MASTER OF SCIENCE BY RESEARCH

Systematic Review of The Effect of High Pressure Ventilation Compared to Low Pressure Ventilation in Chronic Obstructive Pulmonary Disease Patients

Antoine-Pitterson, Pearlene Louisa

Award date:
2018

Awarding institution:
Coventry University

Systematic Review of The Effect of High Pressure Ventilation Compared to Low Pressure Ventilation in Chronic Obstructive Pulmonary Disease Patients

By

Pearlene Antoine-Pitterson

MScR

May 2018

Systematic Review of the Effect of High Pressure Ventilation Compared to Low Pressure Ventilation in Chronic Obstructive Pulmonary Disease Patients:

By

Pearlene Antoine-Pitterson

MScR

May 2018

Coventry University

Supervisors Dr Amir Khan and

Professor Derek Renshaw

A thesis submitted is part of the university's requirements for the degree of Master of Research Funded by HEE/NIHR

Certificate of Ethical Approval

Applicant:

Pearlene Antoine-Pitterson

Project Title:

A systematic review to establish the effectiveness of high pressure Non -Invasive Ventilation compared to low pressure Non-invasive ventilation in Chronic Obstructive Pulmonary disorder.

This is to certify that the above-named applicant has completed the Coventry University Ethical Approval process and their project has been confirmed and approved as Low Risk

Date of approval:

18 January 2018

Project Reference Number:

P64907

Contents

List of Tables

Table of Figures

Glossary of Terms

Airflow obstruction a ratio of forced expiratory volume in one second to forced vital capacity which is < 0.7 (NICE 2010).

Chronic Hypercapnic Respiratory Failure is indication of a raised partial pressure of carbon dioxide in the blood and a low concentration of oxygen in the blood, a normal pH is maintained, there is a high bicarbonate (Davidson et al. 2016).

Chronic Obstructive Pulmonary Disease is a progressive lung disease characterized by airflow limitation (World Health Organisation 2017)

Domiciliary non-invasive ventilation is the provision of non-invasive ventilation in a non-acute setting usually home or facility for long-term care.

Dyspnoea is difficulty or labored breathing (Booth 2006, ES and HW 2001)

Exacerbation A worsening state of symptoms from baseline, it is a natural course of the disease and includes a worsening of cough, dyspnoea, sputum production which results in a change of treatment. (M. W. Hess 2017)

Hypercapnia A state of increase in Partial Pressure of Carbon dioxide in the blood above 6 Kpa (Davidson et al. 2016)

Hypoxemia A state of low partial pressure of oxygen in the blood <8Kpa (Davidson et al. 2016)

Non-Invasive Ventilation Mechanical ventilatory support as provided by a nasal mask or an oral nasal mask for the treatment of respiratory failure by maintain adequate gaseous exchange It is also referred to non- invasive positive pressure

Stable COPD Referring to patients who are absent of symptoms for more than 4 weeks (NICE 2010)

Standard Care/Usual Care A multidisciplinary approach to assessment and management of COPD, it is dependent on the stage of disease severity and includes pulmonary rehabilitation, Bronchodilation, with or without an inhaled cortico-steroid, mucolytic therapies and long-term oxygen therapy.(M. W. Hess 2017)

List of abbreviation

Table 1 list of Abbreviations

6 MWT	Six Minute Walk Test
A&E	Accident and Emergency
AECOPD	Acute Exacerbation COPD
AHRF	Acute Hypercapnic Respiratory Failure
ANOVA	Analysis of Variance
CASP	Critical Appraisal Skills Programme
CHRF	Chronic Hypercapnic Respiratory Failure
CI	Confidence Interval
CMH_20	Centimetre of Water
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
CPAP	Continuous Positive Airway Pressure
CPET	cardiopulmonary exercise testing
CPO	Cardiogenic Pulmonary Oedema
CT	Computer Tomography
CTIMPS	Clinical Trials of Investigational Medicinal Products
CWD	Chest Wall Deformity
EBP	Evidence Based Practice
EPAP	Expiratory Positive Airway Pressure
ERV	Expiratory Reserve Volume
ET	Exercise Tolerance
FEV_1	Forces Expiratory Volume in 1 second
FRC	Functional Residual Capacity
FVC	Forced Vital Capacity
GOLD	Global Initiative for Chronic Lung Disease
GP	General Practitioner
GRADE	Grading, Recommendations, Assessment and Evaluation

