye *et al.,* 2021). Evidence suggests that shorter waiting times for treatment initiation was associated with higher treatment adherence, patient satisfaction and symptomatic improvement (Thornton *et al.,* 2020). Therefore, to maintain momentum and to make best use of the window of opportunity, system interventions to address resource issues and long waiting times are essential and could be utilised to modify patient behaviour with consequent improved treatment adherence and clinical outcomes.

5.6.2 Summary of Findings from Clinician Study

Consistent with the patient interview study, findings from the clinician interview study identified barriers and enablers of the diagnosis and treatment of OSA in CHF that spanned across all stages of the diagnostic pathway. A key barrier in the 'patient care seeking' stage was that patients perceived OSA as a low priority compared to their diagnosis of CHF. Consistent with Ye *et al.* (2021), the role of the partner in reporting symptoms of OSA, was a key enabler.

Most clinician barriers and enablers were identified in the 'clinical recognition' stage and were consistent with the knowledge, skills, professional boundaries, beliefs about capabilities and consequences, and the environmental context and resources domains of the TDF. Consistent with previous findings, lack of awareness, lack of knowledge, lack of education, and lack of awareness of guidelines were likely to impact on the detection and assessment of patients at risk of OSA. The variable use of screening questionnaires and insufficient information provided to patients at the time of referral further contributed to the low perceived confidence reported by HCPs (Malaweera, 2015, Bakhia *et al.,* 2017). In addition to the above barriers, the perceived time burden associated with completing a screening questionnaire, assessing a patient at risk of OSA, and generating a referral to the sleep disorders service was likely to contribute to the low priority assigned to OSA by HF clinicians, identifying a need here to understand better the implicit hierarchies of problems that clinicians attend to. Key enablers reported by clinicians were perceived outcomes expectancy, their belief that assessment of conditions that impact on CHF is part of their role, education, high confidence, and prompts build into their assessment template.

Clinician barriers reported in the 'investigation, diagnosis and treatment' domain were consistent with those reported by patient participants and previous studies (Malaweera, 2015, Bakhia *et al.,* 2017). Variable access, long waiting times and poor uptake and adherence to CPAP treatment were key barriers. An important enabler in this domain was clinician outcome expectancy.

In the elicitation of data across the interviews, by the later interviews, there were no new themes emerging and it was considered that theoretical saturation of themes was achieved.

There were several barriers and enablers that were identified from both patient and clinician perspectives. Firstly, in the 'patient care seeking domain', the role of the partner was recognised as a key enabler to the detection of OSA in this patient group. Secondly, in the 'clinical recognition' domain, insufficient information provided by the HCP was a key barrier that was likely to be impacted by lack of clinician knowledge, awareness and education and patient

lack of understanding. In this domain, high confidence in their HCP and high self-confidence reported by clinicians were key enablers. Finally, in the 'investigation, diagnosis and treatment' domain, long waiting time and poor uptake and adherence to CPAP treatment were key barriers, whilst the perceived outcomes expectancy was identified as a key enabler in this domain.

5.6.3 Strengths and limitations

5.6.3.1 Strengths

There were several strengths associated with the qualitative component of this thesis. Firstly, this is the first study to explore and describe the barriers to and enablers of the diagnosis and treatment of OSA from both individual CHF patients' and clinicians' perspectives. Findings from both the patients' and clinicians' interview data contribute more fully to the understanding of the key barriers to and enablers of the detection, diagnosis, and treatment of OSA in this patient group, making a meaningful contribution to the understanding of related issues. Secondly, the clinician interview study included key members of the HF multidisciplinary team, exploring barriers and enablers from nurses, doctors, and pharmacists' perspectives. These clinical groups work closely with CHF patients for the management of symptoms and up titration of medication and would therefore be best placed to detect comorbidities that may require further investigation and treatment. Thirdly, the qualitative component of this thesis utilised the TDF, a recognised theoretical framework, to inform the design and analysis of interview data. Finally, the qualitative component forms part of a MMR design which will allow triangulation of the clinicians' interview data and the survey data, enhancing the trustworthiness of study findings.

5.6.3.2 Limitations

The qualitative component was associated with several limitations.

The intended sample size for the patient interview study was between 20 and 30 participants. Recruitment for the interview study was dependent on the number of participants recruited for the diagnostic validation study. Due to low referral numbers and subsequent low recruitment numbers for the diagnostic validation study, it was not possible to recruit the sample size as planned. From

the sample of 10 participants, there were no new themes emerging and it appeared that theoretical saturation was achieved. Because the patient sample lacked ethnic diversity and had low female representation, it is possible that if more female or ethnic diverse participants were recruited, that theoretic saturation might not have been achieved. Therefore, findings from the patient interview study may not be entirely transferable to the rest of the CHF population.

Participants in the patient study sample were from a single geographical area with access to both HF and sleep disorders specialist services. It is possible that study participants might have access to a wider range of services compared to patients in other locations across the UK. Considering the importance of the role of the partners in the detection and treatment of OSA, single patient interviews, rather than the patient-partner dyads, were considered a limitation.

In the clinician study sample, nurses were overrepresented, compared to the medical and pharmacist participants. Furthermore, medical participants were from a single secondary care institution, whilst the pharmacist participants were from a single primary care institution, raising the question of generalisability and transferability of findings.

Because the researcher's status was known to the organisation, it is important to understand their role and the implications of a participant researcher. Positionality of the researcher may have influenced how participants responded to interview questions. It might be that they provided socially acceptable reasons for their lack of knowledge or withheld information because of the researcher's status being known to the organisation and the assumption that the researcher might know the information. Furthermore, the experiences and barriers expressed by participants were subjective and might be influenced by recall bias, particularly in the patient sample.

5.6.4 Implications for clinical practice

Although the barriers identified in the qualitative component appeared mostly consistent with previous findings, there are currently no evidence that treatment

of OSA in CHF improve CV outcomes in the patient group. Patients with CHF do not present with EDS and a previous clinical trial that investigated the impact of CPAP treatment on CV outcomes in patients with minimal EDS, have been neutral (McEvoy, et al., 2016).

The publication of the NICE guideline (2021) for OSAHS and obesity hypoventilation syndrome in over 16s is timely and likely to contribute to clinician understanding and knowledge, however, these guidelines are relevant to the general population rather than the CHF population.

5.6.5 Implications for research

This work has highlighted the need for targeted interventions to address the gaps and barriers associated with CHF patients and clinicians in the detection, diagnosis, and treatment of OSA, however, hard outcome data to justify screening and treatment of OSA in CHF, is lacking. The findings of the ADVENT-HF trial are eagerly awaited. With a neutral outcome, evidence will remain inadequate to justify the screening and treatment of OSA in CHF. However, if the trial shows that the use of ASV for the treatment of OSA in CHF improves CV outcomes, findings from this study will provide a foundation for the development of interventions for the upskilling of HF clinicians and the improvement of CPAP uptake and adherence through targeted interventions.

5.6.6 Conclusion

Findings from the qualitative component of this thesis identified several key barriers and enablers across the OSA diagnostic pathway which are likely to provide a foundation for targeted interventions to improve the diagnosis of OSA in CHF. However, outcome data to justify screening and treatment of OSA in CHF is currently lacking. It is anticipated that findings from the ADVENT-HF trial will provide further insight into the management of OSA in CHF.

To build on the findings from this chapter, Chapter 6 of this thesis will evaluate HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

6

Evaluating Heart Failure Clinicians' Knowledge, Attitudes and Clinical Practices in relation to the Diagnosis and Treatment of Obstructive Sleep Apnoea

6.1 Introduction

Clinicians play a key role in the recognition of OSA and should have a high index of suspicion for OSA in at-risk patient groups. In Chapter 5 of this thesis, HF clinicians reported variable awareness and knowledge of OSA as a barrier to the diagnosis and treatment of OSA. There are several reports documenting lack of awareness amongst clinicians across clinical specialities, notably for patients with CHF who share many of the salient risk factors for OSA (Chung *et al.,* 2001; Southwell *et al.,* 2008; Wang *et al.*, 2012; Chérrez Ojeda *et al.*, 2013; Corso *et al.,* 2017; Solanki *et al.,* 2019).

Due to a lack of evidence pertaining to the level of understanding of OSA among HF clinicians in the UK and to further explore the findings from Chapter 5 of this thesis, the aim of this survey study was to evaluate HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

6.2 Aim

The aim of this chapter is to describe the evaluation of HF clinicians' knowledge, attitudes and clinical practice in the diagnosis and treatment of OSA through the utilisation of a web survey.

6.3 Materials and Methods

6.3.1 Study Design

A web based (Jisc Online survey), cross-sectional survey study was conducted among HF clinicians (doctors, nurses, and pharmacists) from England, Scotland and Wales between March 2018 and January 2019. The study was approved by the Health Research Authority and the East Midlands-Leicester South Ethics Committee (REC 17/EM/0400). Details of regulatory approval and ethical considerations are discussed in Chapter 2.

6.3.2 Study Participants

Study participants included clinicians with an interest and expertise in the active management of patients with CHF. Medical consultants, trainees, associate specialists, general practitioners with specialist interest, nurses and pharmacists were eligible to participate. Clinicians other than doctors, nurses or pharmacists were excluded from participating in the study.

6.3.3 Study Procedures

6.3.4 Sampling

Non-probability, convenience sampling was utilised for this web-based survey.

Although non-probability sampling has proven to be a more cost and time-efficient sampling approach, one of its key limitations is underrepresentation of the population. A lack of random selection associated with non-probability sampling often poses the risk of under coverage and non-response, making statistical inference inappropriate (De Leeuw *et al.*, 2008; Baker *et al.*, 2013).

Probability sampling would have been the sampling strategy of choice, however, it proved difficult to access a representative list of HF clinicians in England, Scotland, and Wales. The BSH has a membership of more than 1200 HF clinicians. Access to a sample of the BSH membership would have been preferential, however, it is BSH policy not to promote individual research

studies and consequently the request to distribute the survey to the BSH membership was declined by the BSH Board.

6.3.5 Recruitment

The survey was promoted as an inclusion in the British Cardiovascular Society (BCS) members newsletter and distributed through the membership of the British Association for Nursing in Cardiovascular Care (BANCC), HF Pharmacist Group, Scottish HF Specialist Nurse Forum, and the Pumping Marvellous Foundation Facebook page for HF nurses. In addition, the survey details were posted on the webpage and in the first newsletter of the BSH Nurses Forum.

Members of the BANCC (229 members), Scottish HF Specialist Nurse Forum and HF Pharmacist Group (20 members) received an email to inform them of the web-based survey (**Appendix 32**). It gave the rationale for the survey and invited them to participate. A reminder email was sent after 2 weeks (**Appendix 33**). The participant information sheet and the survey link were embedded in both emails (**Appendix 34**).

Seventy-eight members of BANCC opened the email and 11 clicked on the link. Eight members (40%) of the pharmacist group completed the survey. It was not possible to determine the responses from the BCS, Pumping Marvellous Foundation Facebook page or the BSH Nurses Forum.

As a result of the above distribution strategy, clinicians from other professions might have received the invitation to participate. Therefore, the letter of invitation clearly stated that if they were not a doctor, nurse, or pharmacist, that they were not eligible to participate. All respondents were asked to divulge and record their profession in the survey.

6.3.6 Survey Responses

Response rates are generally a key challenge in survey research. Coverage and sampling error can both result from the sampling method applied in web-based surveys. Not every individual uses the internet, resulting in coverage

error whilst not everyone that uses the internet will necessarily have an equal chance of being selected to participate in the web-based survey, resulting in sampling error. Furthermore, with non-probability sampling, it is not possible to determine the probability of selecting members of the target population and therefore results cannot be generalised to the main population (Couper, 2000).

Completion of web surveys often take place within the first few hours or days upon receipt and will increase with pre-notification and follow-up reminders with a maximum response after four repeated reminders. Pre-notification can influence a potential respondents' decision to log in to the web survey, whilst a first reminder email is most effective two days after the initial invitation contact (Crawford *et al.*, 2001). Surveys sponsored by an academic or government organisation are likely to have higher response rates (Heerwegh & Loosveldt, 2003).

Questionnaire content and presentation are also closely related to survey response rates. Heerwegh & Loosveldt (2003) suggest that the use of personalisation in the design of the email invitation can yield higher response and completion rates. Furthermore, the wording, ordering and visual display of the questions in the survey questionnaire can affect response rates and have a direct impact on measurement error (Couper, 2000). Potential respondents are also more likely to complete the survey if it is shorter as evidence suggests that completion time of ≤13 minutes is likely to generate a good response rate (Handwerk *et al.*, 2000). Web-based surveys frequently have lower response rates, often ≤10%. Additionally, higher drop-off rates are reported after 10-15 questions, suggesting that drop-offs are negatively and directly correlated with the length of the questionnaire (Fan & Yan, 2010).

Technical challenges are not uncommon in web-based surveys. The use of low internet coverage and spam filters often have an adverse effect of survey responses (Callegaro *et al.*, 2015). Additionally, variance in devices, browsers and internet connections often result in respondents not being able to browse or submit their survey responses (Fan & Yan, 2010).

Topic salience strongly influences survey responses, suggesting that potential respondents are more likely to complete the survey if the survey topic is of interest to them (Dillman, 2007). It is therefore possible that respondents may differ from non-respondents. Not only are respondents more likely to be conscientious and agreeable than non-respondents, but they also appear to have a higher emotional stability and therefore more likely to complete the survey when they log in (Fan & Yan, 2010). Response rates commonly vary with socio-demographic factors, including age and ethnicity (Couper, Conrad & Tourangeau, 2007).

To maximise the response rate for this survey, the survey link was sent in an introductory email that gave an overview of the project, including the time required to complete the survey. The invitation email was sent from an institutionally sanctioned email address to validate the researcher's identity. Similarly, an institutionally sanctioned survey provider was used.

In this survey, all personal and demographic information was obtained at the beginning of the survey and respondents were not asked for email addresses or contact details. The survey format was simple and avoided unnecessary graphics, grid, and open-ended questions. Respondents were given clear instructions on how to complete the questionnaire, and where possible, a follow-up reminder was sent.

Due to a set number of questions in the modified OSAKA questionnaire, it was not possible to limit the number of questions to the suggested 15. Consequently, it took on average 15 minutes to complete the survey, instead of the recommended 10 minutes.

Applying the same basic principles relevant to mail surveys, survey questions should be simple and unbiased. Due to the set number of questions in the modified OSAKA questionnaire it was not possible to modify the survey questions, however, the additional questions on participant demographics and clinical practice that was constructed were simple and clear to understand. Dillman and Smyth (2014) suggested that when transforming a mail survey in

paper-pencil format to a web-based survey, it might be more challenging for participants to select the correct answer with an online questionnaire than to circle it in a mail survey. However, feedback from the pilot survey did not suggest either changes to the question format, or issues with selecting the correct answers.

Although pre-paid incentives may favourably affect survey response rates, no incentives were offered for completing this survey (Porter, 2004).

6.3.7 Informed Consent

The latest version of the participant information sheet, embedded in the letter of invitation, was emailed to participants. The letter of invitation explained the purpose and the rationale for the survey study. It stated clearly that participation is voluntary and that participants can withdraw at any time. Participants were also free to omit any questions. The letter of invitation addressed the possibility of risk. Although there were no known risks associated with completing the survey, there was the potential of breach with online related activity. To minimise this risk, survey responses were encrypted to ensure secure data transmission. The importance of anonymity and confidentiality were emphasised in the invitation letter and in the survey itself. Following data export, electronic databases had restricted access, were password protected and contained no personal identifiers. Completion and submission of the survey were accepted as implied consent.

6.3.8 Data Collection Tool

The survey questionnaire was uploaded to the Jisc Online Surveys and consisted of a demographics section, the OSAKA questionnaire and a section on diagnostic methods used in clinical practice (**Appendix 35**) (Southwell *et al.*, 2008).

6.3.8.1 Questionnaire Preparation

The modified OSAKA questionnaire was originally designed as a paper-based questionnaire consisting of 22 statements (true/false/don't know), two multiple

choice questions on prevalence, one rank question and five attitude/confidence statements (Likert Scale responses) (Schotland & Jeffe, 2003). Using a simple design approach, the above paper-based questionnaire was transformed into an online questionnaire.

Page one of the survey hosted the introduction page. It outlined the purpose of the study and details of the research sponsor and research team. It emphasised that participation was voluntary and that respondents can withdraw at any time. The introduction page informed respondents about potential risk of data breach and the measures that were put in place to mitigate this risk, including encryption and password protection. It addressed the issues of consent and informed respondents that the survey may take an estimated 15 minutes to complete.

To reduce the number of drop-offs, a progress indicator was used and visible from the first page with an option to "finish later". The University of Leicester Logo was displayed on all the pages of the survey against a slate background. A 12-point Arial font size with a white font colour against a darker slate background. The use of the font, font size and background colour were consistent across the survey.

The survey consisted of 12 pages of which page one was the introduction page followed by five demographic questions on page two. Clear instructions were provided on the completion of the questions and answer options were in the format of radio buttons and one free text box. Participants were free to omit any questions with no push to complete all the survey questions.

The next five pages consisted of the Modified OSAKA questionnaire. Each page accommodated five to six questions with answer options in the format of radio buttons. The answer format for the two questions on risk factors and association of OSA with other conditions were in the form of tick boxes with the option to tick "all that apply". The only rank question was in the format of a grid allowing only one answer per row and per column. The answer format for the

questions on clinical practice were tick boxes with the option to tick "all that apply".

The final page of the survey consisted of a debriefing sheet thanking all respondents and reminding them of the purpose of the study, confidentiality, and contact details of the research team. Participants were also reminded that they have the right to withdraw and may request a summary of the study results.

6.3.8.2 Questionnaire Content

6.3.8.2.1 Demographics

The first section of the survey consisted of five questions about the demographics of the respondents and included the place of work, level of current practice, gender, age, year, and primary qualification

6.3.8.2.2 (Modified) OSAKA Questionnaire

The main section of the survey consisted of the OSAKA questionnaire (Southwell *et al.,* 2008), an adaptation of validated OSAKA questionnaire that was developed and validated to assess physicians' knowledge and attitudes about OSA in the United States (Schotland & Jeffe, 2003).

The original OSAKA questionnaire was designed as a paper-based questionnaire consisting of 18 knowledge and five attitude questions. The knowledge question set consisted of 18 true, false or "don't know" statements and included questions on the following domains: (1) Epidemiology (2) Pathophysiology (3) Symptoms (4) Diagnosis (5) Treatment. All "don't know" responses were considered as incorrect responses.

The five attitude questions utilised a five-point Likert scale format (not important, somewhat important, important, very important, extremely important) to allow respondents to rate their level of agreement with the relevant statements. The first two attitude questions consisted of statements about the importance of OSA as a clinical condition and the importance of identifying individuals with the disease.

The remaining three questions consisted of statements about respondents' confidence (strongly disagree, disagree, neither agree nor disagree, agree, strongly agree) in the diagnosis and treatment of OSA (Schotland & Jeffe, 2003).

To determine cardiologists' knowledge of the relationship between sleep apnoea and CV disease, the original OSAKA questionnaire was modified to include an additional 20 question items and additional attitude questions. The supplemental questions were reviewed by three sleep medicine specialists and relevant modifications were made on their feedback. None of the original questions from the OSAKA questionnaire were modified. The modified version of the OSAKA questionnaire therefore consisted of 38 knowledge question items and six attitude questions. (Southwell *et al.*, 2008).

The knowledge component of the modified questionnaire now consisted of 22 statements (true, false, don't know responses), two multiple choice questions on prevalence (selecting one correct answer per question), one question on known risk factors for OSA and one question on conditions associated with OSA. Both questions allowed respondents to select any number of correct responses. As part of the attitude questions, participants were asked to rank OSA according to relative importance to other clinical conditions, including diabetes mellitus, hypertension, degenerative joint disease, and asthma. A further two questions related to respondents' attitude to OSA as a clinical condition and to the importance of identifying patient with possible OSA. Three questions related to respondents' confidence in identifying patients with OSA and management of patient with OSA and on CPAP. All attitude and confidence questions were based on a five-point Likert scale (Southwell *et al.*, 2008).

6.3.8.2.3 Clinical Practice

The third section of the survey consisted of four questions related to diagnostic methods and OSA screening questionnaires used by HF clinicians in clinical practice.

6.3.8.3 Pilot Survey

A pilot survey was conducted prior to distributing the survey to the target audience of HF clinicians. The purpose of the pilot survey was to:

- evaluate the functionality of the web-based survey,
- ensure technical correctness, including stability across browsers, operating systems and that the survey displayed correctly for all respondents including those who viewed the survey on a mobile phone, tablet, or screen reader,
- discover and address practical problems, and
- to evaluate the ease of data entry and to ensure that respondents understand the questions (Callegaro *et al.*, 2015).

For the pilot study, the survey was emailed to HF specialist nurses (n=20), HF consultants (n=9), cardiology specialist trainees (n=3) and pharmacists (n=7). Of this group, 22 clinicians, including consultants (n=4), specialist trainee (n=1), HF specialist nurses (n=14) and pharmacists (n=3) completed the pilot survey.

A feedback sheet consisting of seven questions were available at the end of the pilot survey. All respondents reported that they were able to access the participant information sheet from the invitation email and had no difficulty to access the survey from the survey link.

Respondents used desktop and laptop computers to access the survey. None of the respondents reported any difficulty with the visual display of the survey. All the respondents reported that the instructions for completing the survey were clearly written.

Ninety five percent of respondents felt that the questions were easy to understand. None of the respondents had any suggestions regarding the clarification of instructions or improvements in the format. Participants took on average 16 minutes to complete the survey. Several general feedback comments from the pilot survey included:

- "Spelling apnoea"

- "The questionnaire was wide ranging. My knowledge of OSA is not that great and I found that I was unsure regarding many of the questions but felt that I should have a go at answering rather than clicking don't know."
- "I think sleep apnoea is a poorly recognised risk factor in many conditions in physical and mental health. I think this is a very interesting study."

6.4 Data Analysis

Data were explored using descriptive statistics. Demographic data and results from the survey were analysed using MS Excel and STATA 16 (STATA Statistical Software: Release 16. College Station, TX: StataCorp LLC. StataCorp.).

Data were assessed for normality. Empirical distribution of the knowledge scores for all three professional groups (doctors, nurses, pharmacists) did not fit normal distribution. In view of the data distribution and small sample sizes, numerical data were reported as the median and interquartile range.

A total knowledge score was calculated for each respondent (per professional group). The overall knowledge scores out of 37 were allocated as follows:

One point for each correct answer for the 22 knowledge statements,

One point for each correctly identified as a risk factor and one point each for those correctly identified as not being a risk factor (6 points). One item from the risk factor responses was omitted in the survey and as such the overall knowledge score were out of 37 and not 38 as in the modified OSAKA questionnaire.

One point for each correctly identified associated condition and one point each for those correctly identified as not being associated with OSA. (7 points)

One point for each of the correct answers to the prevalence questions (2 points)

6.5 Results

6.5.1 Characteristics of Respondents

One hundred and two health care clinicians (doctors n=32, nurses n=62, pharmacists n=8), with an interest and expertise in the management of CHF, completed a web-based survey that assessed their knowledge of the relationship between OSA and CV disease. Most respondents were HF specialist nurses (56%) and Medical Consultants (20%) of which 70% of respondents worked in Specialist HF Services (70%) and the majority (72%) were female. Respondent characteristics are summarised in **Table 35.**

Table 35 Participant Characteristics

Description	Category	Frequency *N*=102 (%)
Place of work	Specialist HF Service	71 (70%)
	General Cardiology	18 (18%)
	General Medicine	2 (2%)
	Care of the Elderly	1 (1%)
	Community based/General Practice	5 (5%)
	Pharmacy	1 (1%)
	Tertiary Cardiology	1 (1%)
	Interventional Cardiology	1 (1%)
	Electrophysiology	1 (1%)
	University	1 (1%)
Level of Practice	Consultant	20 (20%)
	Specialist trainee (CT/ST 1+2)	9 (9%)
	Trainee (CT/ST 1+2)	0 (0%)
Doctors (n=32)	Foundation doctor	0 (0%)
	Trust Grade Registrar	1 (1%)
	GP with Specialist Interest	1 (1%)
	Clinical Research Fellow	1 (1%)
Nurses (n= 62)	Clinical Nurse Specialist	57 (56%)
	Staff Nurse	2 (2%)
	Advanced Nurse Practitioner	2 (2%)
	Consultant Nurse	1 (1%)
Pharmacist (n=8)	Pharmacists	8 (8%)
Gender	Female	73 (72%)
	Male	29 (28%)
Age Group	20-29	2 (2%)
	30-39	27 (27%)

Description	Category	Frequency *N*=102 (%)
	40-49	33 (32%)
	50-59	37 (36%)
	60-70	2 (2%)
	>70	0 (0%)
Year Group of Primary Qualification	1970-1980	3 (3%)
	1981-1990	29 (28%)
	1991-2000	29 (28%)
	2001-2010	32 (31%)
	2011-2020	2 (2%)
	Not reported	7 (7%)

6.5.1.1 Knowledge

Data were assessed for normality. Empirical distribution of the knowledge scores for all three professional groups (doctors, nurses, pharmacists) did not fit normal distribution. In view of the data distribution and small sample sizes, numerical data were reported as the median and interquartile range.