HCO_3	Bicarbonate
High-IPAP	High Inspiratory Positive Airway Pressure
Hi-NPPV	High Intensity Non-Invasive Positive Ventilation
HRA	Health Research Authority
HRF	Hypercapnic Respiratory Failure
HRQOL	Health Related Quality of Life
IPAP	Inspiratory Positive Airway Pressure
IRV	Inspiratory Reserve Volume
LF	Lung Function
ll-NPPV	Low Intensity Non-Invasive Positive Pressure Ventilation
Low-IPAP	low Inspiratory Positive Airway Pressure
LTOT	Long Term Oxygen Therapy
MEP	Maximum Expiratory Pressure
NHS	National Health Service
NIV	Non-Invasive Ventilation
NMD	Neuromuscular Disease
O_2	Oxygen
PA	Posterior anterior
P_aCO_2	Partial Pressure Carbon Dioxide
P_aO_2	Partial Pressure Oxygen
PEEP	Positive Expiratory End Pressure
pH	Potential Hydrogen
PS	Pressure Support
QOL	Quality of Life
RCT	Randomised Control Trials
SGRQ	St Georges Respiratory Insufficiency Questionnaire
SNIP	Sniff Nasal Inspiratory Pressure
SR	Systematic Reviews
SRI	Severe Respiratory Insufficiency Questionnaire
TLC	Total Lung Capacity

V/Q	Ventilation Perfusion
VT	Tidal Volume
WOB	Work of Breathing

Acknowledgements

The journey to completion of this project would not have been possible without support. I would like to take a moment to thank all of those involved and for individuals who offered support. Firstly, this amazing journey would not have been possible without the financial support of Health Education England and the National Institute of Health and Research. Without their vision of research been conducted by practitioners and the Integrated Clinical Academia Pathway this opportunity may not have been possible. It has been with the backing of this program that has helped to support my career goals. They provided the funding to embark on the Master by Research program to make steps towards my career in clinical academia. I would like to thank the Centre for Innovation and Research Across the Life Course at Coventry University for providing resources to conduct my research.

I would like to thank my supervisors, for whom I have had the honor and pleasure of working with Dr Amir Khan and Professor Derek Renshaw. Their guidance has been invaluable throughout this project and have supported me throughout my academic journey, offering advice as I take my steps towards my career in clinical academia and hope to work together again in the future. I would like to acknowledge my professional mentors, who have offered guidance and support and have been great value to both my personal and professional development over the years and I look forward to collaborating with them on future research projects. I would also like to thank those who I have had the honor of working with and meeting during this time who have offered guidance.

Last, nonetheless the most significant group of people I would like to thank are my close friends and family. Particularly my parents Cleverina Antoine and Larkland Pitterson, who have been a solid support throughout, their love has provided me with the strength to pursue my career and would not be where I am today without them. Without their academic experience and knowledge, I would not have had their strength to persevere with this project, they are my mentor's, role models, inspiration, guides and teachers and extend my external gratitude.

Scientific Abstract

Title: Systematic Review of the Effect of High-Pressure Ventilation Compared to Low Pressure Ventilation in Chronic Obstructive Pulmonary Disease Patients.

Background: Chronic Obstructive Lung disease (COPD) is a progressive lung condition made from a group of diseases. It is characterised by productive cough, dyspnoea and reduced exercise tolerance. Exacerbations often lead to hospital admission, reduced QOL (QOL), a decline in lung function (LF) and inefficient ventilation. The disease currently challenges the NHS. Hypercapnic respiratory failure is treated with Non-Invasive Ventilation (NIV), domiciliary NIV is provided by a nasal or face mask and improves gaseous exchange. Pressure pre-set mode involves setting an Inspiratory Positive Airway Pressure (IPAP), there is debate regarding support of high inspiratory pressure ventilation being the effective at reducing partial pressure of carbon dioxide (P_aCO_2), however despite this low inspiratory positive pressures are recorded in primary studies the results have suggested although an improvement in hypercapnia, results on clinical outcomes are not significant.

Objective: This systematic review explored the effects of low-pressure ventilation compared to high pressure ventilation on Lung Function, Arterial Blood Gas, Quality Of life , exercise tolerance, adherence, and identify any risks in patients with COPD on domiciliary NIV.