Out of a maximum knowledge score of 37, the number of correct answers provided by doctors, ranged from 21 to 35, with a score of 18 recorded as an outlier, and a median of 29 (78%) (IQR, 26-31).

No question was answered correctly by all doctors. For the epidemiology, pathophysiology, and symptom domains, >74% of doctors provided correct responses. In contrast, 67% provided correct responses in the diagnosis domain, whilst 57% of doctors provided correct responses in the treatment domain.

The highest percentage of correct responses (97%) was recorded for the association between untreated OSA and incidence of motor vehicle accidents (question 13). In contrast, the lowest percentage of correct responses (19%) was recorded for the use of laser-assisted uvuloplasty of severe OSA, also

generating the highest number of "don't know" responses (53%). In addition, 25%-41% of doctors provided "don't know" responses to six of the seven questions in the treatment domain (**Appendix 36**).

All respondents correctly identified obesity as a risk factor for OSA. Ninety four percent of doctors correctly identified male sex as a risk factor for OSA whilst only 66% correctly selected age and family. More than 91% percent of doctors were aware that cardiac arrhythmias and CHF were associated with OSA **(Appendix 37).**

Similarly, the number of correct answers provided by the nurses, ranged from 15 to 35 with a score of 11 recorded as an outlier, and a median of 26 (70%) (IQR, 22-28).

No question was answered correctly by all the nurses. For the epidemiology, pathophysiology, and symptom domains, >68% of nurses provided correct responses. Sixty one percent provided correct responses in the diagnosis domain, whilst only 46% of nurses provided correct responses in the treatment domain.

The highest percentage of correct responses (94%) was recorded for the statement "alcohol at bedtime improves OSA" (question 12). Similar to the doctors, the lowest percentage of correct responses (15%) was recorded for the use of laser-assisted uvuloplasty of severe OSA. In addition, this question also generated the highest number of "don't know" responses (71%). Sixty one percent of nurses provided "don't know" responses to the statement "uvulopalatopharyngoplasty is curative for many patients with OSA".

Between 26% and 61% of nurses provided "don't know" responses to four of the seven questions in the treatment domain. This is consistent with the low average percentage of correct responses (46%) in this domain.

Eighty two percent of nurses correctly identified male sex as a risk factor for OSA. Seventy three percent correctly selected family history, whilst 53% correctly selected age as a risk factor. Eighty four percent of nurses were aware

that CHF is associated with OSA, in contrast, only 55% were aware of the association with cardiac arrhythmias.

The number of correct answers provided by the pharmacists ranged from 15-25 with a median of 18 (49%) (IQR, 16.5-23.5).

No question was answered correctly by all the pharmacists. The highest percentage of correct responses (88%) was recorded for the statement on higher mortality in patients with Cheyne-Stokes and CHF (question 22). None of the pharmacist correctly responded to the use of laser-assisted uvuloplasty of severe OSA. All the pharmacists selected a "don't know" response to this question. The average percentage correct responses were low (33%-54%) across all five domains, with the lowest average correct responses in the treatment domain.

Seventy five percent of pharmacists correctly identified male sex and family history as risk factors for OSA, whilst only 13% correctly selected age. Seventy five percent of pharmacists were aware that CHF was associated with OSA and 50% with cardiac arrhythmias.

6.5.1.2 Attitudes

Participants answered three questions related to their attitude to OSA. The first question asked participants to rank OSA in terms of relative importance to diabetes mellitus, hypertension, degenerative joint disease, and asthma. The remaining two attitude questions were based on a Likert score and related to the importance of OSA as a clinical condition and the importance of identifying patients at risk of OSA.

When participants were asked to rank OSA as one of five clinical conditions, 56% of doctors, 37% of nurses and 63% of pharmacists felt that Diabetes Mellitus was the most important clinical condition, when compared to hypertension, degenerative joint disease, OSA and Asthma (Figure 7). Forty seven percent of doctors and 69% or nurses felt that degenerative joint disease was the least important clinical condition, whilst 38% of pharmacists felt that

OSA was the least important clinical condition. Forty four percent of doctors and 42% of nurses rated OSA as the third most important clinical condition.

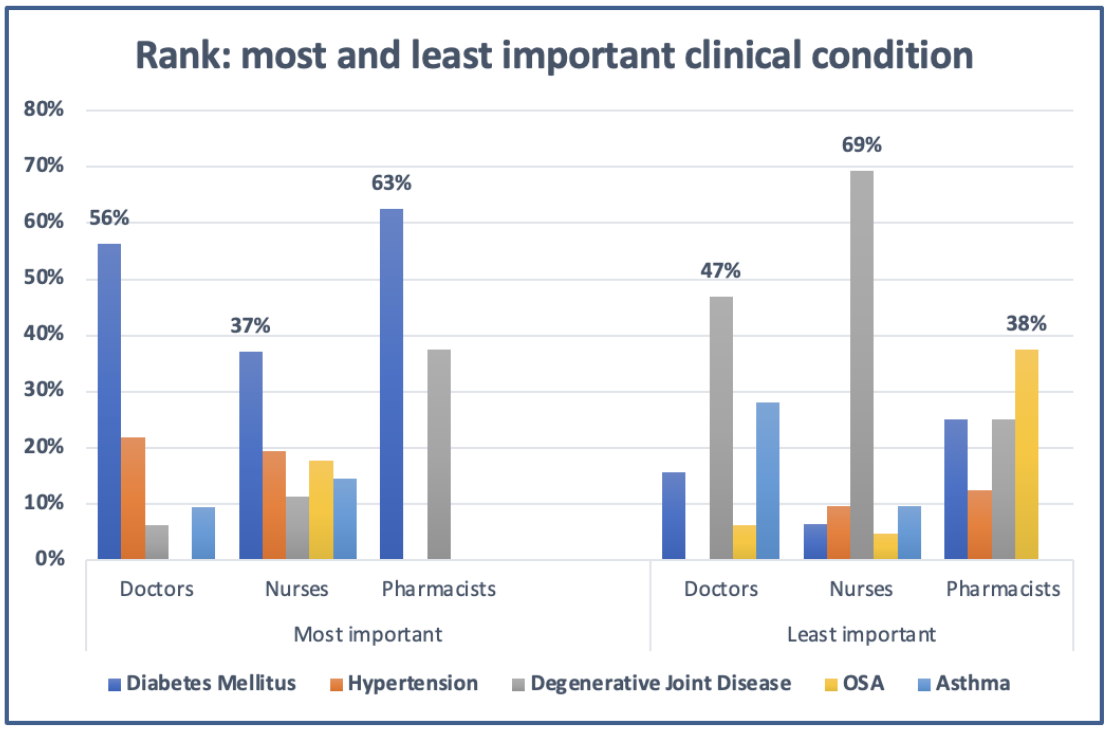


Figure 23 Most Important Clinical Condition ranked by HF Clinicians

Two attitude questions based on a five-point Likert score were interpreted as low importance (not important and somewhat important) and high importance (very important and extremely important). Sixty six percent of doctors and 74% of nurses felt that OSA was at least very important as a clinical condition, whilst six percent of both doctors and nurses felt that OSA had low importance (**Figure 23**). In contrast, only 38% of pharmacists felt that OSA had high importance as a clinical condition. An equal number of pharmacists felt that OSA as a clinical condition is of low importance.

Similarly, 63% of doctors and 77% or nurses felt that it was at least very important to identify patients at risk of OSA, whilst 9% of doctors and 6% of nurses felt that identifying patients at risk of OSA is of low importance (**Figure 24**). In contrast, only 25% of pharmacists felt that identifying patients at risk of

OSA is of high importance. Again, an equal number of pharmacists felt that identifying patients at risk of OSA is of low importance.

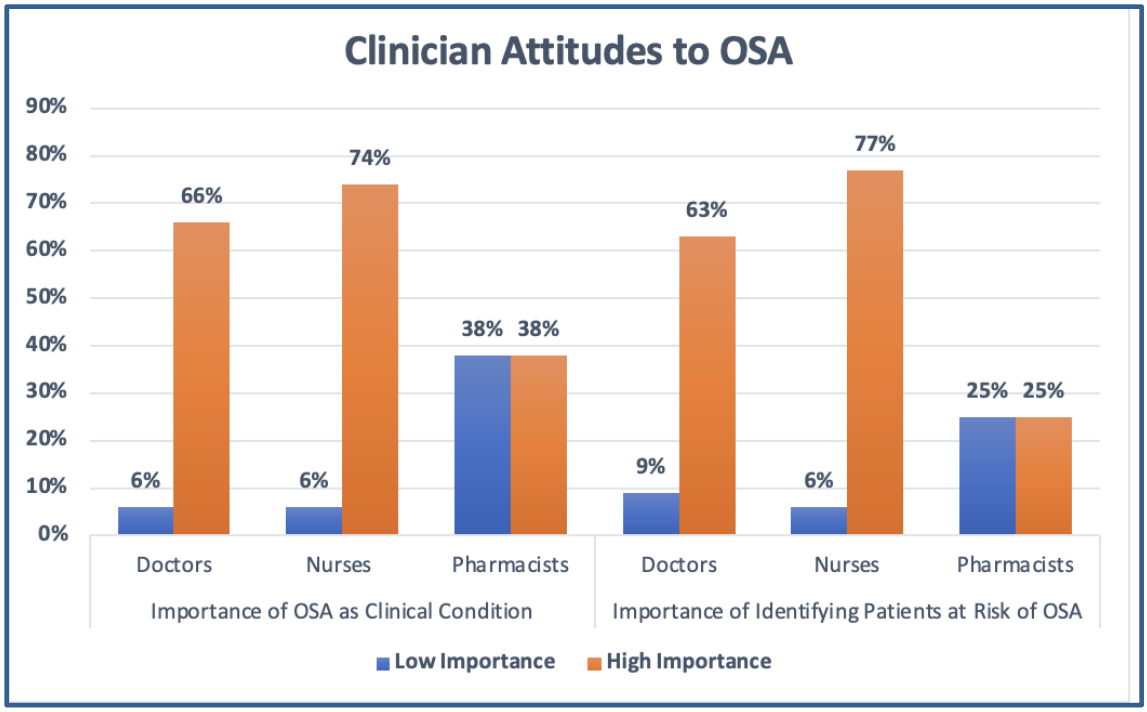


Figure 24 Clinician Attitudes to OSA

6.5.1.3 Confidence

Participants answered three questions about their confidence to identify patients at risk of OSA, managing a patient with OSA and managing a patient on CPAP treatment. Similarly, to the attitude questions, the three confidence questions were based on a five-point Likert score and were interpreted as low importance (not important and somewhat important) and high importance (very important and extremely important).

When participants were asked about their confidence, 66% of doctors felt confident to identify patients at risk of OSA (**Figure 25**). In contrast, only 36% of nurses and none of the pharmacists felt confident to identify patients at risk of OSA. Nineteen percent of doctors and 29% of nurses did not express a view on their confidence to identify patients at risk of OSA.

Twenty five percent of doctors felt confident to manage patients with OSA, whilst only 19% felt confident to manage patients on CPAP. Twelve percent of nurses felt confident to manage patients with OSA whilst 21% of nurses felt confident to manage a patient on CPAP treatment. None of the pharmacists felt confident to manage patients with either OSA or on CPAP treatment. Twenty eight percent of doctors and 27% of nurses did not express a view when asked about their confidence to manage patients with OSA. For the management of patients on CPAP, 13% or doctors and 26% of nurses, did not express a view on their confidence. All pharmacists expressed a view on their confidence levels in the three confidence domains.

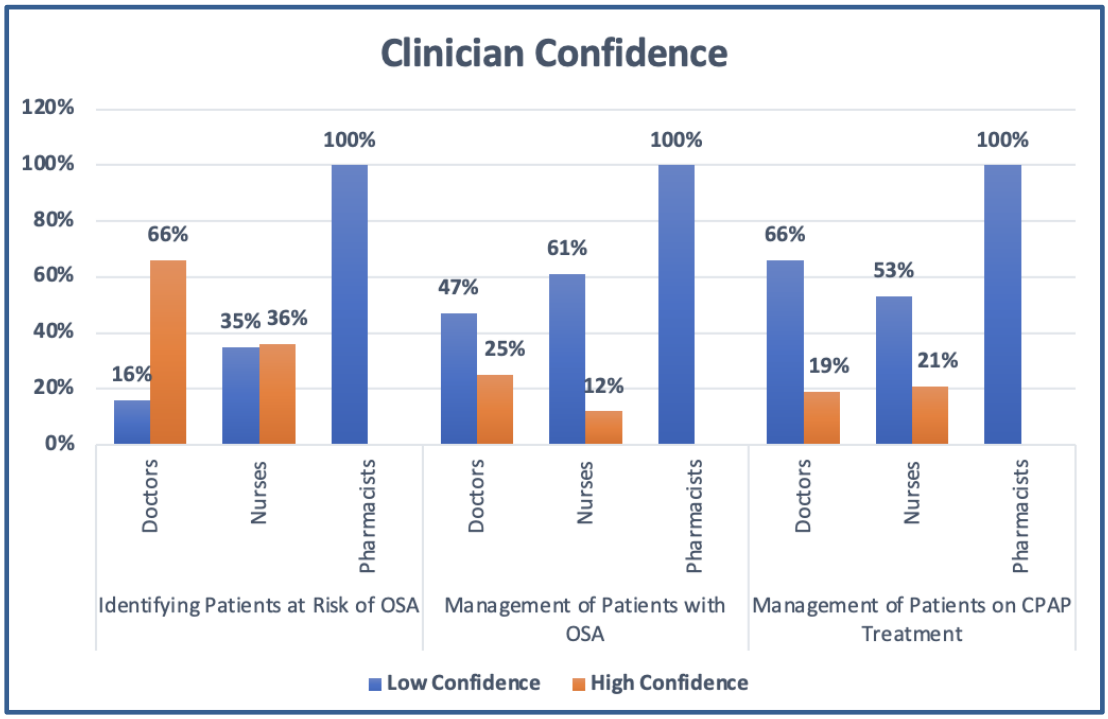


Figure 25 Clinician Confidence to identify and manage patients with OSA

6.5.1.4 Clinical Practice

6.5.1.4.1 Diagnostic Methods

Participants answered three questions on diagnostic methods, screening questionnaires and strategies used to confirm a diagnosis of OSA and were able to select any numbers of answers that apply to their clinical practice (**Figure 26**).

Ninety seven percent of doctors and nurses used clinical history to assess patients' risk of OSA, in contrast to 50% of pharmacists. At least 63% of doctors and nurses use physical examination to assess a patient for possible OSA, whilst only 13% of pharmacists consider OSA during a physical examination. Ninety one percent of doctors consider bed partner observations when assessing a patient for OSA and would refer patients to a sleep service for further investigation. Similarly, 77% of nurses consider bed partner observations when assessing a patient for OSA and 79% refer patients to the sleep service. Only 38% of pharmacists took bed partner observations into account and 25% of pharmacists referred to the sleep service. Forty one percent of doctors, 44% of nurses and only 13% of pharmacists consider sequalae, such as hypertension, when assessing a patient for possible OSA. Sixty three percent of doctors, 47% of nurses and none of the pharmacists indicated that they use screening questionnaires.

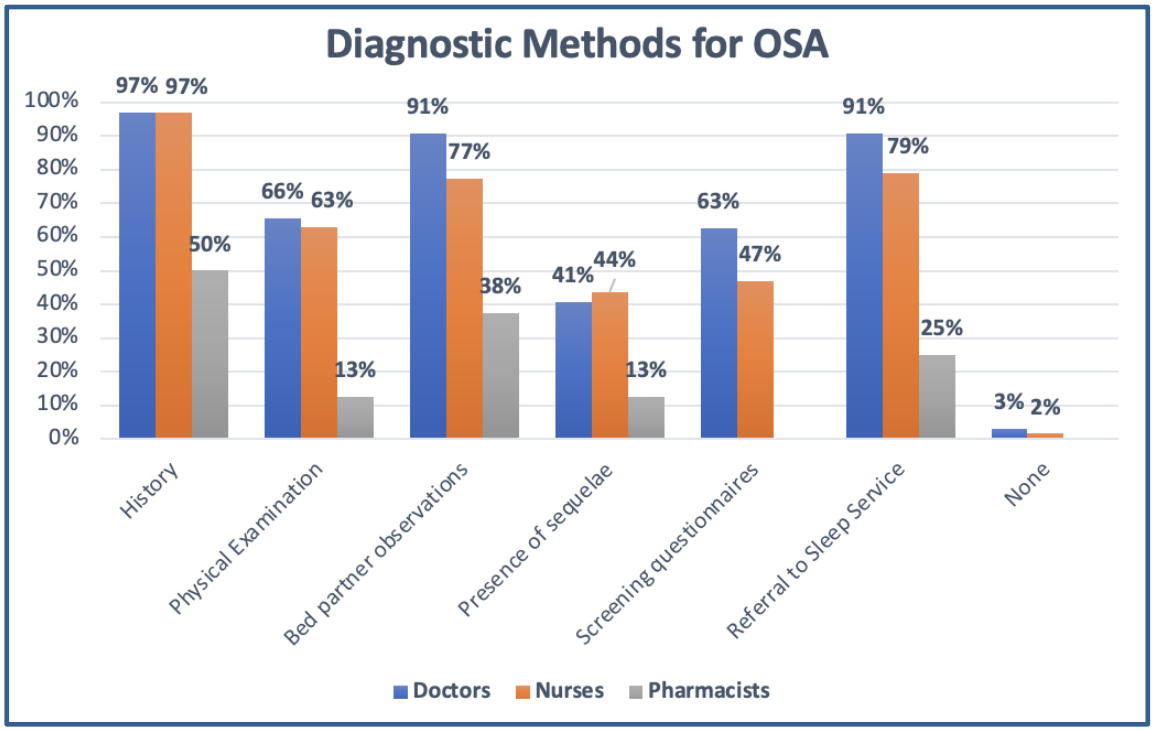


Figure 26 Diagnostic Methods used for OSA

6.5.1.4.2 Screening Questionnaires

When participants were asked in a separate question about the use of screening questionnaires, 31% of doctors indicated that they use screening questionnaires in their clinical practice, compared to the 63% in the previous question about diagnostic methods. Of the 31% who use screening questionnaires in their clinical practice, 25% use the ESS and 6% the STOP-Bang questionnaire.

Forty seven percent of nurses indicated that they use screening questionnaires in the previous question about diagnostic methods, whilst 44% indicated that they use screening questions in the second question. Of the 44%, 27% of nurses use the ESS, 2% use the Berlin questionnaire and the STOP-Bang questionnaire respectively, 2% use a combination of the Berlin questionnaire and the ESS and 11% use a combination of the STOP-Bang questionnaire and the ESS (**Figure 27**).

Pharmacists previously reported that none of them use screening questionnaires in clinical practice. However, when asked in a separate question, 64% indicated that they use screening questionnaire. Thirty eight percent use the ESS, 1% use the STOP-Bang questionnaire and 25% use as combination of the ESS and the STOP-Bang questionnaire.

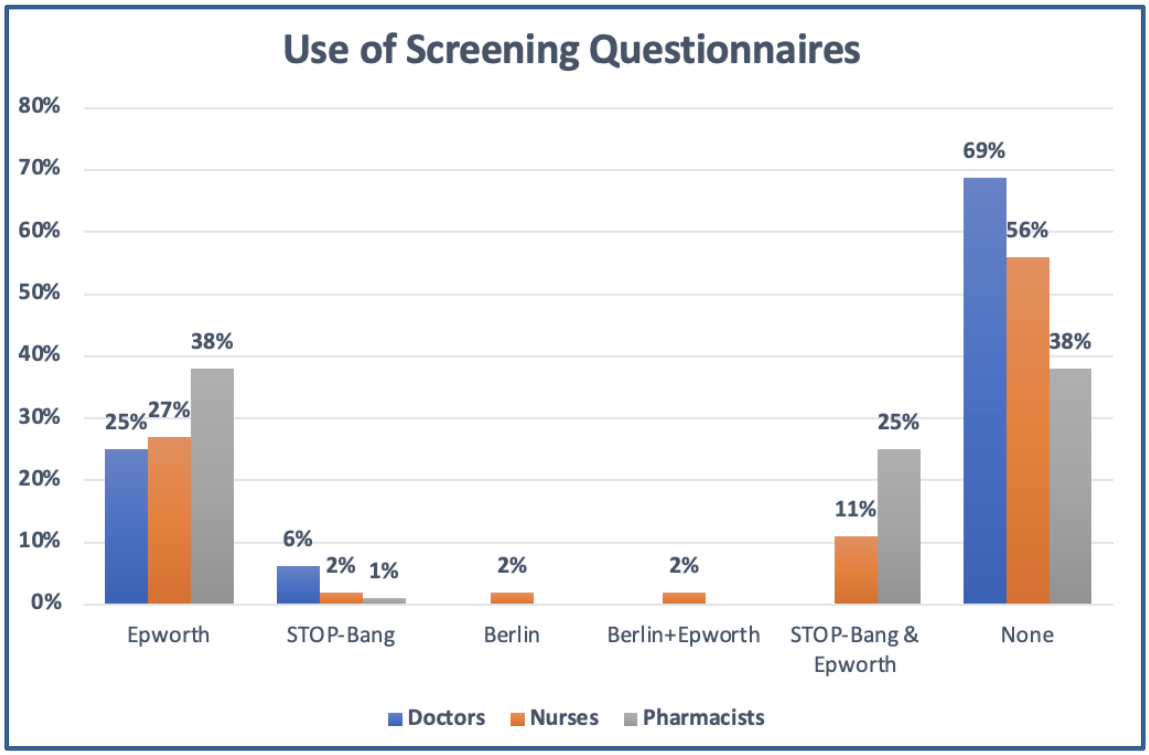


Figure 27 Use of Screening Questionnaires by HF Clinicians

6.5.1.4.3 Strategies to Confirm OSA Diagnosis

When participants were asked what strategies they use to confirm a diagnosis of OSA, 22% of doctors, 35% or nurses and 25% of pharmacists indicated that they would refer patients directly for a sleep study. Similarly, 28% of doctors and 21% of nurses will refer patients to a respiratory physician and 25-27% of doctors, nurses and pharmacists will refer patients to their GP. Forty seven percent of doctors, 32% nurses and 63% pharmacists, indicated that they will refer patients at risk of OSA to the Sleep Service for further investigation. Two percent of nurses indicated that they would use their own clinical judgement to confirm a diagnosis of OSA (**Figure 28**).

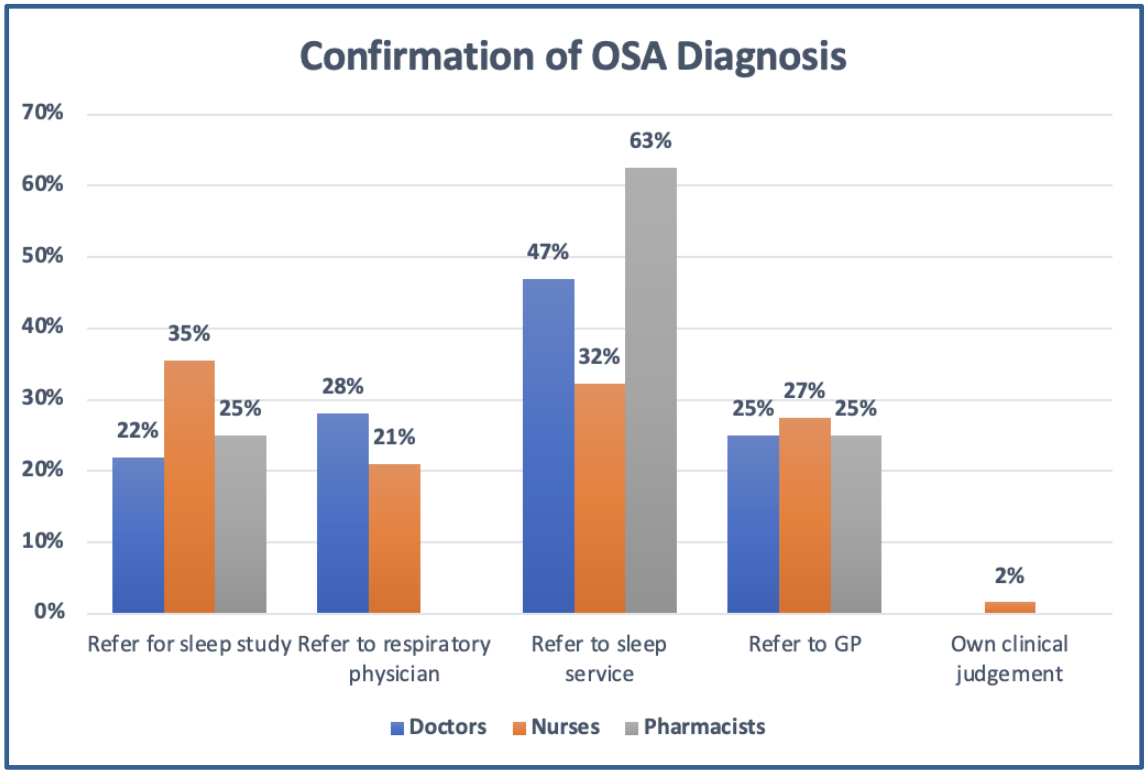


Figure 28 Strategies used by clinicians to confirm a diagnosis of OSA

6.6 Discussion

The objective of this survey study was to build on the findings from the clinician interview study (chapter 5) through evaluating HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

Doctors, nurses, and clinical pharmacists are core members of the HF multi-disciplinary team, with a pivotal role in the diagnosis and management of HF (NICE, 2018). HF treatment strategies comprise the initiation and optimisation of evidence-based medication and device therapy, but also the recognition and management of comorbidities that may exacerbate HF symptoms with a subsequent impact on patient quality of life (McDonagh *et al.,* 2021).