Methods

Information Sources: Bibliographic databases were searched using keywords. CINHAL, MEDLINE, AMED via EBSCO Host and The Cochrane Library. Dates were search for English language studies between 1990 and 2017. Systematic reviews and meta-analysis reference lists were hand searched to assess for additional studies.

Eligibility criteria: English language, randomised control trials. Excluded were observational studies, case studies, quasi experimental, narrative literature reviews and expert commentaries. Risk of bias was assessed using the Cochrane risk bias tool and the Critical

Appraisal tool for RCT's were used to critically appraise the methods completed by one reviewer.

Results: 1613 articles were assessed following deduplication. Titles and abstracts were screened against inclusion and exclusion criteria. 3 randomised control crossover trials were included in the systematic review and meta-analysis. 48 patients were Identified in total a meta-analysis was completed on the following outcomes, P_aCO_2, FEV_1 and HRQOL. There was no significant difference in the effect of High-IPAP compared to low-IPAP in the reduction of P_aCO_2 (p=0.19) with a mean difference of -0.39Kpa (95% CI [-0.96, 0.19]) and results were homogenous (I^2=0%, p=0.83). There was no significant difference in High-IPAP compared to low-IPAP in FEV_1 (p=0.49) (95% CI 0.38 [-0.69,1.45]). Results favoured high IPAP for improvement of HRQOL however there was no significant difference between the effect of High-IPAP compared to Low-IPAP with a mean difference of 0.11 (95%CI [-1.17,0.95] p=0.77) there was no heterogeneity in results (I^2=0%, P=0.59). A meta-analysis could not be completed on adherence, exacerbation and exercise tolerance as there was little or no data provided to complete a meta-analysis.

Conclusion: There was no significant difference in the effect of High-IPAP compared to low-IPAP in the reduction of $PaCO^2$, FEV_1, adherence and HRQOL. Further studies are required to assess the effects on exacerbation, adverse effects and exercise tolerance as there was little or no data available on these outcomes to perform a meta-analysis and explore further. The study has implications as it demonstrates that randomised control trials are required to investigate the effect of pressure to ensure patients are provided with effective treatment of and improve patient outcomes.

Registration PROSPERO CRD42018091592

Lay Summary

Chronic Obstructive Pulmonary Disease (COPD) is a group of diseases which, result in severe breathing difficulties and is often associated with of a history of prolonged smoking. Patients who suffer from COPD are, at risk of sudden worsening of symptoms, including excessive coughing and breathlessness and can often lead to a stay in hospital. As breathing is affected there is a build-up of a gas called Carbon Dioxide and more Oxygen is breathed out which, can be life threatening.

Non-Invasive Ventilation (NIV) is a technique used for the treatment of people who suffer from severe breathing difficulties by providing a pressure on both a breath in and a breath out. This then allows air into the lungs to allow the body to remove carbon dioxide and breath in oxygen. At night this can often be a problem for patients with such severe breathing difficulty and may be offered NIV to use at home overnight, pressure settings for the machine are established by trained specialists in the field and often set due to clinical experience.

It is not yet fully understood which pressure settings is most effective in removing carbon dioxide and preventing hospital admissions. This study has put together the available evidence to assess what settings are ideal used in patients with COPD and identifies what further research is needed.

Chapter 1 Introduction

The use of acute Non-Invasive Ventilation (NIV) has a well-established body of evidence for the treatment of acute hypercapnic respiratory failure (AHRF). AHRF is caused by respiratory disorders including Chronic Obstructive Pulmonary Disease (COPD), Obesity Hypoventilation Syndrome (OHS)/ Obstructive Sleep Apnoea (OSA), Chest Wall Deformities (CWD) and Neuromuscular disorders (NMD) all of which will cause ventilator insufficiency and is supported by up to date guidelines from the British Thoracic Society (BTS) (Davidson et al. 2016). Chronic respiratory disease is an area of medicine currently creating challenges in the NHS. COPD is the 3rd leading cause of death in the world and accounts for 251 million cases per year (World Health Organisation 2017). The Royal College of Physicians (2017) reported a rise in hospital admission secondary to acute exacerbation of COPD (AECOPD) from 2008-2014.