Evidence from observational studies suggested that untreated moderate-severe OSA in HF was associated with increased CV morbidity and mortality (Wang *et*

al., 2007). Additionally, data from small trials showed that the treatment of clinically significant OSA with CPAP improved intermediate cardiac end points, including blood pressure, EF, and arrhythmias (NICE, 2008; Drager *et al.*, 2017). In contrast, findings from the Sleep Apnea cardioVascular Endpoints (SAVE) trial were neutral and did not show CV hospitalisation and mortality benefit when treating OSA in CHF. CPAP treatment was however associated with improved patient reported outcomes and health-related quality of life (McEvoy *et al.*, 2016).

Study findings suggest a knowledge deficit of OSA among HF doctors, nurses, and pharmacists. Despite relatively high median knowledge scores, these data demonstrate a knowledge deficit of between 22-51% across clinical groups. None of the doctors, nurses or pharmacists answered all questions correctly and the largest knowledge deficit was reported in the treatment domain (doctors: 43%; nurses: 54%; pharmacists 67%).

In comparison to previous studies in different clinical specialties, the median knowledge scores for the doctors (78%) and nurses (70%) were similar to the score (76%) reported for cardiologists in the United States (US), but marginally higher than those reported for anaesthetists (62%-66%) and primary care physicians (60%-69%) (Southwell *et al.,* 2008; Wang *et al.*, 2012; Corso *et al.,* 2017; Solanki *et al.,* 2019; Chung *et al.,* 2001; Chérrez Ojeda *et al.*, 2013). Scores for medical students (42% and 59%) were much lower, but in a similar range to the pharmacists (49%) in this study (Ozoh *et al.,* 2015).

Although a high proportion of HF doctors and nurses felt that OSA as a clinical condition was of high importance and that HF clinicians should identify patients with the condition, OSA was ranked as the third most important clinical condition, relative to diabetes mellitus, hypertension, degenerative joint disease, and asthma. Despite the perceived importance of OSA in CHF, findings from survey results showed a knowledge deficit of OSA across professional groups.

In contrast, in previous reports as many as 90% of anaesthetists, 78% of cardiologists and 72% of primary care physicians, felt that OSA was important (Wang *et al.*, 2012; Corso *et al.,* 2017; Solanki *et al.,* 2019; Southwell *et al.,* 2008; Chung *et al.,* 2001; Chérrez Ojeda *et al.*, 2013).

Despite knowledge scores of at least 70% and recognising the importance of OSA, most doctors and nurses were lacking confidence to manage patients with OSA and on CPAP treatment. Furthermore, pharmacists had a very low knowledge score and as such rated the condition as low importance and lacked confidence in all areas.

Confidence levels in the doctors' group were comparable to US cardiologists, anaesthetists, and primary care physicians. In contrast, nurses and pharmacists reported much lower confidence levels (Southwell *et al.*, 2008, Wang *et al.*, 2012, Corso *et al.,* 2017, Chérrez Ojeda et al., 2013; Ozoh *et al.,* 2017, Ozoh *et al.,* 2015, Chérrez Ojeda *et al.*, 2018).

Most doctors, nurses and pharmacists reported that they will refer patients to a sleep service for suspected OSA. Overall, these findings suggest some variability in clinical practice among HF clinicians.

Although existing clinical practice guidelines provide recommendations on the use of CPAP in adults (NICE, 2008), the latest practice guideline offers detailed guidance on the assessment, diagnosis and treatment of OSA (NICE, 2021). Despite being a welcome addition, the above-mentioned guidelines are mostly relevant to the general population due to a current lack of evidence to show prognostic benefit for treating OSA in CHF. From a HF perspective, there is a paucity of evidence-based clinical guidelines to inform the management of co-existing OSA in CHF.

Of the clinicians who reported the use of a screening questionnaire, the ESS was most used, alone or in conjunction with the STOP-Bang questionnaire. The use of the ESS and STOP-Bang questionnaire are recommended in clinical guidelines (NICE, 2021); however, this is again more relevant to the general population. Firstly, CHF patients often report less EDS or indeed atypical

symptoms, therefore rendering absence of sleepiness and the subsequent use of the ESS an unreliable measure to rule out OSA in this patient group (Arzt *et al.*, 2006). Secondly, in addition to the ESS, the use of the STOP-Bang questionnaire is also recommended. The STOP-Bang questionnaire has not been validated in a CHF cohort. As highlighted in chapters 2,3 and 4 of this thesis, many of the STOB-Bang validations studies were conducted in sleep clinic cohorts which are limited by selection bias, spectrum effect and high prevalence which is unlikely to give an indication of the predictive values of this questionnaire in a CHF cohort.

The survey study suffers from the limitations inherent in all survey-based reports. Recognised limitations of the study include the use of a non-probability sampling approach due to cost and time-efficiency, which may be limited by under representation of the population and the relatively small sample size may further affect the generalisability of the survey results. A key strength of the survey is the use of a validated questionnaire.

6.7 Conclusion

Findings from the survey study demonstrated a knowledge deficit in the diagnosis and treatment of OSA, and variable practice among HF clinicians in the UK. The current absence of evidence to support the treatment of OSA in CHF and paucity of HF guidelines to inform the management of co-existing OSA in CHF, is likely to contribute to HF clinicians not prioritising the recognition and treatment of OSA in this patient group.

Findings from the ADVENT-HF trial are likely to influence the requirement to address the knowledge deficit of OSA in CHF. If the trial is neutral, there will be little incentive to increase awareness and knowledge of OSA among CHF clinicians. However, if the trial demonstrates prognostic benefit in treating OSA in CHF, upskilling of HF clinicians in the recognition and management of OSA, will be required.

Chapter 7 will discuss and integrate the findings of the qualitative and quantitative components of this thesis that explored factors associated with the diagnosis and treatment of OSA in CHF.

7

Discussion

Chapter 7 presents the final chapter of this doctoral thesis. The aim is to discuss and integrate the findings of the qualitative and quantitative study components, highlighting the key barriers and the clinical implications of these findings

7.1 Study Synopsis

CHF is a significant health problem associated with a considerable burden of disability and global economic impact. Despite the effect of pharmacological and device therapies on CHF related deaths and disability, many patients continue to experience persistent symptoms and progression of their condition, often exacerbated by the presence of comorbidities, such as OSA, a condition that contributes to both to the development and progression of CHF. Despite a high prevalence, OSA remains largely under diagnosed and under treated with a negative impact on the individual patient and health care systems as complications developed.

The overarching aim of this thesis was to explore factors associated with the diagnosis and treatment of OSA in CHF. A convergent, parallel MMR study design was utilised to achieve the following objectives:

- Evaluation of the accuracy and clinical utility of existing questionnaires, when used alone, as screening tools for the identification of OSA in adults in different clinical cohorts.
- Prospective evaluation of the ability of the STOP-Bang questionnaire to detect or exclude OSA in a sleep clinic population with a co-existing diagnosis of CHF.
- Identification of barriers to and enablers of the diagnosis and treatment of OSA from CHF patients' and clinicians' perspectives.
- Evaluation of HF clinicians' knowledge, attitudes, and clinical practices in relation to the diagnosis and treatment of OSA.

7.2 Factors associated with the Diagnosis and Treatment of OSA in CHF

Key barriers associated with the diagnosis and treatment of OSA in CHF revealed from this thesis, are listed below.

7.2.1 Lack of Evidence

Earlier observational cohort data have indicated a potential causal relationship between OSA and the risk of CV disease. It was suggested that the use of CPAP treatment for severe OSA might reduce CV risk (Somers *et al.,* 2008). However, evidence provided solely by observational data can be misleading, particularly when subsequent randomised trials demonstrate limited treatment benefit or harm. A key example is the SERVE-HF trial that failed to demonstrate treatment benefit and unexpectedly showed increased CV mortality and harm when treating CSA with ASV in CHF (Cowie et al. 2015).

The rationale for OSA treatment is mainly to alleviate symptoms, particularly EDS. However, due to different OSA phenotypes, the recognition and diagnosis of OSA have been challenging. In the general population, individuals with OSA commonly present with EDS (Ye *et al.,* 2014). CPAP treatment of clinically significant OSA in this group has been well established and is supported by clinical practice guidelines (NICE, 2008; NICE, 2021). In CHF patients, who typically present with minimal or no symptoms of OSA, there is currently no real evidence of CV hospitalisation and mortality benefit for OSA treatment (Chapter 1). The SAVE trial was the first to investigate the use of CPAP on CV outcomes in minimal symptomatic CV patients. Findings failed to show CV hospitalisation or mortality benefit when treating moderate-severe OSA with CPAP. In contrast to the general population, there are currently no hard outcome data to suggest that CPAP treatment of minimal symptomatic OSA in CHF improves patient outcomes (McEvoy et al., 2016). A further clinical trial, ADVENT-HF, investigated the effect of ASV on HFrEF with either OSA or CSA and minimal daytime sleepiness (Perger *et al.,* 2017). Whether ASV treatment for SDB will be associated with improved clinical outcomes in CHF will remain unknown until completion of the trial.

Findings from the semi-structured interviews of CHF clinicians highlighted clinicians scepticism about current evidence for the treatment of OSA in CHF (Chapter 5) (e.g. *"I've got loads of evidence on the one side for the drugs and I've got not very much awareness on the other side …."*).

Despite the current lack of hard outcome data, it remains important to recognise the presence of SDB in patients with CHF. Firstly, due to a high risk of mortality, optimisation of evidence-based treatment and effective management of their CV risk factors, might improve their SDB. Secondly, in the minority of patients who might present with EDS or significant fatigue, treatment of OSA could improve their quality of life.

7.2.2 Lack of Clarity in Guidelines and Policy Documents

The current lack of evidence for the treatment of OSA in CHF is likely to contribute to the lack of clarity in CHF clinical guidelines. In respiratory or sleep medicine, patients present with EDS and existing clinical guidelines provide guidance on the diagnosis and treatment of clinically significant OSA. The NICE technology appraisal (2008) concluded that CPAP is a clinically effective and cost-effective treatment option for the treatment of clinically significant OSA, whilst recently, NICE released a clinical guideline for the diagnosis and treatment of OSAHS and obesity hypoventilation syndrome (NICE, 2021). It provides clear guidance on the presentation, diagnosis, and treatment of OSA in patients who present with typical symptoms of OSA. However, these guidelines do not pertain to the CHF population due to differences in presentation and current lack of evidence for the treatment of OSA in CHF.

The current lack of hard endpoint data for the treatment of minimally symptomatic OSA in CHF has contributed to a paucity of guidance on the management of OSA in CHF clinical guidelines. There is currently no information on the management of OSA in the NICE (2018) CHF guidelines, whilst the European Society of Cardiology CHF guidelines (McDonagh *et al.,* 2021) briefly refers to OSA in this patient group. It emphasises the importance of screening questionnaires, and that PSG remains the definitive investigation, however, it provides little detail in this regard. It is therefore unsurprising that the majority of clinicians reported that they were unaware of guidelines

pertaining to the management of OSA (e.g. *"I don't know any of the guidelines for the management of OSA"*).

7.2.3 Lack of Effective Screening Tools

Because CHF patients with OSA often present with no or minimal symptoms, screening questionnaires that rely on patient symptoms, particularly EDS, may be less effective. SDB is briefly covered in the European Society of Cardiology CHF guidelines, although the guidance on screening questionnaires has been vague, providing little insight into which questionnaires are effective and have been validated in a CHF population (McDonagh *et al.,* 2021).

Findings from the clinicians' interviews and the survey study both reported variable use of screening questionnaires by clinicians. Although more than half of clinicians reported during the interviews that they use a screening questionnaire in clinical practice (e.g. *"I would go through the STOP-Bang and the Epworth score…*"), findings showed that some clinicians were unaware of existing screening questionnaires (e.g. "*I couldn't name a screening tool or measure of obstructive sleep apnoea*"), whilst others reported in the survey that they do not use any screening questionnaires in their clinical practice. Despite its lack of effectiveness in CHF, at least a quarter of clinicians reported using the ESS, a measure of sleep propensity, in their clinical practice.

Clinician perception of questionnaire accuracy is likely to contribute to the variable use of screening questionnaires. Interview data highlighted clinician scepticism about the accuracy of existing screening questionnaires (e.g. *"screening questionnaires are not very good…" and "…they are not very precise…").* The diagnostic accuracy and clinical utility of existing screening questionnaires were explored in Chapter 3. Findings showed that the STOP-Bang questionnaire had the highest sensitivity to detect OSA in the sleep clinic and surgical populations, but the use of this questionnaire was limited by low specificity. Most of the included validation studies were conducted in sleep clinic cohorts and none in a CHF cohort. Due to differences in prevalence, risk of selection bias and spectrum effect, validation in sleep clinic populations are unlikely to reflect the true performance of the STOP-Bang questionnaire in a stable CHF population. In view of the asymptomatic presentation of CHF

patients and the reliance of the STOP-Bang questionnaire on OSA symptoms, the true accuracy and utility of the STOP-Bang questionnaire in CHF remain unclear. Should the evidence for the treatment of OSA in CHF change in the future, it is possible that a HF specific questionnaire might be required to patients at-risk of OSA.

7.2.4 Disconnect between clinical importance and level of knowledge

Clinicians stated that they felt that OSA was an important clinical condition, however, study findings demonstrated a disconnect between the stated level of clinical importance and clinicians' actual level of knowledge. Survey findings (Chapter 6) demonstrated that most doctors and nurses felt that OSA was a very important condition and that it is very important to identify OSA in CHF. Similarly, interview data (Chapter 5) showed that clinicians felt that any condition that impacts on CHF, including OSA, was deemed as part of their job and responsibility ("…*I think that anything that impacts upon heart failure is part of our job*…."). Although they did not feel that the management of OSA was part of their role, clinicians reported that identifying patients at risk and referring them for investigation and management of OSA were important and perceived as part of their role ("*patients who are coming to me with other issues …. I need to signpost them on to the appropriate members..."*).

Despite the perceived importance of OSA, both interview and survey data reported low levels of knowledge and confidence among clinicians. Survey findings suggested a knowledge deficit of OSA among clinicians which resonated with the interview results (*"Lack of awareness about what the signs and symptoms are of sleep apnoea, how to access sleep services …")*. In addition to lack of knowledge of the clinical condition, clinicians reported that they were unaware of the referral process ("*People don't know what to do with it, do I go back to the GP, do I refer them direct, …*"). Because they do not have sufficient knowledge of OSA, clinicians reported that they rely on stereotypical presentation of OSA, ("*very overweight and hypertensive and you look like you're falling asleep in clinic")* and that their lack of knowledge also influences the quality and amount of information they provide to patients ("I don't give them any particular information because I don't know…").

Although OSA was perceived as a very important condition, clinicians felt that it is not frequently mentioned and therefore seen as low priority in clinical practice. Knowledge and awareness were likely to be further impacted by a reported lack of information and training opportunities.

In addition to the knowledge deficit, both the survey and interview showed that the nurses and pharmacists reported low confidence in the identification and management of OSA ("*I'm not over-confident and I would find it hard to actually look for someone with sleep apnoea")*.

The current absence of evidence to support the treatment of OSA in CHF and paucity of CHF guidelines to inform the management of OSA in CHF, are likely to contribute to clinicians not prioritising the recognition and treatment of OSA in CHF. Although perceived as an important condition, there is currently little incentive for the upskilling of CHF clinicians in the diagnosis and treatment of OSA.

7.3 Clinical Implications

CHF disease management is supported by multiple, large, randomised trials. The current lack of substantial evidence is likely to explain why the use of CPAP for OSA has not been widely adopted and initiated in CHF. Evidence to justify screening and treatment of OSA in CHF is lacking and because most CHF patients do not present with EDS, the impact of CPAP treatment on quality of life might be less. Despite the neutral findings from the SAVE trial (McEvoy, *et al.,* 2016), results from the ADVENT-HF trial (Perger *et al.,* 2017), are awaited.

If the ADVENT-HF trial (Perger *et al*., 2017) is positive and shows that ASV treatment for SDB is associated with improved clinical outcomes in CHF, targeted interventions will be required to address the gaps and barriers identified from this study.

Firstly, a review of NICE guidelines and associated policy documents will be required to reflect the latest evidence for the diagnosis and treatment of OSA in CHF. Clinicians will require guidance on screening, initial assessment, diagnostic tests, and treatment of OSA in CHF. In addition to a review and update of current clinical guidelines, an implementation strategy will be required

to facilitate guideline implementation and to reduce the gap between the evidence and the implementation in clinical practice.

Secondly, changes to clinical guidance and subsequent screening are likely to have an impact on local clinical pathways and patient flow through clinical services. Due to high prevalence of OSA in CHF and low specificity of existing screening questionnaires, screening is likely to generate a high number of referrals to respiratory and sleep disorders services. Screening and subsequent referrals are likely to further impact on long waiting times, reporting backlogs, and limited resources. CV services will need to consider how to screen effectively for OSA to reduce inappropriate onward referrals and address potential resource implications for respiratory or sleep services.

Thirdly, to identity at-risk patients and to facilitate appropriate referrals to sleep and respiratory services, an effective OSA screening questionnaire with high sensitivity and adequate specificity will be required. Due to reliance on OSA symptoms, particularly EDS, most of the existing screening questionnaires are unlikely to be suitable. Furthermore, many of the validation studies of existing screening questionnaires were conducted in sleep clinic populations. Due to differences in prevalence, risk of selection bias and spectrum effect, validation in sleep clinic populations are unlikely to reflect the true performance of the STOP-Bang questionnaire in a stable CHF population. It is therefore possible that a HF-specific questionnaire will be required for patients with CHF, validated in both patients with HFrEF and HFpEF.

Fourthly, the knowledge deficit and low confidence of clinicians will need to be addressed to facilitate effective detection of patients at risk of OSA. Targeted interventions for clinicians upskilling, focussing on OSA presentation, diagnosis, treatment, and clinical guidelines, will be required.

Finally, low uptake and adherence to treatment in patients will need to be addressed. Targeted interventions will be required to facilitate the uptake and adherence to OSA treatment.

7.4 Limitations

Limitations associated with the methodology and findings of the individual components of this MMR study were discussed in the relevant chapters. Key limitations are listed below.

7.4.1 Systematic Review and Meta-Analysis

Findings were influenced by the limitations of the included studies. In several, the true risk of bias was unclear in several of the QUADAS-2 domains due to underreporting in the Index Test, Reference Standard and Flow and Timing domains.

The decision to exclude seven additional clinical cohorts may be considered a limitation; however, in the context of unclear, and possibly substantial, differences among these studies in the patient spectrum and disease prevalence, it was felt appropriate not to include these in the meta-analysis.

There was a high degree of heterogeneity amongst the included particularly in the sleep clinic population. Pooled results from the sleep clinic population are unlikely to be generalisable to a stable CHF population due to possible selection bias, spectrum effect and higher prevalence than expected in a stable CHF population.

7.4.2 Diagnostic Validation Study

Recruitment proved challenging due to low referral of CHF patients who met the study selection criteria. It is likely that referral numbers were influenced by clinical lack of awareness, low clinical priority, or perceived lack of prognostic benefit due to lack of outcome data for the treatment of OSA in CHF. Recruitment challenges impacted on the sample size and in conjunction with the absence of negative sleep studies, it was not possible to calculate the specificity, NPV and negative likelihood ratio for most of the AHI thresholds. In response to the recruitment challenges, it was not possible to expand recruitment to the local respiratory service due to differences in local clinical practice associated with scoring criteria and pre-screening with pulse oximetry, it was not possible to expand recruitment to this service.

Study quality and risk of bias were assessed in the patient selection, index text, reference standard and flow and timing domains. High pre-test probability and pre-screening by clinical teams have likely introduced a degree of selection bias and spectrum effect. Therefore, there was relatively high risk of bias in the patient selection domain. Risk of bias in the index test, reference standard, and flow and timing domains, were low.

Due to reporting back log, two participants were tested using the WatchPAT™300 system. Using two different devices as the reference standard may introduce verification bias and the possibility of misclassification and overestimation of sensitivity and specificity.

7.4.3 Survey Study

Recognised limitations of the study included the use of a non-probability sampling approach due to cost and time-efficiency, which in turn may have resulted in under representation of the population. Furthermore, the relatively small sample size may further affect the generalisability of the survey results.

7.4.4 Interview Studies

The intended sample size for the patient interview study was between 20 and 30 participants. Recruitment for the interview study was dependent on the number of participants recruited for the diagnostic validation study. Due to low referral numbers and subsequent low recruitment numbers for the diagnostic validation study, it was not possible to recruit the sample size as planned. From the sample of 10 participants, there were no new themes emerging and it appeared that theoretical saturation was achieved. Because the patient sample lacked ethnic diversity and had low female representation, it is possible that if more female or ethnic diverse participants were recruited, that theoretic saturation might not have been achieved. Therefore, findings from the patient interview study may not be entirely transferable to the rest of the CHF population.

Participants in the patient study sample were from a single geographical area with access to both HF and sleep disorders specialist services. It is possible that study participants might have access to a wider range of services compared to patients in other locations across the UK. Considering the

importance of the role of the partners in the detection and treatment of OSA, single patient interviews, rather than the patient-partner dyads, were considered a limitation.

In the clinician study sample, nurses were overrepresented, compared to the medical and pharmacist participants. Furthermore, medical participants were from a single secondary care institution, whilst the pharmacist participants were from a single primary care institution, raising the question of generalisability and transferability of findings.

Positionality of the researcher may have influenced how participants responded to interview questions, either by providing socially acceptable reasons for their lack of knowledge or withheld information based on the assumption that the researcher might know the information. Experiences and barriers expressed by participants were subjective and might be influenced by recall bias.

7.5 Future Research

Research underpinning the identification of barriers and enablers associated with the diagnosis and treatment of OSA in CHF, is limited in the literature. Utilising a MMR design, the purpose of this thesis was to explore and understand the barriers that are likely to influence the effective management of OSA in CHF.

Based on the SAVE trial, there are currently no hard endpoint data to support the treatment of OSA in CHF (McEvoy *et al.,* 2016). The trial showed an improvement in quality of life, depression, and work productivity; however, hard endpoint data are required to change clinical practice. The paucity of clinical guidelines is therefore a direct consequence of the lack of high-quality clinical trials that are adequately powered, with appropriate follow-up periods and with adequate representation of women and diversity in the study populations. If the findings from the ADVENT-HF trial (Perger *et al*., 2017) is positive and shows that ASV treatment for SDB is associated with improved clinical outcomes in CHF, further research may be required to address the barriers identified from this study.

Firstly, considering different phenotypes and asymptomatic presentation of OSA in CHF, it is possible that a HF specific questionnaire will be needed for

CHF patients. Findings highlighted the need for the development of a new HF-specific OSA screening questionnaire with appropriate validation in both HFrEF and HFpEF.

Secondly, the knowledge deficit and low confidence of clinicians will need to be addressed to facilitate effective detection of at-risk patients. Targeted interventions for clinicians upskilling, focussing on OSA presentation, diagnosis, treatment, and clinical guidelines, will be required.

Finally, low uptake and adherence to OSA treatment will need to be addressed. Targeted interventions will be required to facilitate the uptake and adherence to OSA treatment.

Findings from this doctoral thesis, could be utilised as the foundation for the development of co-designed, co-produced, multi-component interventions for clinicians and patients to address the clinician knowledge deficit and patient treatment uptake and adherence.

The Behaviour Change Wheel, a tool that includes the theoretical model of behaviour (COM-B), the TDF and the Behaviour Change Techniques Taxonomy, would be useful for development and description of the intervention content (Michie *et al.* 2011). Effectiveness of the interventions are likely to be varied, depending on the context and the extent of change required in relation to capability, opportunity and/or motivation (Atkins *et al.,* 2020). Therefore, the Behaviour Change Wheel could provide the basis for the selection of interventions and policies, relevant to the design of a proposed multi-component intervention.

7.6 General Conclusion

Despite showing an improvement in quality of life, existing evidence suggest that there are no CV hospitalisation and mortality benefit for the treatment of co-morbid OSA with CPAP in patients with CHF. This lack of hard outcome data has contributed to a paucity of clinical guidelines on the management OSA in CHF. For now, the jury is out on the treatment of OSA in CHF. Whether ASV treatment for SDB in the ADVENT-HF trial will be associated with improved clinical outcomes in CHF patients, will remain unknown until completion of the trial. Findings from this doctoral work has highlighted a variety of barriers

associated with the diagnosis and treatment of OSA in CHF that could form the foundation of targeted interventions to aid the diagnosis and treatment of OSA in CHF, should the evidence change in the future.