1.1 Background

Standard medical treatment of AECOPD includes inhaled therapy, oral steroids, antibiotics as indicated, pulmonary rehabilitation, long-term oxygen (LTOT) therapy if the patients fits within the guidelines for the prescription of Oxygen therapy for adults at home (Hardinge, Suntharalingam and Wilkinson 2015). For persistent Hypercapnic Respiratory Failure (HRF) the National Institute for Health and Clinical Excellence (NICE) (Gruffydd-Jones and Loveridge 2011) recommend nocturnal ventilation. It is recommended for its use to help improve quality of life (QOL) and one recent randomised control trials (RCT) demonstrated that there is a reduction in time to readmission following an acute exacerbation in patients as reported Murphy and Colleagues (2017), the authors investigated the effect of home NIV and home oxygen therapy compared to home oxygen therapy alone using a multicentre RCT. They hypothesised that the addition of home O_2 to NIV would prologue the time to

readmission or death. Over 2000 participants were initially screened for their inclusion and exclusion criteria, and 116 patients were recruited. Random allocation was performed by a computer-generated system and they were either allocated into the NIV and home O_2 or home O_2 alone. Each patient had optimised standard medical therapy bronchodilator therapy, home O_2 nebulised therapy antibiotics as indicated and oral steroids. The main outcome was the time taken from random allocation to re-admission or death. Secondary outcomes included exacerbation frequency, Arterial Blood Gas (ABG), Health related quality of life (HRQOL) and mortality and participants were followed up at 3 months 6 months and 12 months. Their results demonstrated there was a significant difference in time to readmission. The median time for readmission in the home NIV compared to home oxygen therapy was 4.3 months compared to 1.4 months in the group with home O_2 alone. Its secondary outcome there was a significant reduction in P_aCO_2 at 12 months from 7.87Kpa to 7.12Kpa in the home O2 and NIV group compared to home O_2 alone. One possible explanation for this may be from using higher IPAP a median of 24CmH_2O was used with patients in this study.

In assessment of the quality of this research paper using the critical appraisal skills programme tool for RCTs (2017) there was an attempt at reducing bias, random allocation on a 1:1 basis ensuring the participants were matched at baseline and therefore minimising variables such as age and gender and ensuring random sequence generation therefore reducing selection bias and improving allocation concealment. The trial was single blinded as the researcher completing outcome measures was blinded to which treatment arm the participants were in and reducing performance bias, given the nature of the study it would not be possible for the participant to be blinded in the study however the investigator completing the outcome measure was blinded as to what treatment group the patient was in. There were strict inclusion criteria applied as patients were only included on the study diagnosis of COPD to ensure reduction of confounding variables with the absence of overlapping lung conditions such as Obesity Hypoventilation Syndrome (OHS), Obstructive

sleep Apnoea (OSA), uncontrolled Heart Failure, chest wall deformity (CWD) and neuromuscular disease (NMD). Overlapping lung conditions would be treated in a different approach and patients with NMD will respond to a volume assured NIV setting (Rabec et al. 2011) and would have impacted the results equally it was to establish that the cause of their Type II RF was accredited to COPD and not an overlapping lung condition. The design was an RCT, therefore, a control group running parallel with an experimental group strengthens the results and establishes a cause and effect relationship (Bryman 2016). Both groups were optimally treated with standard care for COPD but, the experimental group were given an addition of NIV to long-term oxygen therefore their results demonstrate that any improvement was secondary to the intervention.

The population of patients in this sample were representative of the population of COPD patients in the UK, average age 66 and gender with 54% of the participants are men and therefore results can be generalised to stable COPD patients. The trial demonstrated that NIV in addition to home O_2 and standard therapy can have an effect of COPD and reduce hospital admissions. One of the possible reasons for the reduction of P_aCO_2 and time to readmission in COPD patients may have been secondary to the relatively High-IPAP used in patients and a limitation of the study as the authors have discussed is that there was no sham NIV group to compare to. High-IPAP are seen in patients with COPD who are hypercapnic by reducing dynamic hyperinflation and encouraging alveolar ventilation (Duiverman et al. 2016).

Where Murphy's and colleagues (2017) have demonstrated a significant clinical effect on the reduction of readmission following an exacerbation of COPD in conjunction with NIV systematic reviews (Becker et al. 2015, Dretzke et al.2015, Dretzke 2016 and Kolodziej et al. 2007) have been unable to demonstrate this effect and there has been a paucity of evidence. One theoretical concept which may explain this may be because of the use of high Inspiratory Positive Airway Pressure (High-IPAP). High pressure ventilation has been used

in various trials (Dreher et al. 2010, Dreher et al. 2011, Duiverman et al. 2017) with the aim of maximally reducing the partial pressure of carbon dioxide in the blood (P_aCO_2). Windisch and colleagues (2005) discussed that for there to be greater improvement in physiological parameters in patients with Chronic Hypercapnic Failure (CHRF) receiving high-IPAP when compared with those receiving low-IPAP. They discuss an approach called High-Intensity Non-Invasive positive pressure ventilation (HI-NPPV) where a high-IPAP is combined with a high back up respiratory rate, subsequently there have been various surveys investigating this technique. The systematic review investigates, summarises and assimilates the available literature in the effectiveness of high-IPAP compared to low-IPAP in patients with CHRF caused by ventilatory insufficiency in COPD patient.

1.1.1 What is COPD?

COPD is a group of disease which is classified, diseases under the umbrella of COPD are Chronic Bronchitis, Emphysema and Asthma (Davidson et.al 2011, Alberto, Spiro and Jett 2008). The World Health Organisation (WHO) define COPD as a “lung disease characterised by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible” (WHO 2018) Characteristics of the disease include airflow limitation, persistent dyspnoea on physical activity, wheeze, chest tightness, cough and sputum production. The progression of the disease is not reversible and leads to both physiological decline and a decline in health-related QOL (HRQOL) for the patient and is a tremendous financial burden on the National Health Service (NHS) (Loveridge 2009). It has become one of the leading causes of disability and imposes a heavy burden on health care systems around the world (Vos, Flaxman and Naghavi 2012). Diagnosis is often accompanied by several co-morbidities including Ischemic heart disease, hypertension, diabetes and cancer which demonstrates an inflammatory process beyond the lungs as the disease progresses in severity (Hillas et al. 2015).

COPD has been referred to in the past by different syntax such as chronic obstructive pulmonary disorder, chronic obstructive airway disease, chronic obstructive lung disease. Emphysema and chronic bronchitis are two conditions which can overlap and are referred to as COPD (Kumar 2009). The Global Initiative for Chronic Obstructive Lung Disease (GOLD) produced a classification system for the disease in 2001, in an editorial by Kerstjens (2004) he concludes that the disease is difficult to classify due to the lack of evidence base. Furthermore, Kerstjens explains that this is not related to what matters to the patients. From then there has been advances in quantitative evidence which, have contributed to a greater understanding of how the disease progresses and how the disease effects the patient health and well-being and at different stages of severity (Vogelmeier et al. 2017). Therefore, as a result it provides clinicians guidance as the diagnosis and management of COPD.

1.1.2 Aetiology of COPD

Tobacco smoking is one of the main causes on COPD and is thought that nearly 1 million people in the United Kingdom (UK) are living with the condition and it is a socioeconomic burden (Public Health England 2015). It poses a challenge to the NHS as it contributes to approximately 113000 accident and emergency admissions each year (Public Health England 2015). Although smoking is the primary cause of COPD the definition includes exposure to noxious stimulus and other risk factors associated with COPD include exposure to indoor pollutants, occupational exposure, outdoor air pollutants, genetic factors, age, gender, lung growth and development, Asthma, Chronic Bronchitis and socio economic factors (Vogelmeier et al. 2017)

1.1.3 Pathophysiology of COPD

Following prolonged exposure to noxious stimuli inflammatory changes to the alveolar arise (Chojnowski 2003) leading to a change in ventilation. Ventilation is a complex physiological mechanism which, in itself could take an entire thesis, control of ventilation and the respiratory muscles is controlled by an area of the brain called the medulla oblongata as can be seen in **Figure 2** where the respiratory centres are located, (Dempsey and Smith 2014) and neural control allows for rhythmic ventilation **Figure 2** and **Figure 3** depicts neural control of ventilation. Receptors in skeletal muscle and in the circulatory system detect chemical changes and induce a response for diaphragm and intercostal muscles to contract. There is a change in pressure gradient with a reduction of intrapulmonary pressure and an increase in extrapulmonary pressure, as air moves from a positive pressure gradient to a negative pressure gradient air then enters the lungs.