8

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countries: an analysis of 123 nationally representative surveys. *Lancet.* 394, 639–651. Available from https://doi.org/10.1016/S0140-6736(19)31145-6

9

Appendices

9.1 Appendix 1 Ethics Committee Letter of Approval

NHS
Health Research Authority
East Midlands - Leicester South Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

15 November 2017

Miss Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital, Groby Road, Leicester
LE3 9QP

Dear Miss Bernhardt,

Study title:	**Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach**
REC reference:	**17/EM/0400**
Protocol number:	**0636**
IRAS project ID:	**222909**

Thank you for your letter of 13 November 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

Confirmation of ethical opinion

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

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [PI Indemnity]		
Interview schedules or topic guides for participants [Interview Topic Guide]	v1.0	19 September 2017
IRAS Application Form [IRAS_Form_25092017]		25 September 2017
Letter from sponsor [Confirmation of sponsorship]		
Letters of invitation to participant [First Contact Email]	v1.0	19 September 2017
Other [STOP-Bang Questionnaire]	v1.0	19 September 2017
Other [Clinical Trials Indemnity]		
Other [Interview debrief sheet]	1.0	26 September 2017
Other [Second contact email]	1.0	19 September 2017
Other [SPIRAL_Consent_Questionnaire_Interview]	v1.1	08 November 2017
Other [SPIRAL-Modified_OSAKA_Questionnaire]	v1.1	08 November 2017
Other [SPIRAL_OSAKA_Questionnaire]	v1.1	08 November 2017
Other [SPIRAL_PIS_Questionnaire_Interview]	v1.1	08 November 2017
Other [SPIRAL_PIS_Survey]	v1.1	08 November 2017
Other [SPIRAL_Protocol]	v1.1	08 November 2017
Other [SPIRAL_Second_Email]	v1.1	08 November 2017
Other [SPIRAL_Web_Survey]	v1.1	08 November 2017
Other [REC Response Letter]		09 November 2017
Other [further clarification of response to PO]		13 November 2017
Referee's report or other scientific critique report [Peer Review Feedback]	v1.0	23 July 2017
Summary CV for Chief Investigator (CI) [CV L Bernhardt]	v1.0	17 August 2017
Summary CV for student [CV L Bernhardt]	v1.0	17 August 2017
Summary CV for supervisor (student research) [Prof Iain Squire CV]	N/A	
Summary CV for supervisor (student research) [Dr Robertson]		

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website:
http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at
http://www.hra.nhs.uk/hra-training/

17/EM/0400	**Please quote this number on all correspondence**

With the Committee's best wishes for the success of this project.

Yours sincerely,

Mr John Aldridge
Chair

Email:NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

Enclosures: "After ethical review – guidance for researchers"

9.2 Appendix 2 Health Research Authority Letter of Approval

NHS
Health Research Authority

Miss Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital, Groby Road, Leicester
LE3 9QP

Email: hra.approval@nhs.net

15 November 2017

Dear Miss Bernhardt

Letter of HRA Approval

Study title:	**Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach**
IRAS project ID:	**222909**
Protocol number:	**0636**
REC reference:	**17/EM/0400**
Sponsor	**University of Leicester**

I am pleased to confirm that HRA Approval has been given for the above referenced study, on the basis described in the application form, protocol, supporting documentation and any clarifications noted in this letter.

Participation of NHS Organisations in England

The sponsor should now provide a copy of this letter to all participating NHS organisations in England.

Appendix B provides important information for sponsors and participating NHS organisations in England for arranging and confirming capacity and capability. **Please read *Appendix B* carefully**, in particular the following sections:

- *Participating NHS organisations in England* – this clarifies the types of participating organisations in the study and whether or not all organisations will be undertaking the same activities
- *Confirmation of capacity and capability* - this confirms whether or not each type of participating NHS organisation in England is expected to give formal confirmation of capacity and capability. Where formal confirmation is not expected, the section also provides details on the time limit given to participating organisations to opt out of the study, or request additional time, before their participation is assumed.
- *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* - this provides detail on the form of agreement to be used in the study to confirm capacity and capability, where applicable.

Further information on funding, HR processes, and compliance with HRA criteria and standards is also provided.

IRAS project ID	222909

It is critical that you involve both the research management function (e.g. R&D office) supporting each organisation and the local research team (where there is one) in setting up your study. Contact details and further information about working with the research management function for each organisation can be accessed from the HRA website.

Appendices

The HRA Approval letter contains the following appendices:

- A – List of documents reviewed during HRA assessment
- B – Summary of HRA assessment

After HRA Approval

The 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.

In addition to the guidance in the above, please note the following:

- HRA Approval applies for the duration of your REC favourable opinion, unless otherwise notified in writing by the HRA.
- Substantial amendments should be submitted directly to the Research Ethics Committee, as detailed in the *After Ethical Review* document. Non-substantial amendments should be submitted for review by the HRA using the form provided on the HRA website, and emailed to hra.amendments@nhs.net.
- The HRA will categorise amendments (substantial and non-substantial) and issue confirmation of continued HRA Approval. Further details can be found on the HRA website.

Scope

HRA Approval provides an approval for research involving patients or staff in NHS organisations in England.

If your study involves NHS organisations in other countries in the UK, please contact the relevant national coordinating functions for support and advice. Further information can be found through IRAS.

If there are participating non-NHS organisations, local agreement should be obtained in accordance with the procedures of the local participating non-NHS organisation.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application

IRAS project ID	222909

procedure. If you wish to make your views known please use the feedback form available on the HRA website.

HRA Training

We are pleased to welcome researchers and research management staff at our training days – see details on the HRA website.

Your IRAS project ID is **222909**. Please quote this on all correspondence.

Yours sincerely,

Natalie Wilson
Assessor

Email: hra.approval@nhs.net

Copy to: *Dr Michelle Muessel, University of Leicester, Sponsor contact*
Mrs Carolyn Maloney, University Hospitals of Leicester NHS Trust, Lead NHS R&D contact

IRAS project ID	222909

Appendix A - List of Documents

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

Document	*Version*	*Date*
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [PI Indemnity]		
HRA Schedule of Events	1	15 November 2017
HRA Statement of Activities	1	15 November 2017
Interview schedules or topic guides for participants [Interview Topic Guide]	v1.0	19 September 2017
IRAS Application Form [IRAS_Form_25092017]		25 September 2017
Letter from sponsor [Confirmation of sponsorship]		
Letters of invitation to participant [First Contact Email]	v1.0	19 September 2017
Other [STOP-Bang Questionnaire]	v1.0	19 September 2017
Other [Clinical Trials Indemnity]		
Other [Interview debrief sheet]	1.0	26 September 2017
Other [Second contact email]	1.0	19 September 2017
Other [SPIRAL_Consent_Questionnaire_Interview]	v1.1	08 November 2017
Other [SPIRAL-Modified_OSAKA_Questionnaire]	v1.1	08 November 2017
Other [SPIRAL_OSAKA_Questionnaire]	v1.1	08 November 2017
Other [SPIRAL_PIS_Questionnaire_Interview]	v1.1	08 November 2017
Other [SPIRAL_PIS_Survey]	v1.1	08 November 2017
Other [SPIRAL_Protocol]	v1.1	08 November 2017
Other [SPIRAL_Second_Email]	v1.1	08 November 2017
Other [SPIRAL_Web_Survey]	v1.1	08 November 2017
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Referee's report or other scientific critique report [Peer Review Feedback]	v1.0	23 July 2017
Summary CV for Chief Investigator (CI) [CV L Bernhardt]	v1.0	17 August 2017
Summary CV for student [CV L Bernhardt]	v1.0	17 August 2017
Summary CV for supervisor (student research) [Prof Iain Squire CV]	N/A	
Summary CV for supervisor (student research) [Dr Robertson]		

IRAS project ID	222909

Appendix B - Summary of HRA Assessment

This appendix provides assurance to you, the sponsor and the NHS in England that the study, as reviewed for HRA Approval, is compliant with relevant standards. It also provides information and clarification, where appropriate, to participating NHS organisations in England to assist in assessing and arranging capacity and capability.

For information on how the sponsor should be working with participating NHS organisations in England, please refer to the, *participating NHS organisations, capacity and capability* and *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* sections in this appendix.

The following person is the sponsor contact for the purpose of addressing participating organisation questions relating to the study:

Name: Lizelle Bernhardt
Email: lb382@le.ac.uk

HRA assessment criteria

Section	HRA Assessment Criteria	Compliant with Standards	Comments
1.1	IRAS application completed correctly	Yes	No comments
2.1	Participant information/consent documents and consent process	Yes	No comments
3.1	Protocol assessment	Yes	No comments
4.1	Allocation of responsibilities and rights are agreed and documented	Yes	This is a non-commercial, single site study taking place in the NHS. A Statement of Activities has been submitted. This will act as the agreement between Sponsor and participating NHS organisations. No other agreements are expected.
4.2	Insurance/indemnity arrangements assessed	Yes	Where applicable, independent contractors (e.g. General Practitioners) should ensure that the professional indemnity provided by their medical

IRAS project ID	222909

Section	HRA Assessment Criteria	Compliant with Standards	Comments
			defence organisation covers the activities expected of them for this research study
4.3	Financial arrangements assessed	Yes	Sponsor is not providing funding to participating NHS organisations.
5.1	Compliance with the Data Protection Act and data security issues assessed	Yes	No comments
5.2	CTIMPS – Arrangements for compliance with the Clinical Trials Regulations assessed	Not Applicable	
5.3	Compliance with any applicable laws or regulations	Yes	No comments
6.1	NHS Research Ethics Committee favourable opinion received for applicable studies	Yes	No comments
6.2	CTIMPS – Clinical Trials Authorisation (CTA) letter received	Not Applicable	
6.3	Devices – MHRA notice of no objection received	Not Applicable	
6.4	Other regulatory approvals and authorisations received	Not Applicable	

Participating NHS Organisations in England

This provides detail on the types of participating NHS organisations in the study and a statement as to whether the activities at all organisations are the same or different.
This is a non-commercial, single site study. Therefore, only one site-type is involved in the research. Activities and procedures as described in the research will take place at participating NHS organisations. The Chief Investigator or sponsor should share relevant study documents with participating NHS organisations in England in order to put arrangements in place to deliver the study. The documents should be sent to both the local study team, where applicable, and the office providing the research management function at the participating organisation. For NIHR CRN Portfolio studies, the Local

IRAS project ID	222909

LCRN contact should also be copied into this correspondence. For further guidance on working with participating NHS organisations please see the HRA website.

If Chief Investigators, sponsors or Principal Investigators are asked to complete site level forms for participating NHS organisations in England which are not provided in IRAS or on the HRA website, the Chief Investigator, sponsor or Principal Investigator should notify the HRA immediately at hra.approval@nhs.net. The HRA will work with these organisations to achieve a consistent approach to information provision.

Confirmation of Capacity and Capability

This describes whether formal confirmation of capacity and capability is expected from participating NHS organisations in England.

Participating NHS organisations in England **will be expected to formally confirm their capacity and capability to host this research**.

- Following issue of this letter, participating NHS organisations in England may now confirm to the sponsor their capacity and capability to host this research, when ready to do so. How capacity and capacity will be confirmed is detailed in the *Allocation of responsibilities and rights are agreed and documented (4.1 of HRA assessment criteria)* section of this appendix.
- The Assessing, Arranging, and Confirming document on the HRA website provides further information for the sponsor and NHS organisations on assessing, arranging and confirming capacity and capability.

Principal Investigator Suitability

This confirms whether the sponsor position on whether a PI, LC or neither should be in place is correct for each type of participating NHS organisation in England and the minimum expectations for education, training and experience that PIs should meet (where applicable).

The Chief Investigator (CI) will be responsible for research activity at participating NHS organisations.

Sponsor expects relevant research staff to have undertaken Good Clinical Practice (GCP) training.

GCP training is not a generic training expectation, in line with the HRA statement on training expectations.

HR Good Practice Resource Pack Expectations

This confirms the HR Good Practice Resource Pack expectations for the study and the pre-engagement checks that should and should not be undertaken

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

IRAS project ID	222909

contract. 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. For research team members only administering questionnaires or surveys, a Letter of Access based on standard DBS checks and occupational health clearance would be appropriate.

Other Information to Aid Study Set-up

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

9.3 Appendix 3 Sponsor Green Light Confirmation Letter

UNIVERSITY OF LEICESTER

Research & Enterprise Division
University of Leicester
Research Governance Office
Fielding Johnson Building
University Road
Leicester, LE1 7RH
Email: uolsponsor@le.ac.uk
Tel: 0116 373 6410 / 223 1660

9 January 2018

Miss Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre, Glenfield Hospital
Leicester, LE3 9QP

Dear Miss Bernhardt

Ref:	**UOL 0636/ IRAS project ID: 222909**	**End Date:**	**31/12/2019**
Title:	**Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach**		
Status:	**Approved**		
Site:	**University Hospitals of Leicester NHS Trust**		

I am pleased to advise you that following confirmation of a Favourable Opinion from an Ethics Committee, HRA and NHS Trust R&D Capacity and Capability confirmation and where relevant regulatory authority agreements have been received, the University are able to confirm sponsorship for the above research at the above site.

I would be grateful if you can forward a copy of this letter to the Principal Investigator for their Site File.

Please note you are required to notify the Sponsor and provide copies of:

- Changes in personnel to the Study
- Changes to the end date
- All substantial amendments and provisional and favourable opinions
- All minor amendments
- All serious adverse events (SAEs) and SUSARS
- Annual progress reports
- Annual MHRA (DSUR) safety reports (if applicable)
- End of study declaration form
- Notifications of significant breaches of Good Clinical Practices (GCP)or Protocol

If your study is adopted onto the Clinical Research Network Portfolio please ensure that your recruitment figures, end dates and study status are the same on the EDGE database and Open Database Platform (ODP) CPMS.

Please copy the Sponsor into all correspondence and emails by using uolsponsor@le.ac.uk.

Please note it is essential that you notify us as soon as you have recruited your first patient to the study.

I would like to wish you well with your study and if you require further information or guidance please do not hesitate to contact me.

Yours sincerely

Dr Michelle Muessel
Research Governance Manager

9.4 Appendix 4 Protocol Substantial Amendment 1

Health Research Authority

East Midlands - Leicester South Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

26 March 2018

Miss Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital,
Groby Road,
Leicester
LE3 9QP

Dear Miss Bernhardt,

Study title:	**Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach**
REC reference:	**17/EM/0400**
Protocol number:	**0636**
Amendment number:	**1**
Amendment date:	**06 March 2018**
IRAS project ID:	**222909**

The above amendment was reviewed on 26 March 2018 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Decision: No ethical issues.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Letters of invitation to participant [SPIRAL_Invitation_Letter_v1.0_06.03.2018.docx]	1	06 March 2018
Notice of Substantial Amendment (non-CTIMP) [AmendmentForm_ReadyForSubmission.pdf]	1	06 March 2018
Other [SPIRAL_Web_Survey_v1.3_06.03.2018.docx]	1.3	06 March 2018
Other [SPIRAL_First_Contact_Email_v1.1_06.03.2018.docx]	1.1	06 March 2018
Participant information sheet (PIS) [SPIRAL_PIS_Survey_v1.3_06.03.2018.docx]	1.3	06 March 2018
Participant information sheet (PIS) [SPIRAL_PIS_Questionnaire_Interview_v1.3_06.03.2018_.docx]	1.3	06 March 2018
Research protocol or project proposal [SPIRAL_Protocol_v2_06.03.2018.docx]	2	06 March 2018

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

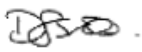
Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/EM/0400:	**Please quote this number on all correspondence**

Yours sincerely



PP
Mr John Aldridge
Chair

E-mail: NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Mrs Carolyn Maloney,*

East Midlands - Leicester South Research Ethics Committee

Attendance at Sub-Committee of the REC meeting on 26 March 2018

Committee Members:

Name	*Profession*	*Present*	*Notes*
Mr John Aldridge (Chair)	Retired Senior Lecturer in Nursing	Yes	
Ms Elizabeth Gibbons	Senior Research Scientist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Miss Daniella Sarno	REC Assistant

9.5 Appendix 5 Protocol Substantial Amendment 2

Health Research Authority

East Midlands - Leicester South Research Ethics Committee

The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Please note: This is the favourable opinion of the REC only and does not allow the amendment to be implemented at NHS sites in England until the outcome of the HRA assessment has been confirmed.

12 March 2019

Miss Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital, Groby Road, Leicester
LE3 9QP

Dear Miss Bernhardt

Study title:	**Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach**
REC reference:	**17/EM/0400**
Protocol number:	**0636**
Amendment number:	**2**
Amendment date:	**18 February 2019**
IRAS project ID:	**222909**

The above amendment was reviewed 11 March 2019 by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Discussion

There were no ethical issues raised.

Health Research Authority

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Interview schedules or topic guides for participants	1	18 February 2019
Notice of Substantial Amendment (non-CTIMP)	2	18 February 2019
Other [Debrief clinican interview]	1	18 February 2019
Other [Invitation email clinician interview]	1	18 February 2019
Other [Reply slip clinican interview]	1	18 February 2019
Other [HRA schedule of events]		
Participant consent form [Clinican interview]	1	18 February 2019
Participant consent form [questionnaire interview]	2	18 February 2019
Participant information sheet (PIS) [Clinician interview]	1	18 February 2019
Participant information sheet (PIS) [Questionnaire interview]	2	18 February 2019
Research protocol or project proposal	3	18 February 2019

Membership of the Committee

The members of the Committee who took part in the review are listed on the attached sheet.

Working with NHS Care Organisations

Sponsors should ensure that they notify the R&D office for the relevant NHS care organisation of this amendment in line with the terms detailed in the categorisation email issued by the lead nation for the study.

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

We are pleased to welcome researchers and R & D staff at our Research Ethics Committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

17/EM/0400:	**Please quote this number on all correspondence**

Health Research Authority

Yours sincerely

pp Sulya Rybicki

Mr John Aldridge
Chair

E-mail: NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

Enclosures: *List of names and professions of members who took part in the review*

Copy to: *Ms Carolyn Maloney , University Hospitals of Leicester NHS Trust*
Miss Lizelle Bernhardt

9.6 Appendix 6 Systematic Review Excluded Studies

Author	Title	Reasons
Abumuamar[2018]	The STOP-BANG questionnaire shows an insufficient specificity for detecting obstructive sleep apnea in patients with atrial fibrillation	Studies in which the data presented was not capable to be extrapolated.
Best[2013]	Utility of the Berlin questionnaire for predicting obstructive sleep apnea in individuals with treatment-resistant depression	Study population not a clinical cohort.
Cepeda[2019]	Identifying the risk of obstructive sleep apnea in metabolic syndrome patients: Diagnostic accuracy of the Berlin	Studies in which the data presented was not capable to be extrapolated.
Chung[2007]	Preoperative identification of sleep apnea risk in elective surgical patients, using the Berlin questionnaire.	Studies that did not use PSG as reference standard.
Chung[2013]	Predictive Performance of the STOP-Bang Score for Identifying Obstructive Sleep Apnea in Obese Patients	Study population not a clinical cohort.
Costa[2020]	STOP-Bang and NoSAS questionnaires as a screening tool for OSA: which one is the best choice?	Studies in which the data presented was not capable to be extrapolated.

Author	Title	Reasons
Costa[2019]	Validation of NoSAS (Neck, Obesity, Snoring, Age, Sex) score as a screening tool for obstructive sleep apnea: Analysis in a sleep clinic	NoSAS a clinical score not a questionnaire.
Cruces-Artero[2020]	Diagnostic accuracy of STOP-Bang questionnaire on moderate sleep apnoea in primary care	Studies in which the data presented was not capable to be extrapolated.
Duarte[2020]	Validation of the GOAL Questionnaire as an Obstructive Sleep Apnea Screening Instrument in Bariatric Surgery Candidates: a Brazilian Single-Centre Study	Not a questionnaire, but a clinical score
Economou[2013]	Use of the Sleep Apnea Scale of the Sleep Disorders Questionnaire (SA-SDQ) in adults with epilepsy.	Studies in which the data presented was not capable to be extrapolated.
Edelmann[2017]	A pictorial sleepiness and Sleep Apnoea Scale to recognize individuals with high risk for obstructive sleep apnea syndrome	Studies that did not use PSG as reference standard.
Eijsvogel[2016]	Obstructive Sleep Apnea Syndrome in Company Workers: Development of a Two-Step	Studies in which the data presented was not capable to be extrapolated.

Author	Title	Reasons
	Screening Strategy with a New Questionnaire.	
Farney[2011]	The STOP-Bang Equivalent Model and Prediction of Severity of Obstructive Sleep Apnea: Relation to Polysomnographic Measurements of the Apnea/Hypopnea Index	Retrospective Studies
Friedman[2010]	Screening for obstructive sleep apnea/hypopnea syndrome: subjective and objective factors	Retrospective Studies
Gasparini[2015]	Diagnostic Accuracy of Obstructive Airway Adult Test for Diagnosis of Obstructive Sleep Apnea	Studies in which the data presented was not capable to be extrapolated
Geiger-Brown[2013]	Occupational screening for sleep disorders in 12-h shift nurses using the Berlin Questionnaire	Study population not a clinical cohort.
Gong[2020]	Diagnostic accuracy of the Berlin questionnaire and therapeutic effect of nasal continuous positive airway pressure in OSAHS patients with glucose metabolic dysfunction	Studies in which the data presented was not capable to be extrapolated.
Gupta[2016]	Hindi translation of Berlin questionnaire and its validation	Studies in which the data presented

Author	Title	Reasons
	as a screening instrument for obstructive sleep apnea.	was not capable to be extrapolated.
Hrubos Ström[2011]	A Norwegian population-based study on the risk and prevalence of obstructive sleep apnea	Study population not a clinical cohort.
Jinmei[2014]	STOP-Bang questionnaire is superior to Epworth sleepiness scales, Berlin questionnaire and STOP questionnaire in screening obstructive sleep apnea hypopnea syndrome patients	Studies in which the data presented was not capable to be extrapolated
Jinmei[2014]	Value of STOP-Bang questionnaire in screening patients with obstructive sleep apnea hypopnea syndrome in sleep disordered breathing clinic	Studies in which the data presented was not capable to be extrapolated.
Kang[2013]	Usefulness of the Berlin Questionnaire to identify patients at high risk for obstructive sleep apnea: a population-based door-to-door study	Studies in which the data presented was not capable to be extrapolated.
Kuniyoshi[2011]	Diagnostic Accuracy of the Berlin Questionnaire in Detecting Sleep-Disordered Breathing in Patients with a Recent Myocardial Infarction	In-patient population

Author	Title	Reasons
McMahon[2017]	Using the STOP-Bang questionnaire and other pre-test probability tools to predict OSA in younger, thinner patients referred to a sleep medicine clinic	Retrospective Studies
Miller[2018]	Comparisons of measures used to screen for obstructive sleep apnea in patients referred to a sleep clinic	Studies that did not use PSG as reference standard.
Nahapetian[2016]	Weighted STOP-Bang and Screening for Sleep Disordered Breathing	Studies in which the data presented was not capable to be extrapolated.
Neves Junior[2020]	Cut-off points in STOP-Bang questionnaire for obstructive sleep apnea	Retrospective Study
Nishadh[2017]	The Accuracy of the STOP-Bang Questionnaire in the Identification of Obstructive Sleep apnoea (OSA) with polysomnography as the gold standard in adult patients with symptoms of Sleep Disordered breathing in a Tertiary Care Centre in South India	Reviews, case reports, letters, personal opinions, book chapters and conference abstracts
Onen[2008]	Observation-Based Nocturnal Sleep Inventory: Screening Tool for Sleep Apnea in Elderly People	Not a patient-based questionnaire

Author	Title	Reasons
Pavarangkul[2016]	The STOP-Bang questionnaire as a screening tool for obstructive sleep apnea-induced hypertension in Asian population	Studies that did not use PSG as reference standard.
Popevic[2017]	Screening commercial drivers for obstructive sleep apnea: validation of STOP-Bang questionnaire	Studies that did not use PSG as reference standard.
Popevic[2016]	Screening commercial drivers for obstructive sleep apnea: translation and validation of Serbian version of Berlin Questionnaire	Studies that did not use PSG as reference standard.
Prasad[2017]	Assessing the likelihood of obstructive sleep apnea: a comparison of nine screening questionnaires	Retrospective Studies
Rebelo-Marques[2017]	STOP-Bang questionnaire: the validation of a Portuguese version as a screening tool for obstructive sleep apnea (OSA) in primary care.	Studies that did not use PSG as reference standard.
Romero-Lopez[2010]	Development and validation of a questionnaire to identify patients with sleep apnea in Mexican population.	Studies in which the data presented was not capable to be extrapolated.

Author	Title	Reasons
Sagaspe[2010]	Might the Berlin Sleep Questionnaire applied to bed partners be used to screen sleep apnoeic patients?	Studies in which the data presented was not capable to be extrapolated.
Sargento[2014]	Measurement properties of a screening questionnaire of obstructive sleep apnea risk: Little information, great prediction?	Studies that did not use PSG as reference standard.
Sharma[2006]	Validation of the modified Berlin questionnaire to identify patients at risk for the obstructive sleep apnoea syndrome	Studies that used a modified version of the screening questionnaire.
Sico[2017]	Development, validation, and Assessment of an Ischemic Stroke or Transient Ischemic Attack-specific Prediction Tool for Obstructive Sleep Apnea.	Studies in which the data presented was not capable to be extrapolated.
Silva[2011]	Identification of Patients with Sleep Disordered Breathing: Comparing the Four-Variable Screening Tool STOP, STOP-Bang, and Epworth Sleepiness Scales.	Retrospective Studies
Singh[2017]	A study to estimate prevalence and risk factors of Obstructive Sleep Apnea Syndrome in a semi-urban Indian population	Studies that did not use PSG as reference standard.

Author	Title	Reasons
Srijithesh[2010]	Validity of the Berlin Questionnaire in identifying obstructive sleep apnea syndrome when administered to the informants of stroke patients.	Studies in which the data presented was not capable to be extrapolated.
Steier[2011]	Screening for sleep-disordered breathing in neuromuscular disease using a questionnaire for symptoms associated with diaphragm paralysis	Study population not a clinical cohort.
Subramanian[2011]	The NAMES assessment: a novel combined-modality screening tool for obstructive sleep apnea	Retrospective Studies
Suksakorn[2014]	Reliability and Validity of a Thai Version of the Berlin Questionnaire in Patients with Sleep Disordered Breathing	Retrospective Studies
Teng[2018]	STOP-Bang questionnaire screening for obstructive sleep apnea among Chinese patients with type 2 diabetes mellitus	In-patient population
Thurtell[2011]	The Berlin questionnaire screens for obstructive sleep apnea in idiopathic intracranial hypertension	Retrospective Studies

Author	Title	Reasons
Traxdorf[2017]	The Erlangen Questionnaire: a new 5-item screening tool for obstructive sleep apnea in a sleep clinic population - A prospective double-blinded study	Studies that did not use PSG as reference standard.
Ulasli[2014]	Predictive value of Berlin Questionnaire and Epworth Sleepiness Scale for obstructive sleep apnea in a sleep clinic population	Studies in which the data presented was not capable to be extrapolated.
Weatherwax[2003]	Obstructive sleep apnea in epilepsy patients: The Sleep apnea scale of the Sleep Disorders Questionnaire (SA-SDQ) is a useful screening instrument for obstructive sleep apnea in a disease-specific population.	Studies in which the data presented was not capable to be extrapolated.
Wilson[2014]	Screening for Sleep Apnoea in Mild Cognitive Impairment: The utility of the Multivariable Apnoea Prediction Index	Studies in which the data presented was not capable to be extrapolated.
Wu[2016]	Screening and managing obstructive sleep apnoea in nocturnal heart block patients: an observational study	Retrospective Studies
Xiong[2019]	The Screening Value Of ESS, SACS, BQ, And SBQ On	Studies in which the data presented

Author	Title	Reasons
	Obstructive Sleep Apnea In Patients With Chronic Obstructive Pulmonary Disease	was not capable to be extrapolated

9.7 Appendix 7 Study Characteristics

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
SLEEP CLINIC POPULATION									
Abdullah 2018	Malaysia	STOP-Bang	134	Level 1 - Lab PSG	AHI≥5	Complete cessation of airflow for ≥10 seconds.	A reduction of airflow of ≥50% for ≥10 seconds associated with 3% desaturation.	3%	AASM 2012
Alhouqani 2015	UAE	STOP-Bang	193	Level 1 - Lab PSG	AHI≥5	A cessation of airflow for > 10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation and/or arousal.	3%	AASM 2012
Amra 2013	Iran	Berlin	157	Level 1 - Lab PSG	AHI>5	Complete cessation of airflow for ≥10 seconds.	A reduction of airflow of ≥50% for ≥10 seconds associated with ≥3% desaturation.	≥3%	AASM 1999
Amra 2018	China	Berlin, STOP-Bang	400	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline for ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation	3%	AASM 2012

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							and/or arousal.		
Oktay Arslan 2020	Turkey	Berlin	1003	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline for ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation and/or arousal.	3%	AASM 2012
Avincsal 2017	Turkey	STOP-Bang	162	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and was associated with ≥ 4% desaturation.	≥4%	AASM 2007
BaHammam 2015	Saudi Arabia	STOP-Bang	100	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation and/or arousal.	≥3%	AASM 2012
Boynton 2013	USA	STOP-Bang	219	Level 1 - Lab PSG	AHI>5	Complete absence of airflow for ≥10 seconds.	≥50% decrease in airflow followed by an arousal, awakening,	≥3%	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							or ≥3% desaturation.		
Deflandre 2018	Belgium	STOP-Bang, OSA50	159	Level 1 - Lab PSG	AHI>30	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and associated with ≥ 4% desaturation.	≥4%	AASM 2012
Delgado-Vargas 2020	Spain	STOP-Bang	193	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and associated with ≥ 4% desaturation.	≥4%	AASM 2012
Duarte 2017	Brazil	STOP-Bang	456	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation and/or arousal.	≥ 3%	AASM 2012
Duarte 2020	Brazil	STOP-Bang	3606	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation	≥ 3%	AASM 2012

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							and/or arousal.		
El Sayed 2012	Egypt	Berlin, STOP, STOP-Bang	234	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and associated with ≥ 4% desaturation.	≥ 4%	AASM 2007
Ha 2014	China	Berlin, STOP, STOP–BANG, ASA checklist	141	Level 1 - Lab PSG	RDI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and associated with ≥ 4% desaturation.	≥ 4%	AASM 2007
Hu 2019	China	STOP-Bang	196	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30 % decrease in airflow with 3% oxygen desaturation and/or arousal.	3%	AASM 2012
Kashaninasab 2017	Iran	Berlin, STOP, STOP-BANG	250	Level 1 - Lab PSG	AHI≥5	A decrease in airflow that lasted ≥10 seconds.	A reduction in airflow by ≥50% or a 3% desaturation.	≥ 3%	AASM 2005

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
Khaledi-Paveh 2016	Iran	Berlin	100	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and associated with ≥4% desaturation.	≥ 4%	AASM 2007
Kim 2015	Korea	Berlin, STOP-Bang, SA-SDQ	592	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and was associated with ≥4% desaturation.	≥ 4%	AASM 2007
Ong 2010	Singapore	STOP-Bang	314	Level 1 - Lab PSG	AHI>5	Cessation of airflow for > 10 seconds.	≥30% decrease in airflow with 4% oxygen desaturation or with 3% oxygen desaturation and arousal.	Unclear	Rechtschaffen, & Kales 1968
Pataka 2016	Greece	STOP, STOP-Bang, Berlin	204	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and was	≥4%	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							associated with ≥ 4% desaturation.		
Pecotic 2012	Croatia	STOP	425	Level 1 - Lab PSG	AHI>5	Complete cessation of airflow for ≥10 seconds.	A decrease in airflow >50% from baseline for ≥10 and ≥3% desaturation.	≥3%	Not referenced
Pereira 2013	Canada	Berlin, STOP-Bang	128	Level 1 - Lab PSG	AHI≥5	A cessation of airflow ≥ 50% for ≥10 seconds.	A decrease in airflow of >50% for ≥ 10 seconds followed by ≥ 3% oxygen desaturation.	≥ 3%	AASM 2007
Perumalsamy 2017	Chennai	STOP-Bang, Berlin	62	Level 1 - Lab PSG	AHI≥5	Not described	Not described	Not described	AASM Manual-not referenced
Sadeghniiat-Haghighi 2015	Iran	STOP, STOP-Bang	603	Level 1 - Lab PSG	AHI>5	Total cessation of airflow for ≥10 seconds.	reduction of airflow for >50 % for ≥10 seconds with 3% desaturation or with arousal.	3%	AASM 2007
Saleh 2011	Egypt	Berlin	100	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline,	≥30% reduction in airflow that	≥ 4%	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
						which lasted ≥10 seconds.	lasted ≥10 seconds and was associated with ≥ 4% desaturation.		
Sangkum 2017	USA	STOP, STOP-Bang	208	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30 % decrease in airflow with 3 % oxygen desaturation and/or arousal.	≥ 3%	AASM 2012
Suksakorn 2014	Thailand	Berlin	132	Level 1 - Lab PSG	AHI>5	Not reported or referenced	Not reported or referenced	Not reported or referenced	Not reported or referenced
Vana 2013	USA	STOP-Bang	47	Level 1 - Lab PSG	AHI>5	complete cessation of airflow >10 seconds In paper	≥30% reduction in airflow that lasted ≥10 seconds and associated with 4% desaturation or arousal.	4%	AASM 2007
Yüceege 2015	Turkey	Berlin	433	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	A ≥ 50% drop in flow for ≥10 associated with ≥ 3%	≥ 3%	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							oxygen desaturation		
SURGICAL POPULATION									
Chung 2008a	Canada	Berlin, STOP, ASA checklist	177	Level 1 - Lab PSG	AHI>5	Complete cessation of breathing.	A decrease of >50% of airflow for ≥10 seconds and >3% desaturation or an arousal.	>3%	AASM1999
Chung 2008b	Canada	STOP, STOP-Bang	177	Level 1 - Lab PSG	AHI≥5	Complete cessation of breathing.	A decrease of >50% of airflow for ≥10 seconds and >3% desaturation or an arousal.	≥3%	AASM 1999
Chung 2013	Canada	STOP-Bang	384	Level 2- Portable PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥ 30% reduction in airflow that lasts ≥10 seconds and ≥4% desaturation.	≥ 4%	AASM 2007
Chung 2014	Canada	STOP-Bang	516	Level 2- Portable PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥50% reduction in airflow that lasted ≥ 10 seconds followed by	≥ 3%.	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
							≥3% oxygen desaturation.		
Deflandre 2017	Belgium	STOP-Bang, OSA50	150	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥ 30 % decrease in airflow for ≥ 10 seconds with ≥ 3 % oxygen desaturation and/or arousal.	≥ 3%	AASM 2012
Nunes 2015	Brazil	STOP-Bang, Berlin	81	Level 1 - Lab PSG	AHI≥15	Apnea was defined as complete cessation of airflow for ≥10 seconds.	≥50 % reduction in airflow for 10 seconds associated with desaturation of >3 % or an arousal.	>3%	AASM 2007
Xia 2018	China	STOP-Bang	790	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in air flow and ≥4% desaturation	≥ 4%	AASM 2012
RESISTANT HYPERTENSION									
Giampá 2018	Brazil	Berlin	119	Level 1 - Lab PSG	AHI>5	≥90% drop in airflow from baseline,	At least 30 % decrease in airflow with 3 %	3%	AASM 2007

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
						which lasted ≥10 seconds.	desaturation and/or arousal.		
Margallo 2014	Brazil	Berlin	422	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	At least 30% decrease of airflow for ≥10 seconds accompanied by desaturation ≥4%.	≥ 4%	AASM 2007
ASTHMA POPULATION									
Lu 2017	China	Berlin, STOP-Bang	123	Level 1 - Lab PSG	AHI≥5	apnoea was defined as the absence of oronasal airflow for ≥10 seconds.	≥50% reduction in airflow accompanied by oxygen desaturation ≥4%.	≥ 4%	AASM 2007
COMMUNITY CLINIC									
Gantner 2010	China	Berlin	143	Level 1 - Lab PSG	AHI≥15	Not considered necessary to distinguish apnoeas from hypopnoeas.	>50% reduction in airflow for ≥10 seconds associated with >3% desaturation or arousal.	>3%	AASM 1999

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
HIGHWAY BUS DRIVERS									
Firat 2012	Turkey	Berlin, STOP, STOP-BANG, OSA50	85	Level 1 - Lab PSG (daytime)	AHI>15	≥90% decrease in airflow persisting for ≥10 seconds	≥50% decrease in the airflow with 3% desaturation or arousal, persisting for at least 10 seconds.	≥3%	AASM 2007
NEUROLOGY POPULATION									
ElKholy 2012	Egypt	Berlin	30	Level 1 - Lab PSG	AHI≥5	Not reported.	Not reported.	Not reported.	Rechstchaffen and Kales (1968)
PRIMARY CARE									
Bouloukaki 2013	Crete	Berlin	129	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and was associated with ≥4% desaturation.	≥ 4%	AASM 2007
RESPIRATORY POPULATION									
Yunus 2013	Malaysia	Berlin	144	Level 1 - Lab PSG	AHI≥5	Not reported	Not reported	Not reported	Not reported

Study	Country	Questionnaire	*N*	Validation Tool	OSA Definition	Apnoea Definition	Hypopnoea Definition	% Desaturation	Scoring Criteria
SNORING CLINIC									
Banhiran 2014	Thailand	STOP, STOP-Bang	303	Level 1 - Lab PSG	AHI≥5	≥90% drop in airflow from baseline, which lasted ≥10 seconds.	≥30% reduction in airflow that lasted ≥10 seconds and was associated with ≥4% desaturation.	≥ 4%	AASM 2007

N: number of participants; OSA: obstructive sleep apnoea; PSG: polysomnography; AHI: apnoea hypopnoea index

9.8 Appendix 8 Demographic Data

Study	Age (mean±SD)	Gender (%) Male	BMI (kg/m^2)	NC (cm) (mean±SD)	WC (cm) (mean±SD)	AHI (mean±SD)
SLEEP CLINIC POPULATION						
Abdullah 2018	41.22±12.66	63.4	n/a	n/a	n/a	n/a
Alhouqani 2015	42.87±11.838	77.7	34.9±8.602	39.5±3.463	n/a	34.87±31.273
Amra 2013	52.3±13.6	55.4	31.5±6	n/a	n/a	37.8±30.8
Amra 2018	49.29±9.75	58.5	32.4±7.43	40.8±3.13	n/a	n/a
Oktay Arslan 2020	50.65±11.38	70	32.5±5.9	41.6±3.3	n/a	n/a
Avincsal 2017	50±0.79	69.8	34.2±0.42	41.3±0.32	n/a	n/a
BaHammam 2015	46.6±14	61.0	34.4±7.8	38.0±3.81	n/a	50±37
Boynton 2013	46.3±13.9	44.8	33.4±8.76	39.9±5.4	n/a	n/a
Deflandre 2018	55.8±14	68.0	31.8±12.07	n/a	n/a	n/a
Delgado-Vargas 2020	50.42±12.05	73	29.83±6.12	n/a	n/a	n/a
Duarte 2017	43.7±12.5	63.0	32.1±7.8	40.8±4.3	n/a	24.6±25.2

Study	Age (mean±SD)	Gender (%) Male	BMI (kg/m^2)	NC (cm) (mean±SD)	WC (cm) (mean±SD)	AHI (mean±SD)
Duarte 2020	45.7±14.6	54	32.9±7.7	40.5±4.8	n/a	n/a
El Sayed 2012	50.38±11.29	85.5	37.8±9.54	42.4±4.26	n/a	45.57±32.74
Ha 2014	45±11	81.6	26.0±4	n/a	n/a	25±24
Hu 2019	18-70 (range)	84	27.23±4.03	40.41±3.7	n/a	n/a
Kashaninasab 2017	48.1±12	76.0	n/a	40.2±3.8	n/a	44.1±31.2
Khaledi-Paveh 2016	47.8±14.1	60.0	29.5±6.1	n/a	n/a	24±21.5
Kim 2015	47.6±12.7	83.3	24.7±3.5	39.2±3.5	n/a	25.9±21.8
Ong 2010	46.8±15	70.5	27.9±6	39.8±4.1	n/a	26.2±26.9
Pataka 2016	51.8±13.8	77.5	32.8±6.2	41.6±3.9	1±0.4	29.7±24.7
Pecotic 2012	55	70.0	30.1±4.7	n/a	n/a	31.4±22.6
Pereira 2013	50±12.3	65.6	31.0±6.6	41.0±4.4	n/a	33.1±28
Perumalsamy 2017	53	59.7	n/a	n/a	n/a	n/a

Study	Age (mean±SD)	Gender (%) Male	BMI (kg/m^2)	NC (cm) (mean±SD)	WC (cm) (mean±SD)	AHI (mean±SD)
Sadeghniiat-Haghighi 2015	45.8±12.7	74.8	29.2±5.9	39.7±3.6	n/a	n/a
Saleh 2011	45	51.0	33.1	n/a	n/a	n/a
Sangkum 2017	52±0.9	36.0	36.9±0.7	40.6±0.4	0.95±0.01	n/a
Suksakorn 2014	48.15±8.8	68.2	29.2±6.8	n/a	n/a	28±29.7
Vana 2013	46.4±13.2	34.0	36.3±9.2	n/a	n/a	n/a
Yüceege 2015	47.5±10.5	65.8	31.1±5.6	39.4±3.9	102.9±12.9	28.27±26.5
SURGICAL POPULATION						
Chung 2008a	55±13	49.7	30.0±6	39.0±6	n/a	20±6
Chung 2008b	55±13	49.7	30.0±6	39.0±6	n/a	20±6
Chung 2013	60±11	46.0	31.2±7	39.1±4	n/a	n/a
Chung 2014	59.5±12	54.0	30.6±7	39.0±4	n/a	n/a
Deflandre 2017	59.66±12.41	70.0	32.4±2.26	42.0±4.64	n/a	n/a

Study	Age (mean±SD)	Gender (%) Male	BMI (kg/m^2)	NC (cm) (mean±SD)	WC (cm) (mean±SD)	AHI (mean±SD)
Nunes 2015	56±07	70.0	29.5±5	n/a	n/a	n/a
Xia 2018	41.4±10	58.5	28.5±4.7	40.0±4	n/a	13.1±4.4
RESISTANT HYPERTENSION						
Giampá 2018	52±9	43	52±9	40.0±4	104±14	27±24
Margallo 2014	62.4±9.9	31.3	37.8±3.7	37.8±3.7	101±12.1	n/a
ASTHMA POPULATION						
Lu 2017	47.56±12.12	57.7	26.4±2.99	36.3±2.97	n/a	15.07±12.87
COMMUNITY CLINIC						
Gantner 2010	62.2±7.6	40.5	26.6±3.7	37.5±4	n/a	n/a
HIGHWAY BUS DRIVERS						
Firat 2012	48±5.7	100	29.1±3.8	41.1±2.8	99.6±9.8	21.1±17.4
NEUROLOGY POPULATION						
ElKholy 2012	50.67±14.94	60	n/a	n/a	n/a	29.11±33.16

Study	Age (mean±SD)	Gender (%) Male	BMI (kg/m^2)	NC (cm) (mean±SD)	WC (cm) (mean±SD)	AHI (mean±SD)
PRIMARY CARE						
Bouloukaki 2013	47±13	61.9	35.0±25.1	n/a	n/a	41±32
RESPIRATORY POPULATION						
Yunus 2013	44.7±11.5	64	36.3±11	39.3±4.9	94.1±16.9	38.8±31.9
SNORING CLINIC						
Banhiran 2014	49.6	61.4	27.5	37.05	n/a	n/a

BMI: body mass index; NC: neck circumference; WC: waist circumference; AHI: apnoea hypopnoea index; n/a: not applicable

9.9 Appendix 9 QUADAS-2 Assessment

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PS	IT	RS	F&T	PS	IT	RS
Abdullah 2017	Unclear	Unclear	Unclear	Low	Low	Low	Low
Alhouqani 2015	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Amra 2013	Low	Unclear	Unclear	Unclear	Low	Low	Low
Amra 2018	Unclear	Low	Low	Unclear	Low	Low	Low
Oktay Arslan 2020	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Avincsal 2017	Low	Low	Low	Low	Low	Low	Low
BaHammam 2015	Low	Low	Low	Unclear	Low	Low	Low
Banhiran 2014	Low	Low	Low	Unclear	Low	Low	Low
Bouloukaki 2013	Low	Low	Low	Unclear	Low	Low	Low
Boynton 2013	Unclear	Low	Low	Low	Low	Low	Low
Chung 2008a	Low	Low	Low	Unclear	Low	Low	Low
Chung 2008b	Low	Low	Low	Unclear	Low	Low	Low

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PS	IT	RS	F&T	PS	IT	RS
Chung 2013	Unclear	Low	Low	Low	Low	Low	Low
Chung 2014	Unclear	Low	Low	Unclear	Low	Low	Low
Deflandre 2017	Low	Unclear	Unclear	Unclear	Low	Low	Low
Deflandre 2018	Unclear	Low	Low	Unclear	Low	Low	Low
Delgado-Vargas 2020	Low	Unclear	Unclear	Unclear	Low	Low	Low
Duarte 2017	Low	Low	Low	Unclear	Low	Low	Low
Duarte 2020	Low	Low	Low	Low	Low	Low	Low
El Kholy 2017	High	Unclear	Unclear	Unclear	Low	Low	Low
El Sayed 2012	Unclear	Low	Low	Unclear	Low	Low	Low
Firat 2012	Unclear	Low	Low	Unclear	Low	Low	Low
Gantner 2010	Low	Low	Low	Unclear	Low	Low	Low
Giampa 2018	Low	Unclear	Unclear	Unclear	Low	Low	Low
Ha 2014	Low	Low	Low	Low	Low	Low	Low

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PS	IT	RS	F&T	PS	IT	RS
Hu 2019	Unclear	Low	Low	Unclear	Low	Low	Low
Kashaninasab 2017	Unclear	Low	Low	Unclear	Low	Low	Low
Khaledi-Paveh 2016	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Kim 2015	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Lu 2017	Low	Low	Low	Unclear	Low	Low	Low
Margallo 2014	Low	Low	Low	Unclear	Low	Low	Low
Nunes 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low
Ong 2010	Low	Low	Low	Unclear	Low	Low	Low
Pataka 2016	Unclear	Low	Low	Low	Low	Low	Low
Pecotic 2012	High	Unclear	Unclear	Unclear	Low	Low	Low
Pereira 2013	Low	Low	Low	Unclear	Low	Low	Low
Perumalsamy 2017	Unclear	Low	Low	Unclear	Low	Low	Low
Sadeghniiat-Haghighi 2015	Low	Unclear	Unclear	Low	Low	Low	Low

STUDY	RISK OF BIAS				APPLICABILITY CONCERNS		
	PS	IT	RS	F&T	PS	IT	RS
Saleh 2011	Unclear	Unclear	Unclear	Unclear	Low	Low	Low
Sangkum 2017	Unclear	Low	Low	Low	Low	Low	Low
Suksakorn 2014	High	Unclear	Unclear	Unclear	Low	Low	Low
Vana 2013	Low	Unclear	Unclear	Unclear	Low	Low	Low
Xia 2018	Low	Low	Low	Low	Low	Low	Low
Yuceege 2015	Low	Unclear	Unclear	Unclear	Low	Low	Low
Yunus 2013	Low	Unclear	Unclear	Low	Low	Low	Low

PS: patient selection; IT: index test; RS: reference standard; F&T: flow and timing

9.10 Appendix 10 Sensitivity Analyses for Berlin Questionnaire (Sleep Clinic)

Parameter	All OSA AHI≥5		Moderate-Severe OSA AHI≥15		Severe OSA AHI≥30	
	All Studies 13 Studies n=3503	SA 9 Studies n=2579	All Studies 11 Studies n=3374	SA 7 Studies n=2300	All Studies 8 Studies n=1345	SA 5 Studies n=863
Sensitivity (95% CI)	0.848 (0.79,0.891)	0.848 (0.792,0.890)	0.843 (0.785,0.887)	0.870 (0.812,0.912)	0.886 (0.804,0.936)	0.915 (0.851,0.953)
Specificity (95% CI)	0.433 (0.296,0.582)	0.359 (0.251,0.484)	0.298 (0.204,0.413)	0.208 (0.147,0.286)	0.334 (0.211,0.458)	0.239 (0.167,0.330)
DOR (95% CI)	4.270 (0.718,7.822)	3.121 (1.169,5.072)	2.279 (1.309,3.249)	1.762 (1.082,2.442)	3.882 (2.06,5.704)	3.371 (1.646,5.096)
LR+ (95% CI)	1.497 (1.066,1.927)	1.424 (1.070,1.577)	1.201 (1.049,1.353)	1.099 (1.021,1.176)	1.330 (0.110,1.550)	1.202 (1.098,1.306)
LR- (95% CI)	0.350 (0.155-0.546)	0.424 (0.233,0.615)	0.527 (0.361,0.693)	0.624 (0.422,0.826)	0.343 (0.210,0.475)	0.357 (0.191,0.522)

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; SA: sensitivity analysis; DOR: diagnostic odds ratio; CI: confidence interval; LR: likelihood ratio; +: positive; -: negative

9.11 Appendix 11 Sensitivity Analysis for STOP-Bang (Sleep Clinic)

Parameter	All OSA AHI≥5		Moderate-Severe OSA AHI≥15		Severe OSA AHI≥30	
	All Studies 21 Studies n=9250	SA 16 Studies n=7770	All Studies 19 Studies n=8819	SA 15 Studies n=8083	All Studies 16 Studies n=7203	SA 12 Studies n=6467
Sensitivity (95% CI)	0.919 (0.874,0.949)	0.939 (0.899,0.964)	0.945 (0.920,0.963)	0.947 (0.922,0.964)	0.959 (0.930,0.976)	0.967 (0.950,0.979)
Specificity (95% CI)	0.345 (0.248,0.457)	0.309 (0.216,0.421)	0.271 (0.181,0.384)	0.210 (0.140,0.302)	0.282 (0.199,0.384)	0.222 (0.162,0. 297)
DOR (95% CI)	5.969 (4.410,7.529)	6.897 (5.095,8.698)	6.383 (3.255,9.511)	4.768 (2.692,6.908)	1.336 (1.184,1.488)	8.492 (4.994,11.989)
LR+ (95% CI)	1. 403 (1.232,1.598)	1.359 (1.194,1.524)	1.296 (1.125,1.466)	1.199 (1.088,1.310)	0.146 (0.095,0.196)	1.244 (1.144,1.344)
LR- (95% CI)	0.235 (0.183,0.301)	0.197 (0.143,0.251)	0.203 (0.123,0.466)	0.251 (0.155,0.348)	9.168 (5.932,12.405)	0.147 (0.091,0.202)