A typical healthy lung is designed to be efficient in ventilation **Figure 1** depicts this. The lungs are responsible for gaseous where oxygen (O_2) enters the blood and carbon dioxide (CO_2). Each lung is divided by horizontal fissures dividing them into lobes, pleural is a thin membrane: the visceral pleura is the inner layer lines the lung whilst parietal pleura is the outer membrane which is the outer layer and lines the chest wall. The two membranes adhere to each other and so within the pleura space is a small amount of fluid which acts as lubrication. During inspiration, surface tension is created, this is vital as it allows the alveoli to maximally inflate during inspiration (Albert, Spiro and Jett 2008). There are three lobes in the right lung and two lobes in the left lung. The trachea bifurcates into the right and left main bronchus and feeds into the corresponding lung. The bronchiole tree then divides into the bronchi of the lobes and further sub-divided into segmental bronchi with an estimation of 20-25 generations which branch off and end with terminal bronchioles (Kumar 2009). They then give way to alveolar ducts, alveolar sacs and finally pulmonary alveolus where gaseous exchange occurs.

Figure 1 Anatomy of the Lungs
Schematic diagram of typical lungs, bronchiole tree and major structures (Rikxoor and Ginneken 2013)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

Figure 2 Diagram of Medulla oblongata and, Respiratory control centre (Aminoff 2014)
Key structures of the respiratory control centre and neural pathways taken in ventilation. DRG- Dorsal Respiratory Group PRG-Pontine Respiratory Group, VRG-Ventral respiratory group, NA-Nucleus Ambigus

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

Figure 3 Neural Control of Ventilation adapted from Spiro Albert Spiro and Jett (2012)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

The alveoli have several properties which make them efficient at gaseous exchange, a thin membrane, with a thickness measuring $1_{\mu m}$, and has a large capillary alveolar surface area (Petersson and Glenny 2014). Pneumocytes are alveolar cells and there are two which have important functions in gaseous exchange, Type I pneumocytes account for 90% of the alveolar surface, they are large squamous cells, which, are responsible for gaseous exchange into the blood stream by the process of osmosis. Type II pneumocytes function in two ways, by secreting surfactant, compromising of phospholipids and proteins and reduces surface tension within the alveoli. Type II pneumocytes are also able to divide therefore, when lung tissue is damaged it can increase in number due to cell division. The functions of these cell are vital for efficient gaseous exchange and Type I cells are susceptible to damage during exposure to noxious stimuli (Kumar 2009). A venous blood supply carries

mixed venous blood with a low partial pressure of O_2 (P_aO_2) and a higher partial pressure of CO_2 (P_aCO_2). The difference in pressure gradient allows exchange of O_2 across the membrane to enrich capillary blood flow with O2 and creating a higher pressure P_aO_2 in the capillaries and lower pressure P_aCO_2 in the capillaries (Petersson and Glenny 2014).

1.1.4 Chronic Bronchitis

The pathology of COPD results in an inefficiency in the gaseous exchange and subsequently respiratory failure. There is a rise in the number and size of mucus secreting goblet cells in the bronchial mucosa in both the large bronchi and bronchioles. Both acute and chronic inflammatory cells line the walls of the bronchioles and the epithelial layer can become thickened, excessive mucus secretions and thickened walls lead to a reduction in the lumen size of the small airways as well as infiltrate the epithelial cells with inflammatory mediator's neutrophils and lymphocytes. A reduction in diameter then leads to airflow limitation. In the acute stages this damage is reversible if tobacco smoking is stopped, however the inflammation continues in later stages even when exposure is stopped. It is theorised that there is a change in the behaviour of T lymphocytes and plasma cells suggestive of a possible to immune response resulting in continued inflammatory response following smoking cessation in the later stages (Hogg 2006). As the disease progressed there is squamous cell metaplasia and fibrosing of the airway (Albert, Spiro and Jett 2012).

In the acute stages of the disease small airways are affected however, as the disease progresses to a chronic stage there is destruction of lung parenchymal; a reduction in lung elasticity, air flow limitation; reduced alveolar ventilation; mucociliary escalator dysfunction ; increased secretion production and impaired gaseous exchange. Alpha1-antitrypsin is an enzyme inhibitor which, prevents against destruction of lung tissue however, exposure to noxious stimuli prevents the inhibitor from functioning and leads to the destruction of Type I

pneumocytes. Type II pneumocytes proliferate and differentiate into Type I pneumocytes and there is an adverse effect on surfactant leading to a loss of elastic recoil and dilatation of the lung tissue.