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; SA: sensitivity analysis; DOR: diagnostic odds ratio; CI: confidence interval; LR: likelihood ratio; +: positive; -: negative

9.12 Appendix 12 Sensitivity Analysis for the STOP (Sleep Clinic)

Parameter	All OSA AHI≥5		Moderate-Severe OSA AHI≥15		Severe OSA AHI≥30	
	All Studies 7 Studies; n=2063	SA 6 Studies n=1638	All Studies 6 Studies n=1638	SA 5 Studies n=1388	All Studies 6 Studies n=1637	SA 5 Studies n=1388
Sensitivity (95% CI)	0.904 (0.824,0.950)	0.901 (0.802,0.953)	0.903 (0.754,0.966)	0.936 (0.861,0.972)	0.945 (0.883,0.975)	0.958 (0.897,0.983)
Specificity (95% CI)	0.306 (0.148,0.528)	0.283 (0.117,0.540)	0.290 (0.098,0.606)	0.185 (0.083,0.364)	0.214 (0.104,0.391)	0.169 (0.085,0.307)
DOR (95% CI)	4.174 (0.767,7.581)	3.588 (1.194,5.982)	3.825 (1.700,5.949)	3.297 (1.136,5.458)	4.704 (2.615,6.794)	4.571 (1.749,7.393)
LR+ (95% CI)	1.304 (0.970,1.637)	1.256 (0.943,1.570)	1.273 (0.904,1.642)	1.148 (0992,1.304)	1.203 (1.029,1.379)	1.152 (1.031,1.272)
LR- (95% CI)	0.312 (0.118,0.506)	0.350 (0.179,0.522)	0.333 0.194,0.472)	0.348 (0.150,0.547)	0.256 (0.154,0.357)	0.252 (0.103,0.401)

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; SA: sensitivity analysis; DOR: diagnostic odds ratio; CI: confidence interval; LR: likelihood ratio; +: positive; -: negative

9.13 Appendix 13 Study selection for SA (desaturation criteria)

Criteria	Berlin AHI>5	Berlin AHI≥15	Berlin AHI≥30	STOP AHI >5	STOP AHI≥15	STOP AHI≥30	SBQ AHI>5	SBQ AHI≥15	SBQ AHI≥30
≥3% Desaturation Criteria Applied									
Included in SA	Amra 2013 (32) Amra 2018 (33) Oktay Arslan 2020 (34) Kashaninasab 2017 (45) Pereira 2013 (51)	Amra 2013 (32) Oktay Arslan 2020 (34) Kashaninasab 2017 (45) Pereira 2013 (51) Yüceege 2015 (58)	Amra 2013 (32) Pereira 2013 (51)	Kashaninasab 2017 (45) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Oktay Arslan 2020 (34) BaHammam 2015 (36) Boynton 2013 (37) Duarte 2017 (40) Duarte 2020 (41) Hu 2019 (44) Kashaninasab 2017 (45) Pereira 2013 (51) Sadeghniiat-Haghighi 2015 (53)	Oktay Arslan 2020 (34) Boynton 2013 (37) Duarte 2017 (40) Duarte 2020 (41) Hu 2019 (44) Pereira 2013 (51) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Boynton 2013 (37) Duarte 2017 (40) Duarte 2020 (41) Hu 2019 (44) Pereira 2013 (51) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)

Criteria	Berlin AHI>5	Berlin AHI≥15	Berlin AHI≥30	STOP AHI >5	STOP AHI≥15	STOP AHI≥30	SBQ AHI>5	SBQ AHI≥15	SBQ AHI≥30
							Sangkum 2017 (55)		
Excluded: ***Risk of Bias***	None	None	None	Pecotic 2012 (50)	Kashaninasab 2017 (45)	Kashaninasab 2017 (45)	Abdullah 2018 (30) Alhouqani 2015 (31) Amra 2018 (33)	Alhouqani 2015 (31) BaHammam 2015 (36) Delgado-Vargas 2020 (39) Kashaninasab 2017 (45)	Alhouqani 2015 (31) BaHammam 2015 (36) Delgado-Vargas 2020 (39) Kashaninasab 2017 (45)
Excluded: Desaturation criteria not specified	Perumalsamy 2017 (52) Suksakorn 2014 (56)	Suksakorn 2014 (56)	Suksakorn 2014 (56)	None	None	None	Ong 2010 (48) Perumalsamy 2017 (52)	Ong 2010 (48)	Ong 2010 (48)
Excluded: ***≥ 4% desaturation criteria***	El Sayed 2012 (42) Ha 2014 (43) Khaledi-Paveh 2016 (46) Kim 2015 (47)	El Sayed 2012 (42) Ha 2014 (43) Khaledi-Paveh 2016 (46) Kim 2015 (47)	El Sayed 2012 (42) Ha 2014 (43) Khaledi-Paveh 2016 (46)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	Avincsal 2017 (35) El Sayed 2012 (42) Ha 2014 (43) Kim 2015 (47)	Avincsal 2017 (35) El Sayed 2012 (42)	Avincsal 2017 (35) El Sayed 2012 (42) Ha 2014 (43)

Criteria	Berlin AHI>5	Berlin AHI≥15	Berlin AHI≥30	STOP AHI >5	STOP AHI≥15	STOP AHI≥30	SBQ AHI>5	SBQ AHI≥15	SBQ AHI≥30
	Pataka 2016 (49) Saleh 2011 (54)	Pataka 2016 (49)	Pataka 2016 (49)				Pataka 2016 (49) Vana 2013 (57)	Ha 2014 (43) Pataka 2016 (49) Kim 2015 (47) Vana 2013 (57)	Pataka 2016 (49)
≥4% Desaturation Criteria Applied									
Included in SA	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)	El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49) Vana 2013 (57)	Avincsal 2017 (35) El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49) Kim 2015 (47) Vana 2013 (57)	Avincsal 2017 (35) El Sayed 2012 (42) Ha 2014 (43) Pataka 2016 (49)
Excluded: Risk of Bias	Khaledi-Paveh 2016 (46) Kim 2015 (47)	Khaledi-Paveh 2016 (46) Kim 2015 (47)	Khaledi-Paveh 2016 (46)	None	None	None	Abdullah 2018 (30)	Alhouqani 2015 (31)	Alhouqani 2015 (31)

Criteria	Berlin AHI>5	Berlin AHI≥15	Berlin AHI≥30	STOP AHI >5	STOP AHI≥15	STOP AHI≥30	SBQ AHI>5	SBQ AHI≥15	SBQ AHI≥30
		Saleh 2011 (54)					Alhouqani 2015 (31) Amra 2018 (33)	BaHammam 2015 (36) Delgado-Vargas 2020 (39) Kashaninasab 2017 (45)	BaHammam 2015 (36) Delgado-Vargas 2020 (39) Kashaninasab 2017 (45)
Excluded: Desaturation criteria not specified	Suksakorn 2014 (56)	Perumalsamy 2017 (52) Suksakorn 2014 (56)	Suksakorn 2014 (56)	None	None	None	Ong 2010 (48) Perumalsamy 2017 (52)	Ong 2010 (48)	Ong 2010 (48)
Excluded: ≥3% desaturation	Amra 2013 (32) Oktay Arslan 2020 (34) Kashaninasab 2017 (45) Pereira 2013 (51) Yüceege 2015 (58)	Amra 2013 (32) Amra 2018 (33) Oktay Arslan 2020 (34) Kashaninasab 2017 (45) Pereira 2013 (51)	Amra 2013 (32) Kashaninasab 2017 (45) Pereira 2013 (51)	Kashaninasab 2017 (45) Pecotic 2012 (50) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Kashaninasab 2017 (45) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Kashaninasab 2017 (45) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	A Oktay Arslan 2020 (34) BaHammam 2015 (36) Boynton 2013 (37) Duarte 2017 (40)	Oktay Arslan 2020 (34) Boynton 2013 (37) Duarte 2017 (40) Duarte 2020 (41) Hu 2019 (44)	Boynton 2013 (37) Duarte 2017 (40) Duarte 2020 (41) Hu 2019 (44) Pereira 2013 (51) Sadeghniiat-

Criteria	Berlin AHI>5	Berlin AHI≥15	Berlin AHI≥30	STOP AHI >5	STOP AHI≥15	STOP AHI≥30	SBQ AHI>5	SBQ AHI≥15	SBQ AHI≥30
							Duarte 2020 (41) Hu 2019 (44) Kashaninasab 2017 (45) Pereira 2013 (51) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Pereira 2013 (51) Sadeghniiat-Haghighi 2015 (53) Sangkum 2017 (55)	Haghighi 2015 (53) Sangkum 2017 (55)

9.14 Appendix 14 Sensitivity Analysis for STOP-Bang (Surgical)

Parameters	All OSA AHI >5	All OSA AHI ≥5	Moderate-Severe OSA AHI ≥15	Moderate-Severe OSA AHI ≥15	Moderate-Severe OSA AHI ≥15	Severe OSA AHI ≥30	Severe OSA AHI ≥30
	All Studies	≥3% Desaturation	All Studies	≥3% Desaturation	≥4% Desaturation	All Studies	≥3% Desaturation
	4 Studies n=1227	3 Studies n=843	6 Studies n=2098	4 Studies n=924	2 Studies n=1174	3 Studies n=1050	2 Studies n=666
Sensitivity (95% CI)	0.846 (0.881; 0.876)	0.856 (0.806; 0.894)	0.903 (0.871; 0.927)	0.915 (0.865; 0.948)	0.890 (0.848; 0.921)	0.960 (0.924; 0.979)	0.953 (0.905; 0.977)
Specificity (95% CI)	0.394 (0.298; 0.498)	0.397 (0.262; 0.551)	0.269 (0.189; 0.367)	0.223 (0.124; 0.367)	0.344 (0.313; 0.376)	0.261 (0.232; 0.292)	0.229 (0.157; 0.323)
DOR (95% CI)	3.564 (2.311;4.817)	3.901 (2.093; 5.727)	3.421 (1.892; 4.949)	3.089 (0.741; 5.436)	3.421 (1.892; 4.949)	8.406 (2.650; 14.162)	6.039 (0.648; 11.429)
LR+ (95% CI)	1.395 (1.187; 1.603)	1.420 (1.113; 1.726)	1.235 (1.093; 1.377)	1.177 (0.999; 1.356)	1.356 (1.271; 1.441)	1.299 (1.236; 1.362)	1.237 (1.096; 1.377)
LR- (95% CI)	0.391 (0.304; 0.479)	0.363 (0.261; 0.466)	0.361 (0.235; 0.487)	0.381 (0.143; 0.620)	0.321 (0.212; 0.430)	0.155 (0.054; 0.255)	0.205 (0.039; 0.370)

OSA: obstructive sleep apnoea; AHI: apnoea hypopnoea index; SA: sensitivity analysis; DOR: diagnostic odds ratio; CI: confidence interval; LR: likelihood ratio; +: positive; -: negative

9.15 Appendix 15 Sensitivity Analysis Berlin questionnaire (Sleep Clinic)

Parameter	All OSA AHI≥5	All OSA AHI≥5	All OSA AHI≥5	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Severe OSA AHI≥30	Severe OSA AHI≥30	Severe OSA AHI≥30
	All Studies 13 Studies n=3503	≥3% Desaturation 5 Studies n=1938	≥4% Desaturation 3 Studies n=579	All Studies 11 Studies n=3374	≥3% Desaturation 5 Studies n=1971	≥4% Desaturation 3 Studies n=579	All Studies 8 Studies n=1345	≥3% Desaturation 2 Studies n=285	≥4% Desaturation 3 Studies n=579
Sensitivity (95% CI)	0.848 (0.79,0.891)	0.860 (0.823; 0.889)	0.824 (0.597; 0.937)	0.843 (0.785,0.887)	0.847 (0.793; 0.889)	0.858 (0.682; 0.944)	0.886 (0.804,0.936)	0.885 (0.817; 0.929)	0.929 (0.825; 0.973)
Specificity (95% CI)	0.433 (0.296,0.582)	0.465 (0.294; 0.644)	0.245 (0.156; 0.363)	0.298 (0.204,0.413)	0.310 (0.169; 0.500)	0.163 (0.070; 0.335)	0.334 (0.211,0.458)	0.226 (0.167; 0.298)	0.248 (0.142; 0.395)
DOR (95% CI)	4.270 (0.718,7.822)	5.326 (2.145; 8.507)	1.520 (-0.581; 3.621)	2.279 (1.309,3.249)	2.490 (1.214; 3.766)	1.173 (0.462; 1.885)	3.882 (2.06,5.704)	2.236 (0.768; 3.705)	4.286 (1.178/ 7.395)
LR+ (95% CI)	1.497 (1.066,1.927)	1.607 (1.096; 2.119)	1.092 (0.799; 1.384)	1.201 (1.049,1.353)	1.228 (0.982; 1.475)	1.025 (0.931;1.119)	1.330 (0.110,1.550)	1.143 (1.022; 1.263)	1.234 (1.074; 1.394)
LR- (95% CI)	0.350(0.155-0.546)	0.302 (0.211; 0.303)	0.718 (-0.084; 1.520)	0.527 (0.361,0.693)	0.493 (0.335; 0.651)	0.873 (0.422;1.325)	0.343 (0.210,0.475)	0.511 (0.226; 0.796)	0.288 (0.089; 0.486)

LR: likelihood ratio; =: positive; -: negative; DOR: diagnostic odds ratio; SA: sensitivity analysis; AHI: apnoea hypopnoea index; OSA: obstructive sleep apnoea; CI: confidence interval

9.16 Appendix 16 Sensitivity Analysis STOP questionnaire (Sleep Clinic)

Parameter	All OSA AHI≥5	All OSA AHI≥5	All OSA AHI≥5	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Severe OSA AHI≥30	Severe OSA AHI≥30	Severe OSA AHI≥30
	All Studies 7 Studies; n=2063	≥3% Desaturation 3 Studies n=1061	≥4% Desaturation 3 Studies n=579	All Studies 6 Studies n=1638	≥3% Desaturation 2 Studies n=811	≥4% Desaturation 3 Studies n=579	All Studies 6 Studies n=1637	≥3% Desaturation 2 Studies n=811	≥4% Desaturation 3 Studies n=579
Sensitivity (95% CI)	0.904 (0.824,0.950)	0.892 (0.725; 0.963)	0.897 (0.762; 0.959)	0.903 (0.754,0.966)	0.956 (0.860; 0.987)	0.915 (0.784; 0.969)	0.945 (0.883,0.975)	0.967 (0.887; 0.991)	0.934 (0.824; 0.938)
Specificity (95% CI)	0.306 (0.148,0.528)	0.376 (0.141; 0.689)	0.186 (0.052; 0.488)	0.290 (0.098,0.606)	0.182 (0.051; 0.477)	0.180 (0.062; 0.421)	0.214 (0.104,0.391)	0.146 (0.043; 0.369)	0.177 (0.080; 0.347)
DOR (95% CI)	4.174 (0.767,7.581)	4.982 (2.819; 7.145)	1.986 (0.332; 3.640)	3.825 (1.700,5.949)	4.836 (0.758; 9.913	2.351 (0.373; 4.330)	4.704 (2.615,6.794)	5.044 (0.645;10.733)	3.524 (1.045; 6.002)
LR+ (95% CI)	1.304 (0.970,1.637)	1.430 (0.893; 1.967)	1.102 (0.892; 1.312)	1.273 (0.904,1.642)	1.169 (0.918; 1.419)	1.116 (0.938; 1.295)	1.203 (1.029,1.379)	1.133 (0.938; 1.327)	1.145 (1.021; 1.268)
LR- (95% CI)	0.312 (0.118,0.506)	0.287 (0.182; 0.392)	0.555 (0.186; 0.924)	0.333 0.194,0.472)	0.242 (0.064; 0.419)	0.474 (0.132; 0.817)	0.256 (0.154,0.357)	0.225 (-0.008; 0.457)	0.325 (0.100; 0.550

LR: likelihood ratio; =: positive; -: negative; DOR: diagnostic odds ratio; SA: sensitivity analysis; AHI: apnoea hypopnoea index; OSA: obstructive sleep apnoea; CI: confidence interval

9.17 Appendix 17 Sensitivity Analysis STOP-Bang questionnaire (Sleep Clinic)

Parameter	All OSA AHI≥5	All OSA AHI≥5	All OSA AHI≥5	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Moderate-Severe OSA AHI≥15	Severe OSA AHI≥30	Severe OSA AHI≥30	Severe OSA AHI≥30
	All Studies 21 Studies n=9250	≥3% Desaturation 10 Studies n=6506	≥4% Desaturation 4 Studies n=626	All Studies 19 Studies n=8819	≥3% Desaturation 8 Studies n=6419	≥4% Desaturation 6 Studies n=1380	All Studies 16 Studies n=7203	≥3% Desaturation 7 Studies n=5361	≥4% Desaturation 4 Studies n=531
Sensitivity (95% CI)	0.919 (0.874,0.949)	0.942 (0.872; 0.975)	0.935 (0.863; 0.971)	0.945 (0.920,0.963)	0.952 (0.923; 0.971	0.941 (0.880; 0.972)	0.959 (0.930,0.976)	0.969 (0.956; 0.978)	0.961 (0.882; 0.988)
Specificity (95% CI)	0.345 (0.248,0.457)	0.286 (0.167; 0.445)	0.367 (0.214; 0.553)	0.271 (0.181,0.384)	0.265 (0.178; 0.375	0.116 (0.052; 0.239)	0.282 (0.199,0.384)	0.254 (0.197; 0.322)	0.137 (0.061; 0.279)
DOR (95% CI)	5.969 (4.410,7.529)	6.479 (3.945; 9.013)	8.378 (4.986; 11.771)	6.383 (3.255,9.511)	7.206 (4.766; 9.646	2.078 (0.233; 3.923)	1.336 (1.184,1.488)	10.703 (6.275;15.130)	3.898 (1.109; 6.688)
LR+ (95% CI)	1. 403 (1.232,1.598)	1.319 (1.115; 1.524)	1.478 (1.135; 1.821)	1.296 (1.125,1.466)	1.296 (1.144; 1.448)	1.064 (0.967; 1.161)	0.146 (0.095,0.196)	1.300 (1.194; 1.406)	1.114 (1.014; 1.213)
LR- (95% CI)	0.235 (0.183,0.301)	0.204 (0.116; 0.291)	0.176 (0.101; 0.252)	0.203 (0.123,0.466)	0.180 (0.125; 0.235)	0.512 (0.099; 0.925)	9.168 (5.932,12.405)	0.121 (0.077; 0.166)	0.286 (0.086; 0.486)

LR: likelihood ratio; =: positive; -: negative; DOR: diagnostic odds ratio; SA: sensitivity analysis; AHI: apnoea hypopnoea index; OSA

9.18 Appendix 18 Point Estimates for STOP-Bang Questionnaire

Questionnaire	Population	AHI	Sensitivity	Specificity	Prevalence	PPV	NPV
STOP-Bang	Sleep Clinic	≥5	0.919	0.345	0.7998	0.8486	0.5160
STOP-Bang	Sleep Clinic	≥15	0.945	0.271	0.5878	0.6489	0.7755
STOP-Bang	Sleep Clinic	≥30	0.959	0.282	0.3925	0.4632	0.9141
STOP-Bang	Surgical	≥5	0.846	0.394	0.1756	0.7784	0.5042
STOP-Bang	Surgical	≥15	0.903	0.269	0.3279	0.3760	0.8504
STOP-Bang	Surgical	≥30	0.960	0.261	0.2124	0.2594	0.9603

AHI: apnoea hypopnoea index; PPV: positive predictive value; NPV: negative predictive value

9.19 Appendix 19 Invitation Questionnaire/Interview Study (Patients)

Leicester Biomedical Research Centre
Cardiovascular Theme
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3862

AN INVITATION TO PARTICIPATE IN RESEARCH

Title of Project: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

We are writing to invite you to take part in the above study.

You are being invited to participate because your doctors have referred you for a test called a sleep study, to find out if you have a condition called obstructive sleep apnoea.

Obstructive sleep apnoea is a condition that is often seen in patients with heart failure. During sleep, the walls of the throat relax and narrow and as a result interrupts normal breathing. It affects large numbers of people, but many are undiagnosed. As a result, individuals with untreated obstructive sleep apnoea, may be at greater risk of developing high blood pressure, stroke or other health conditions.

A simple, effective questionnaire could help to identify heart failure patients at risk of obstructive sleep apnoea. Limited research has been carried out on sleep apnoea screening questionnaires in the United Kingdom, therefore, this study aims to see how well a screening questionnaire (the STOP-Bang questionnaire) can identify heart failure patients at risk of obstructive sleep apnoea that may benefit from further investigation and treatment.

As well as determining how well a screening questionnaire can identify people at risk of obstructive sleep apnoea, the second part of the study aims to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.

This research is split into two stages. The first will involve you answering a few health-related questions and completing a short questionnaire and the second will involve an interview with the researcher.

Please be assured that your participation is entirely voluntary and will not affect your care.

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We would like to invite you to take part in this important study, details of which are given in the enclosed information sheet. If you would like to take part or have any questions, please contact the Lizelle Bernhardt on 0116 258 3862.

We hope that you are happy to participate.

Thank you for your consideration.

Yours sincerely,

Lizelle Bernhardt
Postgraduate Research Student

Prof Iain Squire
Academic Supervisor

9.20 Appendix 20 Patient Information Sheet – Questionnaire/Interview Study

Leicester Biomedical Research Centre
Cardiovascular Theme
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3385

Patient Information Sheet
Questionnaire and Interview Study

FULL TITLE OF STUDY: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Investigator: Lizelle Bernhardt

Supervised by: Professor Iain Squire & Professor Noelle Robertson

Contact Number: Telephone: 0116 258 3385

You are being invited to take part in a research study. This study is being carried out in fulfilment of the Chief Investigator's (Lizelle Bernhardt) completion of a Doctorate in Philosophy (PhD). Before you decide whether or not to take part it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Why have I been chosen?

You have been chosen because your doctors have referred you to undertake a test called a sleep study, to find out if you have a condition called obstructive sleep apnoea hypopnoea syndrome.

What is the purpose of the study?

Obstructive sleep apnoea hypopnoea syndrome is a condition that is often seen in patients with heart failure. During sleep, the walls of the throat relax and narrow and as a result interrupts normal breathing. It affects large num-

bers of people, but many are undiagnosed. As a result, individuals with untreated obstructive sleep apnoea, may be at greater risk of developing high blood pressure, stroke or other health conditions.

The Questionnaire and Interview Study is part of a two-stage project. Stage 1 aims to gain insight into the knowledge, beliefs and current practice of heart failure clinicians regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart failure. Stage 2 aims to determine how well a screening questionnaire can identify people at risk of obstructive sleep apnoea hypopnoea syndrome and to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure and is the stage which you are being asked to participate in.

A simple, effective questionnaire could help to identify heart failure patients at risk of obstructive sleep apnoea. Limited research has been carried out on sleep apnoea screening questionnaires in the United Kingdom, therefore, this study aims to see how well a screening questionnaire (the STOP-Bang questionnaire) can identify heart failure patients at risk of obstructive sleep apnoea that may benefit from further investigation and treatment.

As well as determining how well a screening questionnaire can identify people at risk of obstructive sleep apnoea, the second part of the study aims to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

If you lose capacity to consent, you will be withdrawn from the study. Data collected with consent will be retained and used in the study. However, no further data will be collected, or any research procedures carried out on you.

Who is organising and funding the research?

The research study forms part of an educational project that is being conducted at the Department of Cardiovascular Sciences at the University of Leicester. None of the research team will receive any payment for including you in the study. The study is being sponsored by the University of Leicester.

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What will happen to me if I take part?

This research is split into two stages. The first will involve you completing a short questionnaire and the second optional stage will involve an interview with the researcher.

What will happen to me if I take part in the questionnaire stage?

On your visit, the following will take place:

We will ask you:

1. To provide written consent to take part in the study (15 minutes).
2. To undertake a short interview to take your relevant medical history, current medication and symptoms (20 minutes).
3. Anthropometric measurements: we will take some of your body measurements, including your height, weight, neck circumference and waist circumference (5 minutes).
4. To complete a short questionnaire (5 minutes).

What will happen to me if I take part in the interview stage?

If you agree to take part in the second part of this research, it is important that you understand that you are free to withdraw from the research at any time, without giving a reason. It is also important to understand that a decision to withdraw from this research, will not affect the standard of the care you receive from your clinical team.

This research will involve you undertaking an interview that will last up to an hour. We will ask you some detailed questions about what you think helped or hindered your referral for the investigation and diagnosis of obstructive sleep apnoea hypopnoea syndrome. It is possible that you may find some of the topics difficult to talk about. You can stop the interview at any time if you find any of the topics difficult to talk about. Your responses will be analyses collectively with the responses that other participants give. Interviews will take place in a private room at the Sleep Disorders Service or by telephone and will last up to one hour. All information will be anonymously recorded and how this is done, will be explained to you in full before the interviews take place.

On your visit, the following will take place:

We will ask you:

1. To verbally reaffirm your consent to take part in the study (5 minutes).
2. To undertake an interview (60 minutes).

What are the possible disadvantages and risks of taking part?

We don't expect there to be any risks to you from taking part in this study.

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What are the possible benefits of taking part?

The information we gather during the research may not benefit you directly but will inform the researchers if the STOP-Bang questionnaire can correctly identify heart failure patients with sleep breathing disorders that may require treatment.

The information gathered from part 2, the Interview Study, will help to inform healthcare professionals about the factors that help or hinder the referral of people with obstructive sleep apnoea for further assessment and treatment.

What if something goes wrong?

If you are harmed as a direct result of taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for legal action. Regardless of this, if you have any cause to complain about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms are available to you. If you have any concerns about the way the researcher has carried out this study, or any other aspects of your care, you may contact the Patient Advice & Liaison Service PILS on 0116 2583100 or via e-mail PILS@uhl-tr.nhs.uk.

You may also contact Lizelle Bernhardt on 0116 258 3385, Professor Iain Squire on 0116 256 3021 or 0116 258 3877 or Dr Noelle Robertson on 0116 2231617.

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice in accordance with regulations pertaining to the Data Protection Act (2018).

The University of Leicester is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leicester will keep identifiable information about you for 6-12 months after the study has finished, until 2020.

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

You can find out more about how we use your information at:

https://www2.le.ac.uk/offices/ias

https://www2.le.ac.uk/offices/ias/information/public/public

https://www2.le.ac.uk/offices/ias/dp/subject-access-request

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

The University Hospitals of Leicester will keep identifiable information about you from this study for 6-12 months after the study has finished, until 2020.

All information collected during the study will be identified by a unique code so that you cannot be identified from it. All data will be kept on the University of Leicester secure computer servers and in a secure office environment at the Cardiovascular Research Centre at the Glenfield Hospital.

Interviews will be recorded using a password protected, digital recording device (Dictaphone). The recorded interviews will be transcribed onto a computer by the Chief Investigator, using a software package (NVivo). The data themes and direct quotes from the interviews will be completely anonymous and will not be identifiable in any way. Transcripts will be stored electronically on a secure server in the University of Leicester.

What will happen to the results of the research study?
The results will be presented at medical scientific meetings and will be published in medical journals. You will not be identifiable in any presentations.

A summary of the main study findings will be available to you at the end of the study. You can request a copy of this from Lizelle Bernhardt on 0116 258 3385 or email lb382@le.ac.uk.

Who has reviewed the study?
All research that involves NHS patients or staff must be approved by an NHS Research Ethics Committee and Health Research Authority before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

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Contact for Further Information
If you require further information, you can contact Lizelle Bernhardt on 0116 258 3385 or Professor Iain Squire on 0116 256 3021 or 0116 258 3877 at the Department of Cardiovascular Sciences, or Dr Noelle Robertson on 0116 2231617 at the Department of Neuroscience, Psychology and Behavior, University of Leicester.

Thank you for reading this.

Pre-screening

Eligibility assessment by clinical team.
Send letter of invitation and patient information sheet with appointment letter.

Visit 1

Informed Consent (15 minutes)
Short Interview (25 minutes) to obtain:

- Demographics
- Medical History and medication
- Anthropometric measurements (height, weight, neck circumference, waist circumference)
- Symptoms and NYHA classification

Completion of Questionnaire (5 minutes)
Record Sleep Study Results

Visit 2

Reaffirm Informed Consent (5 minutes)

Participate in Interview (60 minutes)

9.21 Appendix 21 Consent Form (Questionnaire/Interview Study)

Leicester Cardiovascular Biomedical Research Unit
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3385

Patient Identification Number for this study:

CONSENT FORM
Questionnaire and Interview Study

FULL TITLE OF STUDY: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Investigator: Lizelle Bernhardt
Supervised by: Professor Iain Squire & Dr Noelle Robertson

Please initial each box to confirm that you have read, understood and agreed each of the numbered points.

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.3) dated 06/03/2018 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐
3. I understand that I may become upset or distressed about speaking about experiences and I can ask for a break or terminate the interview at any time. ☐
4. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the study team, the Sponsor (University of Leicester), from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

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5. I understand that anonymised data may be transferred between the host organisation (University Hospitals of Leicester NHS Trust) and the Sponsor (University of Leicester). ☐

6. I agree to take part in this study. ☐

Optional Interview Stage

7. I agree to take part in the interview stage of the study. Yes ☐ No ☐

8. I understand that the interview will be audio recorded and transcribed data will be kept confidentially in line with research ethics regulations. ☐

9. I understand that I may become upset or distressed about speaking about experiences and I can ask for a break or terminate the interview at any time. ☐

10. I would like to receive a summary of the study findings on completion of the study. Yes ☐ No ☐

If yes, please enter email address below. Alternatively, please advise the researcher if you would prefer to receive this via post.

Email address _____ postal summary preferred ☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher (If different from person taking consent)	Date	Signature

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the patient. Third original or copy of the original to be kept in the patient's hospitals records. The Information Sheet and Consent Form are one entire document and must not be separated.

9.22 Appendix 22 Tabulation of AHI score and STOP-Bang score

No.	AHI	SBQ Score ≥3	SBQ Score ≥5
1.	0.2	7	7
2.	6.3	5	5
3.	7.2	5	5
4.	7.7	5	5
5.	9.1	5	5
6.	11	7	7
7.	11.1	6	6
8.	11.7	8	8
9.	12	6	6
10.	13	6	6
11.	17.6	7	7
12.	19.3	2	2
13.	20.9	5	5
14.	22.9	7	7
15.	26.7	7	7
16.	27.7	4	4
17.	28.1	6	6
18.	30.7	7	7

No.	AHI	SBQ Score ≥3	SBQ Score ≥5
19.	30.8	5	5
20.	34.8	4	4
21.	35.3	6	6
22.	39.3	6	6
23.	42.5	6	6
24.	45.1	7	7
25.	66.4	8	8

AHI: Apnoea hypopnoea index; SBQ: STOP-Bang questionnaire; AHI: apnoea hypopnoea inde

9.23 Appendix 23 Interview Debrief Sheet (Patients)

INTERVIEW DEBRIEF SHEET

Study title: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Thank you for participating in this Interview Study.

Obstructive sleep apnoea hypopnoea syndrome is a condition that is often seen in patients with heart failure. During sleep, the walls of the throat relax and narrow and as a result interrupts normal breathing. It affects large numbers of people, but many are undiagnosed. As a result, individuals with untreated obstructive sleep apnoea, may be at greater risk of developing high blood pressure, stroke or other health conditions.

The purpose of the Interview study is to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.

We hope that the information provided will help to inform healthcare professionals about the factors that help or hinder the referral of people with obstructive sleep apnoea for further assessment and treatment.

All the information we collect will be confidential and there will be no way of identifying your responses in the data archive.

Please note that you have the right to withdraw at any time and without giving a reason.

If you have any questions about the study, you are welcome to contact Lizelle Bernhardt (lb382@le.ac.uk) or Prof Iain Squire (is11@le.ac.uk) at the Department of Cardiovascular Sciences, University of Leicester.

If you have any concerns about the way the researcher has carried out this study, or any other aspects of your care, you may contact the Patient Advice & Liaison Service PALS on 0116 2583100 or via e-mail PALS@uhl-tr.nhs.uk.

If your participation in this study has caused you concerns, anxiety or otherwise distressed you, you may contact your local doctor and/or local counselling support services. These can be accessed through your GP surgery or workplace.

An information sheet, with a summary of the main study findings, will be available to you at the end of the study. You can request a copy of the information sheet from Lizelle Bernhardt on 0116 258 3862 or email lb382@le.ac.uk.

Thank you again for your participation.

9.24 Appendix 24 Email Invitation (Health Care Professionals)

Subject: Invitation to participate in Research

Interview of Heart Failure Clinicians

Dear Colleague,

As a clinician/health care professional with an interest in Heart Failure, we would like to invite you to participate in an Interview to help us understand what helps or hinders the referral of heart failure patients, at risk of obstructive sleep apnea hypopnoea syndrome, for further assessment and treatment. The interview should take no more than 60 minutes to complete.

We hope that the information provided will help to highlight barriers and facilitators to the diagnosis of obstructive sleep apnoea hypopnoea syndrome in patients with heart failure and inform improvement initiatives that may be required.

The purpose of the Interview Study and further details can be found in the attached Participant Information Sheet. Please read this before deciding whether you would like to participate.

All responses will be anonymised. Individual responses will be combined to provide an overall picture of the barriers and facilitators of the diagnosis of obstructive sleep apnoea hypopnoea syndrome in patients with heart failure.

If, after reading the Participant Information Sheet, you are willing to participate in the Interview Study, please return the completed reply slip. It would be very helpful if you could return the completed reply slip within one week of receiving this email.

We would like to thank you for taking the time to read this email.

Kind regards,

Lizelle Bernhardt
Postgraduate Research Student
Department of Cardiovascular Sciences
University of Leicester

9.25 Appendix 25 Participant Information Sheet (Health Care Professionals)

Leicester Biomedical Research Centre
Cardiovascular Theme
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3385

Participant Information Sheet

Interview Study (Health Care Professionals)

FULL TITLE OF STUDY: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach (SPIRAL Study)

Investigator: Lizelle Bernhardt

Supervised by: Professor Iain Squire & Professor Noelle Robertson

Contact Number: Telephone: 0116 258 3385

You are being invited to take part in a research study. This study is being carried out in fulfilment of the Chief Investigator's (Lizelle Bernhardt) completion of a Doctorate in Philosophy (PhD). Before you decide whether to take part it is important that you understand why we are doing the study and what is involved. Please take time to read this information sheet carefully.

Why have I been chosen?

You have been chosen because you are a Health Care Professional (doctor, nurse, pharmacist) with an interest in Heart Failure.

What is the purpose of the study?

Obstructive sleep apnoea hypopnoea syndrome is among the most under diagnosed and under treated conditions in the United Kingdom. If left untreated, it can contribute to poor sleep, poor quality of life and increase the risk of cardiovascular disease, serious accidents and health care costs.

Despite the prevalence of obstructive sleep apnoea hypopnoea syndrome, the substantial impact and the availability of effective treatment, the condition is generally underdiagnosed and undertreated by health care providers.

The purpose of the interview study is to identify challenges that heart failure clinicians experience to identify obstructive sleep apnoea hypopnoea syndrome in heart failure patients. In addition, the interview will explore heart failure clinicians' perceptions and attitudes towards obstructive sleep apnoea hypopnoea syndrome in heart failure.

We hope that the information provided will help to highlight barriers and inform performance improvement initiatives that may be required to address knowledge, skills and attitudinal issues that impact on the diagnosis of obstructive sleep apnoea hypopnoea syndrome in heart failure.

The Interview Study for Health Care Professionals is part of a two-stage project. Stage 1 aims to gain insight into the knowledge, beliefs and current practice of heart failure clinicians regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart. Stage 2 aims to determine how well a screening questionnaire can identify people at risk of obstructive sleep apnoea hypopnoea syndrome and to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure from both patients' and health care professionals' accounts.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason.

Who is organising and funding the research?

The research study forms part of an educational project that is being conducted at the Department of Cardiovascular Sciences at the University of Leicester. None of the research team will receive any payment for including you in the study. The study is being sponsored by the University of Leicester.

What will happen to me if I take part?

The research involves an interview with the researcher. The interview should take you no longer than 60 minutes.

What will happen to me if I take part in the interview study?
This research will involve you undertaking an interview that will last up to 60 minutes. At the start of the interview, we will ask you a few questions about your place of work, level of practice, gender, age and how long you have worked as a heart failure clinician. We will then ask you some detailed questions about issues that you think may help or hinder assessment and referrals of heart failure patients at risk of obstructive sleep apnoea hypopnoea syndrome, for further investigation and diagnosis.

It is possible that you may find some of the topics difficult to talk about. You can stop the interview at any time if you find any of the topics difficult to talk about. Your responses will be analysed collectively with the responses that other participants give. Interviews will take place at your usual place of work or via telephone. All information will be anonymously recorded and how this is done, will be explained to you in full before the interviews take place.

On your visit, the following will take place:

We will ask you:

1. To provide written consent to take part in the study (15 minutes).
2. To undertake an interview (45 minutes).

If you agree to take part in the interview study, it is important that you understand that you can choose to withdraw your interest and or consent at any time and no reason will be sought for your decision. We would however wish you to note that once data analysis has commenced, it is not possible to remove individual data as these are anonymised. If you lose capacity to consent, you will be withdrawn from the study. Data collected with consent will be retained and used in the study.

What are the possible disadvantages and risks of taking part?

We don't expect there to be any risks to you from taking part in this study.

What are the possible benefits of taking part?

The information gathered from the Interview Study for Health Care Professionals will help to inform the researcher about the factors that help or hinder the referral of heart failure patients at risk of obstructive sleep apnoea hypopnoea syndrome for further assessment and treatment.

What happens if something goes wrong?

If you have any concerns about the study or would like to make a complaint, please contact the:

Research Governance Office,
Academic Department (Ground Floor),
Leicester General Hospital,
Gwendolen Road,
Leicester,
LE5 4PW,
uolsponsor@le.ac.uk,

Tel: 0116 258 4099/4077/4867

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Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice in accordance with regulations pertaining to the Data Protection Act (2018).

The University of Leicester is the sponsor for this study based in the United Kingdom. We will be using information from you in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leicester will keep identifiable information about you for 6-12 months after the study has finished, until 2020.

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

You can find out more about how we use your information at:

https://www2.le.ac.uk/offices/ias

https://www2.le.ac.uk/offices/ias/information/public/public

https://www2.le.ac.uk/offices/ias/dp/subject-access-request

The University of Leicester will use your name and contact details to contact you about the research study, and make sure that relevant information about the study is recorded and to oversee the quality of the study. Individuals from the University of Leicester and regulatory organisations may look at your research records to check the accuracy of the research study. The only people in the University of Leicester who will have access to information that identifies you will be people who need to contact you regarding the research study or audit the data collection process. This information and other personal details will not be included in analysis, or in publications or reports.

All information collected during the study will be identified by a unique code so that you cannot be identified from it. All data will be kept on the University of Leicester secure computer servers and in a secure office environment at the Cardiovascular Research Centre at the Glenfield Hospital.

Interviews will be recorded using a password protected, digital recording device (Dictaphone). The recorded interviews will be transcribed onto a computer by the Chief Investigator, using a software package (NVivo). The data themes and direct quotes from the interviews will be completely anonymous and will not be identifiable in any way. Transcripts will be stored electronically.

All documents will be stored safely in a locked filing cabinet in a secure office

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in the Cardiovascular Research Centre at Glenfield Hospital. Electronic transcribed data will be held on a secure server in the University of Leicester.

What will happen to the results of the research study?

The results will be presented at medical scientific meetings and will be published in medical journals. You will not be identifiable in any presentations.

A summary of the main study findings, will be available to you at the end of the study. You can request a copy of this from Lizelle Bernhardt on 0116 258 3385 or email lb382@le.ac.uk.

Who has reviewed the study?

All research that involves NHS patients or staff must be approved by an NHS Research Ethics Committee and Health Research Authority before it goes ahead. Approval does not guarantee that you will not come to any harm if you take part. However, approval means that the committee is satisfied that your rights will be respected, that any risks have been reduced to a minimum and balanced against possible benefits and that you have been given sufficient information on which to make an informed decision.

Contact for Further Information

If you require further information you can contact Lizelle Bernhardt on 0116 258 3385 or Professor Iain Squire on 0116 256 3021 or 0116 258 3877 at the Department of Cardiovascular Sciences, or Professor Noelle Robertson on 0116 2231617 at the Department of Neuroscience, Psychology and Behavior, University of Leicester.

Thank you for reading this.

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First Contact: Pre-screening

Eligibility assessment by Principal Investigator. Send invitation and participant information sheet by email.

Second Contact

Informed Consent (15 minutes) Participate in Interview (including de-mographics) (45)

9.26 Appendix 26 Reply Slip (Health Care Professionals)

Leicester Biomedical Research Centre
Cardiovascular Theme
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3385

Reply Slip for Interview Participants
(Health Care Professionals)
SPIRAL Study

❑ I would like to volunteer to take part in the interview as part of the above study. I agree to a member of the research team contacting me by telephone, by email or in person to arrange an appointment to be interviewed.
OR
❑ I have decided not to take part in the interview and that I would not like to be contacted further about the study.

FULL NAME: _____
TELEPHONE NUMBER: _____
EMAIL ADDRESS: _____
SIGNATURE: _____
DATE: _____

To help us choose a range of heart failure professionals, it would be very helpful if you could provide the following information about yourself:

1) Are you?
   Male / Female (please delete as appropriate)

2) What is your age? (please tick one box only)
   18-24 ❑ 25-39 ❑ 40-59 ❑ 60-75 ❑

3) How long have you worked as a heart failure clinician? (please tick one box below)

   Less than 6 months ❑ Between 1-3 years ❑ Between 3-10 years ❑ Over 10 years ❑

4) What is your profession? (please tick one box below)
   Nurse ❑ Pharmacist ❑ Doctor ❑ Other ❑

   If selected other, please specify: _____

9.27 Appendix 27 Consent Form (Health Care Professionals' Interviews)

Leicester Cardiovascular Biomedical Research Unit
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Centre
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3385

CONSENT FORM
Interview Study (Health Care Professionals)
SPIRAL Study

FULL TITLE OF STUDY: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Investigator: Lizelle Bernhardt
Supervised by: Professor Iain Squire & Professor Noelle Robertson

Please initial each box to confirm that you have read, understood and agreed each of the numbered points.

Please initial box

1. I confirm that I have read and understand the information sheet (version 1.0) dated 18.02.2019 for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason. ☐
3. I understand that I may become upset or distressed about speaking about experiences and I can ask for a break or terminate the interview at any time. ☐
4. I understand that the interview will be audio recorded and transcribed data will be kept confidentially in line with research ethics regulations. Documents will be stored in a locked filing cabinet in a secure office in the Cardiovascular Research Centre at Glenfield Hospital. Electronically transcribed data will be held on a secure server in the University of Leicester. Access to identifiable information will be limited to those who need to contact you regarding the research study or audit the data collection process. ☐

5. I agree to take part in above Interview Study. ☐

6. I would like to receive a summary of the study findings on completion of the study. Yes ☐ No ☐

If yes, please enter email address below. Alternatively, please advise the researcher if you would prefer to receive this via post.

postal summary preferred

Email address _____

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Person taking consent	Date	Signature
_____	_____	_____
Researcher (If different from person taking consent)	Date	Signature

Original to be kept in the study Investigator Folder; Second original or a copy of the original to be given to the participant. The Information Sheet and Consent Form are one entire document and must not be separated.

9.28 Appendix 28 Debrief Sheet (Health Care Professionals)

INTERVIEW DEBRIEF SHEET

Study title: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Thank you for participating in this Interview Study.

Obstructive sleep apnoea hypopnoea syndrome is a condition that is often seen in patients with heart failure. During sleep, the walls of the throat relax and narrow and as a result interrupts normal breathing. It affects large numbers of people, but many are undiagnosed. As a result, individuals with untreated obstructive sleep apnoea, may be at greater risk of developing high blood pressure, stroke or other health conditions.

The purpose of the Interview study is to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.

We hope that the information provided will help to inform us about the factors that help or hinder the referral of people with obstructive sleep apnoea for further assessment and treatment.

All the information we collect will be confidential and there will be no way of identifying your responses in the data archive.

Please note that you have the right to withdraw at any time and without giving a reason.

If you have any questions about the study, you are welcome to contact Lizelle Bernhardt (lb382@le.ac.uk) or Prof Iain Squire (is11@le.ac.uk) at the Department of Cardiovascular Sciences, or Professor Noelle Robertson (nr6@le.ac.uk) at the Department of Neuroscience, Psychology and Behaviour, University of Leicester.

If you have any concerns about the study or would like to make a complaint, please contact: the Research Governance Office, Academic Department (Ground Floor), Leicester General Hospital, Gwendolen Road, Leicester, LE5 4PW, uolsponsor@le.ac.uk, Tel: 0116 258 4099/4077/4867

If your participation in this study has caused you concerns, anxiety or otherwise distressed you, you may contact your local doctor and/or local counselling support services. These can be accessed through your GP surgery or work place.

An information sheet, with a summary of the main study findings, will be available to you at the end of the study. You can request a copy of the information sheet from Lizelle Bernhardt on 0116 258 3862 or email lb382@le.ac.uk.

Thank you again for your participation.

9.29 Appendix 29 Patient Interview Schedule

Introduction to the Interview

A. Background statement

Untreated moderate-severe OSA can have negative health consequences for patients. Many patients with a diagnosis of heart failure often have co-existing OSA, however, a large proportion of these patients at risk of OSA are not identified and subsequently referred for further investigation and possible treatment.

B. Study aim

To identify barriers to and facilitators of the diagnosis of OSA from patients' accounts.

C. Key areas:

The participant's perspective of what factors helped and hindered the diagnostic process of OSA.

D. Information for participants

- **Thank you** for agreeing to participate in this interview.
- There are **no right or wrong answers**, anything you share will be extremely helpful to my study.
- The interview will take no longer than **1 hour**.
- Your view on this topic is **greatly valued**.
- All responses will be **anonymised**.
- As mentioned in the information sheet, the **purpose** of today's interview is to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.
- We will **start off** with questions around your understanding of OSA, then we will focus on the referral process and your experiences and we will finish off by talking a bit about the treatment.
- Before we start, are you okay with me **starting the recorder**? (begin recording)

Interview Guide

A. Perceptions and knowledge of diagnosis

1. Before being told that you have OSA, had you heard of OSA? If so, please tell me what you know about it?
    a. How did you know about sleep disorders and the sleep clinic before coming to your appointment?
2. What do you now understand about OSA?
3. After having your sleep study, what are your thoughts about OSA and what it means to you?
4. What were your key symptoms? How long?

5. What did these symptoms mean to you?
    a. Did it affect your physical health or mental health? If so, how?
6. What effect has OSA had on your quality of life?
7. Did you seek help for it? If yes, why did you seek help?
8. Is there anyone that has helped you understand what OSA is? Is so, how does this affect your desire to receive treatment?
9. Does sleep, sleeping or sleep environment have any specific meaning to you/your family/spouse/partner?

B. Referral Experience

We are going to go through some questions around your referral to the sleep clinic.

First, can you tell me:

1. Tell me a little bit about what prompted the referral? (explore if needed)
2. Do you know anyone else who has been diagnosed with OSA? If so, how did that impact on you coming to the sleep clinic?
3. Is there anyone who influenced you to seek help/care for this problem?
4. How was your overall impression of your referral? (depending on what it is you are looking for, ask the participant to elaborate)
5. What was your experience with the health care service like up to this point?
6. What is your impression of the pathways/waiting times to arrive at the diagnosis?
7. What do you think went well during the process of referral?
8. What didn't go well – were there any challenges?
9. If you had the chance to make a difference to the referral process, what would you change to make it a better experience?
10. What is your impression of the information you received regarding OSA, the diagnosis and treatment?
    a. By the person who made the referral.
    b. By the person who informed you of the diagnosis.
    c. Communication style of the HCP?
        i. The way in which the information and diagnosis were delivered
    d. Quantity, quality, relevance, timeliness, user friendliness, written/verbal
    e. Participant's perceived relevance of the information provided by staff

C. Treatment Experience

After your sleep study, you were recommended treatment.

1. How do you feel about the treatment recommendations?
2. Do you have any concerns about the diagnosis and treatment?

3. What are your impressions of the benefits of the treatment?

Now that you have started on the treatment,

4. How has the CPAP treatment gone for you?
5. What kinds of problems using CPAP are you experiencing?
6. How would you describe your use of CPAP?
7. What has prevented your regular use of CPAP?
8. What has been helpful in your regular use of CPAP?
9. What are your experiences of using the treatment?
    - Look for barriers to CPAP use:
    - Explore self-image
    - Other barriers: claustrophobia, fear/anxiety, resistance to notion of CPAP, difficulty with the mask, side effects, not perceiving any benefit, low perceived self-efficacy, not having intrusive observable symptoms of OSA
    - Facilitators: relieve observable symptoms; perceived benefits of CPAP, fear of subsequent health problems, partner/peer support
    - Personal characteristics to indicate CPAP usage patterns: different coping styles, avoidance behaviour, confidence levels, autonomy levels, optimisms, perceived self-efficacy.
10. We've heard from other patients that being on CPAP has affected their life. Would you say this is the case for you too? (if yes, then follow up with 'in what way has it affected your life')
11. Do you believe that CPAP treatment is a treatment you can continue to use? Did this belief change since you first learn of your diagnosis? Since starting CPAP.
12. Do you envision yourself using CPAP over the next 3 months, 1 year, 5 years?
13. Do you have any concerns about the CPAP unit and your sleep?
14. How does the diagnosis of OSA and treatment with CPAP affect or been affected by those around you?