1.1.5 Emphysema

Emphysema is the permanent enlargement of airspaces, at the distal terminals of the bronchioles. The loss of structural integrity lead to dynamic hyperinflation and emphysematous changes appear in the lungs. Dilatation is concentrated to the larger bronchioles leaving the smaller airways relatively intact this is known and centrilobular or centri-acinar emphysema. In cases where there is complete destruction of the distal alveolar walls can lead to bullae as seen in pan-acinar emphysema (Faner et al. 2012). The changes lead to Ventilation Perfusion (V/Q) mismatching, this is a result of an increase mucous production causing plugging and due to the loss of elastic recoil and dynamic hyperinflation leads to impaired gaseous exchange. The impairment leads to inefficiency in gaseous exchange, retention of CO_2 in the blood and a reduction of O_2 in the blood. Following an exacerbation of COPD is severe cases it can lead to AHRF leading to hospitalisation and treatment with mechanical ventilation.

Table 2 Clinical features of COPD (Albert, Spiro and Jett 2012)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

1.2 Diagnosis of COPD

COPD is a group of conditions resulting in obstruction and measurable loss of lung volumes. GOLD (Vogelmeier et al. 2017) and National Institute for Care and Excellence (NICE 2010) define a clinical diagnosis. Symptoms reported are often dyspnoea, wheeze, cough productive of sputum and may be accompanied with a history of smoking of 20 pack years or greater. In patients who do not have a history of smoking an initial working diagnosis of Asthma due to the similarity in symptom presentation (Rennard 2012) in the absence of a familiar history of COPD in which case an alternative diagnosis of Alpha1-antitrypsin Deficiency (Albert, Spiro and Jett 2012). Alpha1-antitrypsin deficiency is a genetic disorder, those born with the disease may not all suffer from respiratory disease; however, it poses a significant risk factor for developing COPD for those who smoke cigarettes (Vogelmeier et al. 2017).

1.2.1 Spirometry

On report of a combination of symptoms patients are then subjected to spirometry. Spirometry is a pulmonary function test, it involves a forced expiratory volume (FEV)

manoeuvre which assesses lung volumes, it is often the tool used to screen for patients for abnormalities in air flow and lung volumes. Pulmonary function tests allow for classification of stages of lung disease, however diagnosis is not made from pulmonary function tests alone. It is made in addition with the presence of clinical signs and symptoms as listed in **Table 2**.

Lung volumes are described in the literature as early as the 1800's (Wanger et al. 2005), lung volumes are influenced by height, weight, gender and age (Albert, Spiro and Jett 2012). **Figure 4** demonstrates a spirograph measurement of lung volumes. It will also change in different, positions such as from supine to standing and these changes are normally due to the change in position of the diaphragm. Lung volumes are divided in a combination of lung capacities, Total lung capacity, Capacity is referred to as the combination of volumes which are subdivided, **Table 3** lists the capacity and the subdivisions of volumes (Flesch and Dine 2012).

Table 3 lung volumes and definitions (Wanger et al. 2005)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

Figure 4 Volume-Time Spirograph of Lung Volumes and capacities

(Taken from European Respiratory Society SERIES ‘‘ATS/ERS TASK FORCE: STANDARDISATION OF LUNG FUNCTION TESTING’’(Wanger et al. 2005)

It is the pathogenesis of COPD which leads to responses that begin to form and all too familiar picture for patients who are admitted with exacerbation of COPD. The combined inflammatory responses lead to the increase in exacerbations. An exacerbation may be secondary to viral, bacterial, a combination of the two and in some cases, it may be unknown. Exacerbations often lead to hospital admissions and require treatment in the acute setting.

As the disease progresses there are major developments of abnormalities to the alveolar caused by exposure to noxious particles or gases (Vogelmeier et al. 2017). Pulmonary Function testing is indicated following the reported symptoms, the degree of airflow obstruction is measured through spirometry, forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) are measured. Spirometry has been used as a definitive mode of testing the degree of air flow limitation. It is an apparatus where by the patient is asked to blow long and hard through a machine and it measures the degree at which, there is airflow limitation. There are defined normal spirometric measures which, can be

comparable (Wanger et al. 2005) and deviations are used for diagnosis of COPD. There are additional methods to assess absolute lung volumes including plethysmography, nitrogen gas washout and radiographic imagery techniques. However, other methods are costly whereas, spirometry can be used in the primary care setting which, is a cost effective approach for assessment of LF and aid diagnosis and management in the primary care setting (Siafakas et al. 2018).