D. Conclusion to the interview:

- We are coming to the end of this interview, I feel we have covered all my questions, is there anything else that you wanted to mention that we did not cover in the interview regarding the referral and treatment?
- Is there anything that you would like to ask me?
- Debriefing

9.30 Appendix 30 Clinician Interview Schedule

Introduction to the Interview

A. Background statement

Untreated moderate-severe OSA can have negative health consequences for patients. Many patients with a diagnosis of heart failure often has co-existing OSA, however, a large proportion of these patients at risk of OSA are not identified and subsequently referred for further investigation and possible treatment.

B. Study aim

To identify barriers to and facilitators of the diagnosis of OSA from heart failure clinicians' accounts.

C. Key areas

The participant's perspective of what factors helped and hindered the diagnostic process of OSA.

D. Information for participants

A. **Thank you** for agreeing to participate in this interview.
B. There are **no right or wrong answers**, anything you share will be extremely helpful to my study.
C. The interview will take no longer than **1 hour**.
D. Your views on this topic is **greatly valued**.
E. All responses will be **anonymised**.
F. As mentioned in the information sheet, the **purpose** of today's interview is to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.
G. We will **start off** with questions around your understanding of OSA, then we will focus on the referral process and your experiences and we will finish off by talking a bit about the any issues you may face, including barriers and facilitators.
H. Before we start, are you okay with me **starting the recorder**? (begin recording)

E. Beginning the Interview

- Contextual background and demographic information – **complete demographics on separate reply form**

Interview Guide

Aim: To identify barriers to and facilitators of the diagnosis of OSA from health care professionals' accounts.

I would like to talk to you a little bit about your understanding of obstructive sleep apnoea.

Understanding and knowledge of OSA

1. Can you tell me what your understanding is of obstructive sleep apnoea?
   - Prompts:
     - ✓ signs, symptoms
     - ✓ diagnosis: how, local referral pathways
     - ✓ treatment
2. What is your impression of the current guidelines/recommendations for the management of OSA?
   - Prompts:
     - ✓ are you aware of any guidelines/recommendations?
     - ✓ what does the guideline say?
     - ✓ What are your views about the guideline?
3. How likely are you to assess your patients for OSA?
   - Prompt: Can you give me an example of how you do the assessment; signs/symptoms/history you are looking for.
4. How do you remind yourself to consider possible risk of OSA?
5. What are the reasons for deciding not to refer a patient for further assessment and management? (Prompt: can you tell me more about it?)
6. What are your experiences of using screening questionnaires for identifying patients at risk of OSA?
   - Prompt:
     - ✓ Which OSA screening questionnaires are you aware of?
     - ✓ How did you select the specific questionnaire?
     - ✓ Have you used the STOP-Bang Questionnaire? If so, what was your experience of it (ease of use; time)
     - ✓ If not using a questionnaire, what are the reasons for not using a screening questionnaire?

7. How confident are you that you can identify patients at risk of OSA? (Prompts: tell me more about it; difficult/easy; any problems; solutions)
8. Do you feel that it is an appropriate part of your job to identify patients at risk of OSA and refer for further assessment/treatment? (Prompt: can you give me the reasons for your answer?)

Communication/Information

1. What information/explanation/rationale do you give your patients when assessing for OSA and making a subsequent referral?

Possible Barriers

2. From your perspective and experience, what are the issues that interfere with the assessment/diagnosis/treatment of patients for OSA? (Prompts: expand on named issues)
3. To what extent do resource factors help or hinder you to identify patients at risk of OSA and refer for further assessment and management. (Prompts: competing tasks/time constraints)
4. What are your experiences of the local referral process and pathway? (Prompts: how? where? Views on process?)
9. In your view, what are the main issues that contribute to the under diagnosis and under treatment of OSA in patients with CHF?
    - Prompts: recognition of symptoms, resources, time; personal/organisational barriers
10. Which strategies do you think are required to overcome these barriers?

Possible Facilitators

11. What factors, if any, would make it easier for you to identify patients at risk of OSA that will require further assessment and possible treatment?
    - Prompts: specific examples
12. What do you think need to change to improve the diagnosis and treatment of OSA?
    - Prompts: What might need to be done differently?

Conclusion to the interview:

21. Are there any questions that you would like to ask?

22. Is there anything that you would like to add?

23. Debriefing

Thank you very much for your time.

9.31 Appendix 31 Domains, Definitions, Constructs, and Interview Questions

TDF Domains	TDF Constructs	Example Interview Questions
Knowledge	Knowledge about condition or scientific rationale Procedural knowledge	Can you tell me what your understanding is of OSA? Prompts: signs, symptoms; diagnosis, local referral pathways; treatment
Skills	Skills, competence Ability Interpersonal skills Practice	Can you give me an example of how you do the assessment? Prompts: signs; symptoms; clinical history.
Social/professional role and identity	Professional identity, boundaries, role Group or social identity/norms Organisational commitment/leadership	Do you feel that it is an appropriate part of your job to identify patients at risk of OSA and refer them for further assessment/treatment? (Prompt: can you give me the reasons for your answer?)
Beliefs about capabilities	Self-efficacy Perceived behavioural control Perceived competence Self-confidence Self-esteem	How confident are you that you can identify patients at risk of OSA? (Prompts: tell me more about it; difficult/easy; any problems; solutions)
Beliefs about consequences	Beliefs Outcome expectancies Characteristics of outcome Consequents	How do you think untreated OSA affects patients with CHF?
Intentions	Stability of intentions Stages of change model	How likely are you to refer a patient for assessment of OSA/sleep study? Prompt: any reasons why

TDF Domains	TDF Constructs	Example Interview Questions
	Transtheoretical model and stages of change	you won't refer a patient for assessment; explore further
Goals	Goals, priority, target setting Action planning Implementation intention	What is your impression of the current guidelines/recommendations for the management of OSA? Prompts: are you aware of any guidelines/recommendations? what does the guideline say? What are your views on the guideline?
Memory, attention, and decision processes	Memory Attention, control Decision making Cognitive overload/ tiredness	How do you remind yourself to consider possible risk of OSA?
Environmental context and resources	Environmental stressors Resources Organisational culture/climate Salient events/critical incidents Barriers and facilitators	From your perspective and experience, what are the issues that interfere with the assessment/diagnosis/treatment of patients with OSA? (Prompts: expand on named issues)
Social Influences	Group conformity Social comparisons Social support Power Group identity Modelling Intergroup conflict	Tell me about your service and team? Prompts: Primary/secondary/tertiary care; own clinics? What does the clinics involve? Is the clinics in conjunction with nurses/medics?
Emotion	Fear, Anxiety, stress Affect, Depression Positive/negative affect	How do you feel about identifying patients at risk of OSA and their subsequent management?

TDF Domains	TDF Constructs	Example Interview Questions
	Burn-out	
Behavioural regulation	Self-monitoring Breaking habit Action planning	What do you think need to change to improve the diagnosis and treatment of OSA? Prompts: What might need to be done differently?

OSA: obstructive sleep apnoea; HCPs: health care professionals; TDF: theoretical domains framework (Adapted from Atkins et al., 2017)

9.32 Appendix 32 Web Survey Invitation Email (first contact)

Subject: Invitation to participate in survey about Sleep Apnoea

Clinicians/healthcare professionals' survey on Obstructive Sleep Apnoea

Dear Colleague
As a clinician/health care professional with an interest in Heart Failure, we would like to invite you to participate in a survey of doctors, nurses and pharmacists on the important matter of obstructive sleep apnoea. It should take around 25 minutes to complete.

The University of Leicester is carrying out this survey to gain an understanding of the knowledge, beliefs and current practice of heart failure clinicians with regards to the diagnosis and management of obstructive sleep apnoea in patients with heart failure.

We hope that the information provided will help to highlight variations in practice and topics that could benefit from an education programme for heart failure clinicians.

The purpose of the survey and more detail about the study can be found in the Participant Information Sheet. Please read this before deciding whether you would like to participate.

All responses will be anonymised. Individual responses will be combined to provide an overall picture of the knowledge, beliefs and current practice of heart failure clinicians with regards to the diagnosis and management obstructive sleep apnoea.

If, after reading the Participant Information Sheet, you are willing to complete the survey, then please access the survey web link. It would be very helpful if you could complete the survey within two weeks of receiving this email.

We would like to thank you for taking the time to read this email. We do hope you will participate in this survey.
[Take the Survey]

Please note that if you are not a doctor, nurse or pharmacist, we regret you are not eligible to answer this survey.

Yours sincerely,

Lizelle Bernhardt
Post Graduate Research Student

Prof Iain Squire
Academic Supervisor

9.33 Appendix 33 Web Survey Second Contact Email

Subject: Reminder: Invitation to participate in survey about Sleep Apnoea

Clinicians/healthcare professionals survey on obstructive sleep apnoea

Dear Colleague
We recently sent you an email inviting you to take part in an online survey of doctors, nurses and pharmacists on the important topic of obstructive sleep apnoea.

If you have completed the survey already, we would like to thank you for your participation. If you have not yet had an opportunity to review the information about the survey, we would like to take this opportunity to remind you about it and let you know that if you are interested in completing it, there is still time.

We know it can be annoying to receive a follow up email, but as the survey is entirely anonymous we are not able to track if you have chosen to accept or decline the invitation.

The purpose of the survey and more detail about the study can be found in the Participant Information Sheet. Please read this before deciding whether you would like to participate.

If, after reading the Participant Information Sheet, you are willing to complete the survey, then please access the survey via the web link.

[Take Survey]

It would be very helpful if you could complete the survey within two weeks of receiving this email.

Thank you for taking the time to read this email.

Yours sincerely,

9.34 Appendix 34 Web Survey Participant Information Sheet

Leicester Biomedical Research Centre
Cardiovascular Theme
Lizelle Bernhardt
Department of Cardiovascular Sciences
Cardiovascular Research Unit
Glenfield Hospital
Groby Road
Leicester
LE3 9QP
0116 258 3862

Participant Information Sheet

Survey Study

FULL TITLE OF STUDY: Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach

Investigator: Lizelle Bernhardt

Supervised by: Professor Iain Squire & Dr Noelle Robertson

Contact Number: Telephone: 0116 258 3862

You are being invited to take part in a research study. This study is being carried out in fulfilment of the Chief Investigator's (Lizelle Bernhardt) completion of a Doctorate in Philosophy (PhD). Before you decide whether to take part it is important that you understand why we are doing the study and what is involved. Please take time to read this information sheet carefully.

What is the research about?

Obstructive sleep apnoea hypopnoea syndrome is among the most under diagnosed and under treated conditions in the United Kingdom. If left untreated, it can contribute to poor sleep, poor quality of life and increase the risk of cardiovascular disease, serious accidents and health care costs.

The survey study is part of a two stage project. Stage 1 aims to gain insight into the knowledge, beliefs and current practice of heart failure clinicians regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart failure and is the stage which you are being asked to participate in. Stage 2 aims to determine how well a screening questionnaire can identify people at risk of obstructive sleep apnoea hypopnoea syndrome and to gain an understanding of the factors that may help or hinder the diagnosis of obstructive sleep apnoea in patients with heart failure.

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Previous research suggested that clinician awareness may be contributing to the under diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart failure.

The purpose of the online survey is to gain insights into the knowledge, beliefs and current practice of heart failure clinicians (doctors, nurses and pharmacists) regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart failure.

We hope that the information provided will help to highlight variations in practice and topics that could benefit from an education programme.

Why have I been chosen?
You have been chosen because you are a clinician/health care professional (doctor, nurse, pharmacist) with an interest in Heart Failure.

Who is organising and funding the research?
The research study forms part of an educational project that is being conducted at the Department of Cardiovascular Sciences at the University of Leicester. None of the research team will receive any payment for including you in the study. The study is being sponsored by the University of Leicester.

What will happen to me if I take part?
We are asking you to complete an online survey which asks you about your knowledge, beliefs and current practice regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with chronic heart failure. The survey should take you no longer than 15 minutes to complete and your responses will be entirely anonymous to the research team at the University of Leicester. Completion and submission of the survey will be taken as consent.

If you lose capacity to consent, you will be withdrawn from the study. Data collected with consent will be retained and used in the study.

Are there any benefits in my taking part?
There are no anticipated benefits to you directly. However, more generally, we hope that the information provided will help to highlight variations in practice and topics that could benefit from an education programme.

Are there any risks involved?
We don't expect there to be any risks to you from taking part in this study.

Will my participation be confidential?
The information collected from the survey will be entirely anonymous to the research team at the University of Leicester. All information collected will be kept in the strictest confidence and be secured against unauthorised access. The data from the study will be kept on a password protected computer and will be retained for 5 years in accordance with University regulations.

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What happens if I change my mind?
Your participation in this study is entirely voluntary and you will be completely free to withdraw from the study at any time, without giving a reason.

What will happen to the results of the research study?
The results will be presented at medical scientific meetings and will be published in medical journals. You will not be identifiable in any presentations.

An information sheet, with a summary of the main study findings, will be available to you at the end of the study. You can request a copy of the information sheet from Lizelle Bernhardt on 0116 258 3862 or email lb382@le.ac.uk.

What happens if something goes wrong?
If you have any concerns about the study or would like to make a complaint, please contact:

Research Governance Manager
Dr Michelle Muessel
Research & Enterprise Division
Research Governance Office,
Academic Departments,
Leicester General Hospital,
Gwendolen Road,
Leicester, LE5 4PW, UK

uolsponsor@le.ac.uk
Tel: 0116 258 4099 / 0116 258 4867

Where can I get more information?
If you have any questions about the study after reading this information sheet, please contact the research team (details below).

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9.35 Appendix 35 Survey Questionnaire

WEB SURVEY

Introduction – first page of survey

You are invited to participate in a research study titled: **Factors associated with the diagnosis of Obstructive Sleep Apnoea Hypopnoea Syndrome in Chronic Heart Failure: A mixed methods approach.** The study is being done by Lizelle Bernhardt and supervised by Professor Iain Squire from the University of Leicester.

The purpose of this research study is to gain insights into the knowledge, beliefs and current practice of heart failure clinicians (doctors, nurses and pharmacists) regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with heart failure. We hope that the information provided will help to highlight variations in practice and topics that could benefit from an education programme for heart failure clinicians.

Your participation in the study is entirely voluntary and you can withdraw at any time. You are free to omit any question. Completion of the survey will be taken as consent to participate. It should take around 25 minutes to complete.

We believe there are no known risks associated with this research study, however, as with any online related activity the risk of a breach is always possible. To the best of our ability your answers in this study will remain confidential. To minimise any risks, survey responses will be encrypted to ensure secure data transmission. In addition, following data export, electronic databases will have restricted access, be password protected and contain no personal identifiers.

We would like to thank you for your participation.

Web Survey

1. Please answer the following questions about yourself:

1.1 In which country do you work?

a) England
b) Scotland
c) Wales
d) Other:

1.2 What best describes your place of work and in which speciality?

a) Hospital – Specialist Referral Centre
b) Hospital – Acute Centre
c) Hospital – District General
d) Community clinic/hospital

1.3 What is your cardiology speciality?

1.4 What level do you currently practice at?

a) Consultant
b) Specialist trainee (ST 3+)
c) Trainee (CT/ST 1+2)
d) Foundation doctor
e) Clinical Nurse Specialist
f) Pharmacist
g) Other:

1.5 Gender

a) Female
b) Male

1.6 Age

a) 20-29
b) 30-39
c) 40-49
d) 50-59
e) 60-69
f) >70

1.7 Years in practice: _____

1.8 Year of qualification: _____

2. **Please answer the following questions. If you don't know, it is okay, please tick the box "don't know".**

No.	Question	True	False	Don't Know
1.	Women with obstructive sleep apnoea may present with fatigue alone.			
2.	Uvulopalatopharyngoplasty is curative for the majority of patients with obstructive sleep apnoea.			
3.	The estimated prevalence of obstructive sleep apnoea among adults is between 2 and 10%.			
4.	The majority of patients with obstructive sleep apnoea snore.			
5.	Obstructive sleep apnoea is associated with hypertension.			
6.	An overnight sleep study is the gold standard for diagnosing obstructive sleep apnoea.			
7.	CPAP (continuous positive airway pressure) therapy may cause nasal congestion.			
8.	Laser-assisted uvuloplasty is an appropriate treatment for severe obstructive sleep apnoea.			
9.	The loss of upper airway muscle tone during sleep contributes to obstructive sleep apnoea.			
10.	The most common cause of obstructive sleep apnoea in children is the presence of large tonsils and adenoids.			

No.	Question	True	False	Don't Know
11.	A craniofacial and oropharyngeal examination is useful in the assessment of patients with suspected obstructive sleep apnoea.			
12.	Alcohol at bedtime improves obstructive sleep apnoea.			
13.	Untreated obstructive sleep apnoea is associated with a higher incidence of automobile crashes.			
14.	In men, a collar size 17 inches or greater is associated with obstructive sleep apnoea.			
15.	Obstructive sleep apnoea is more common in women than men.			
16.	CPAP is first line therapy for severe obstructive sleep apnoea.			
17.	Less than 5 apnoeas or hypopneas per hour is normal in adults.			
18.	Cardiac arrhythmias may be associated with untreated obstructive sleep apnoea.			
19.	OSA is associated with diastolic dysfunction.			
20.	Treatment of OSA with CPAP in patients with CHF improves ejections faction.			
21.	Treatment of OSA with CPAP in patients with PAH can worsen this condition.			

No.	Question	True	False	Don't Know
22.	Patients with Cheyne-Stokes respiration and CHF have a higher mortality than patients with CHF alone.			

3. Obstructive Sleep Apnoea Knowledge and Attitudes (OSAKA):

3.1 Which of the following is (are) known risk factor(s) for obstructive sleep apnoea (OSA)? Check all that apply:

a) rheumatoid arthritis (RA)
b) obesity
c) age
d) male gender
e) family history of obstructive sleep apnoea
f) head circumference

3.2 Which of the following is (are) associated with OSA? Check ALL that apply:

a) pulmonary artery hypertension (PAH)
b) rheumatoid arthritis (RA)
c) cardiac arrhythmias
d) chronic heart failure
e) adrenal insufficiency
f) ventricular septal defect
g) hypertension

3.3 The approximate prevalence of sleep related breathing disorder (central and obstructive) in patients with chronic heart failure (EF <45%) is?

a) 0-20%
b) 30-40%
c) 50-60%
d) 70-90%

3.4 The approximate prevalence of OSA in patients with CHF is?

a) 0-40%
b) 41-60%

c) 61-80%
d) 81-100%

4. Using the choices provided for each item below, please check the box that best describes your response:

4.1 As a clinical disorder, obstructive sleep apnoea is:
[not important/somewhat important/important/very important/extremely important]

4.2 Rank the following by relative importance as a medical condition: 1-5 (1 being the most important):

a) Diabetes Mellitus
b) Hypertension
c) Degenerative joint disease
d) Obstructive sleep apnoea
e) Asthma

4.3 Identifying patients with possible obstructive sleep apnoea is:
[not important/somewhat important/important/very important/extremely important]

4.4 I feel confident identifying patients at risk for obstructive sleep apnoea
[strongly disagree/disagree/neither agree nor disagree/ agree/strongly agree]

4.5 I am confident in my ability to manage patients with obstructive sleep apnoea
[strongly disagree/disagree/neither agree nor disagree/ agree/strongly agree]

4.6 I am confident in my ability to manage patients on CPAP therapy.
[strongly disagree/disagree/neither agree nor disagree/ agree/strongly agree]

5. Please select the answer/s that best describe your clinical practice:

5.1 Which of the following diagnostic methods do you use in your clinical practice when assessing patients for OSA? Please select ALL that apply:

a) History
b) Physical examination
c) Bed partner observations
d) Presence of sequelae ie. Hypertension
e) Screening questionnaires
f) Referral to sleep disorders service.
g) None of the above

5.2 Do you use a screening questionnaire in your clinical practice?

i. Yes
ii. No

Pipe next question to apply to "i" only.

5.3 If yes, which of the following screening questionnaires do you use in your clinical practice? Please select all that apply:

a) Epworth Sleepiness Scale
b) Berlin questionnaire
c) STOP-Bang questionnaire
d) STOP questionnaire
e) Other: please list

5.4 How would you confirm a diagnosis of OSA in your patients?

a) Refer directly for a sleep study.
b) Refer to a respiratory physician
c) Refer to sleep disorders service
d) Refer to general practitioner
e) Other: please list

Debriefing – Final page of survey

Thank you for participating in this survey study.

The purpose of this research study is to gain insights into the knowledge, beliefs and current practice of heart failure clinicians (doctors, nurses and pharmacists) regarding the diagnosis and treatment of obstructive sleep apnoea hypopnoea syndrome in patients with heart failure. We hope that the information provided will help to highlight variations in practice and topics that could benefit from an education programme for heart failure clinicians.

All the information we collect will be confidential and there will be no way of identifying your responses in the data archive. We are not interested in any one individual's responses, we want to look at the general patterns that emerge when the data are aggregated together.

If you have any questions or concerns, you are welcome to contact Lizelle Bernhardt (lb382@le.ac.uk) or Prof Iain Squire (is11@le.ac.uk) at the Department of Cardiovascular Sciences, University of Leicester.

If your participation in this study has caused you concerns, anxiety or otherwise distressed you, you may contact your local doctor and/or local counselling support services. These can be accessed through your GP surgery, workplace or university.

Please note that you have the right to withdraw, but that by submitting you are agreeing to participate.

An information sheet, with a summary of the main study findings, will be available to you at the end of the study. You can request a copy of the information sheet from Lizelle Bernhardt on 0116 258 3862 or email lb382@le.ac.uk.

THANK YOU AGAIN FOR YOUR PARTICIPATION.

9.36 Appendix 36 Table for Correct Responses per Question Statement

Questions	% Correct Responses			% Don't Know Responses		
	Drs n=32	Nurses n=62	Pharm n=8	Drs n=32	Nurses n=62	Pharma n=8
1. Women with OSA may present with fatigue alone	75%	65%	50%	19%	18%	50%
2. UPPP is curative for the majority of patients with OSA.	66%	24%	25%	28%	61%	75%
3. The estimated prevalence of OSA among adults is between 2 and 10%.	56%	65%	25%	34%	31%	75%
4. The majority of patients with OSA snore.	63%	77%	50%	6%	2%	25%
5. OSA is associated with hypertension	94%	60%	63%	0%	21%	25%
6. An overnight sleep study is the gold standard for diagnosing OSA.	91%	90%	88%	0%	8%	13%
7. CPAP therapy may cause nasal congestion.	59%	52%	25%	25%	26%	50%
8. Laser-assisted uvuloplasty is an appropriate treatment for severe OSA.	19%	15%	0%	53%	71%	100%
9. The loss of upper airway muscle tone during sleep contributes to OSA.	94%	79%	25%	6%	18%	75%
10. The most common cause of OSA in children is the presence of large tonsils and adenoids.	69%	61%	38%	31%	34%	63%
11. A craniofacial and oropharyngeal examination is useful in the assessment of patients with suspected OSA.	69%	60%	25%	25%	34%	75%
12. Alcohol at bedtime improves OSA.	91%	94%	75%	6%	5%	25%

Questions	% Correct Responses			% Don't Know Responses		
	Drs n=32	Nurses n=62	Pharm n=8	Drs n=32	Nurses n=62	Pharma n=8
13. Untreated OSA is associated with a higher incidence of MVAs.	97%	89%	50%	3%	11%	50%
14. In men, a collar size 17 inches or greater is associated with OSA.	84%	82%	38%	16%	10%	63%
15. OSA is more common in women than men.	81%	77%	50%	13%	18%	25%
16. CPAP is first line therapy for severe OSA.	78%	77%	38%	3%	13%	38%
17. Less than 5 apnoea or hypopnoeas per hour is normal in adults.	41%	32%	13%	41%	42%	88%
18. Cardiac arrhythmias may be associated with untreated OSA.	94%	84%	50%	3%	15%	38%
19. OSA is associated with diastolic dysfunction.	88%	63%	38%	9%	26%	38%
20. Treatment of OSA with CPAP in patients with CHF improves ejection fraction.	44%	31%	38%	28%	34%	38%
21. Treatment of OSA with CPAP in patients with PAH can worsen this condition.	44%	31%	13%	41%	42%	75%
22. Patients with Cheyne-Stokes respiration and CHF have a higher mortality than patient with CHF alone.	78%	89%	88%	22%	8%	13%

OSA: obstructive sleep apnoea; UPPP: Uvulopalatopharyngoplasty; CPAP: continuous positive airway pressure; MVA: motor vehicle accident; PAH: pulmonary artery hypertension; CHF: chronic heart failure; DRS: doctors; Pharm: pharmacists

9.37 Appendix 37 Table of Risk Factors and Conditions associated with OSA

Domain	Average Percentage Correct Responses		
	Doctors (n=32)	Nurses (n=62)	Pharmacists (n=8)
Risk			
Obesity	100%	100%	100%
Age	66%	53%	13%
Male sex	94%	82%	75%
Family History	66%	73%	75%
Association			
PAH	66%	63%	38%
Cardiac Arrhythmias	97%	66%	50%
CHF	91%	84%	75%