FEV_1 is indicative of the predisposition to LF decline, it is important that the measurement is taken once plateau is reached, the reading is normally taken three times to increase accuracy. Lung function (LF) is often affected by age, sex and height COPD in the elderly can over diagnosed as there is an expected reduction in FEV1/FVC of 0.65 to 0.70 (Fernández-Villar, Soriano and López-Campos 2017). Over-diagnosis poses a potential implication of exposing patients to unnecessary pharmacological treatment, which is unnecessary and costly therefore imposing an extra financial burden. Overdiagnosis may happen due to elderly patients not demonstrating bronchodilator reversibility. **Figure 5** demonstrates a volume timed curve of patient with COPD compared to a patient who had normal LF.

Figure 5 Volume Timed Curve of patients with COPD compared to normal (Talag and Wilcox 2008)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

As discussed earlier, an initial working diagnosis of Asthma may be concluded as a diagnosis by the GP however, spirometry can distinguish whether there is a degree of reversibility with bronchodilation which will distinguish between Asthma and COPD as well as identifying the degree of airflow limitation. There are four categories for classification of disease status. It has implications for reviewing the status of the disease and contributes to decisions on management of the disease. **Table 4** depicts the categories and characteristics of airflow limitations.

Table 4 Category and characteristics of airflow limitation

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

Adapted from GOLD classification of airflow limitation in COPD (Vogelmeier et al. 2017).

Arterial blood gases (ABG) are used to establish the degree of hypoxaemia and hypercapnia. As the severity of the disease progresses there is a disparity in ABG there is an increase P_aCO_2 and a reduction P_aO_2. As FEV_1 falls below 50% there is greater disparity in ABG which, is due to V/Q mismatch (Petersson and Glenny 2014). ABG are greatly affected during exacerbation of COPD and overnight, sleep studies may be required to assess nocturnal hypoxia in patients who may have overlapping OHS/OSA. It important to note that sleep tests, for example overnight oximetry are not an indicator of disease severity.

A respiratory muscle function test may be used as a way of assessing the strengths and function of the respiratory muscles (Albert, Spiro and Jett 2008).

1.2.2 Effect on Quality of life

As the disease progresses in severity there is a reduction HRQL, COPD is a leading cause of disability and is often accompanied by psychological implications such as anxiety and depression. The disease therefore not only affects their physiological health, but also their well-being. An assessment of the disability and psychological factors associated is important to establish a patient's health status and it may be used a predictor of their prognosis in a study by Ahmed and colleagues (2016) they performed a cross sectional study on 124 patients in India with a diagnosis of COPD. Patients were asked to perform spirometry and complete a St Georges Health Related QOL Questionnaire (SGRQ) (Weatherall et al. 2009), to assess the correlation between the severity of COPD and reduction in QOL.

The authors demonstrated that there was a strong correlation between the severity of the disease and HRQOL scores. The more severe in stage of COPD the lower the QOL score, this study was a large study and completed in India and may not have matched participants with patients in Europe for example on socioeconomic status, health care provisions and it was also a small sample size. However, it is supported by a European (Jones et al. 2010) a study which, completed a large cross-sectional epidemiological study of over 1817 COPD patients who completed a St Georges Respiratory questionnaire COPD specific (SGRQ-C) (Meguro et al. 2007), Short form Health survey and the functional assessment of chronic illness therapy fatigue scale (FACIT). Characteristics of the patients included a mean FEV_1 of <56% and a mean age 65-year-old. Patients were excluded if they had an asthma or unstable cardiac disease. Information was collected on patient's current medical management, ABG's and medical history were collected, and the GOLD stage of COPD was calculated based on retrospective data on results . Spirometry was completed 6 months prior

to the survey. The authors found that the disease influences patient's HRQOL even in the early stages of the disease. It highlights that there is a relationship between the decline of FEV_1 and their HRQOL depending on the stage of the disease.

It is important however to address the limitations of cross-sectional designs. Although the study design demonstrates a correlation between the stages of the disease and the effects on HRQOL, cross sectional designs provide only a snapshot of disease process at a single point in time and identifying relationships (Bryman 2016) however it is important to recognise that the design does not demonstrate cause and effect and is difficult to predict what will happen in the future as the disease process continues or if the results are sensitive to change in treatment as there is no follow up. It is also difficult to demonstrate if there was a reduction in HRQOL before diagnosis of COPD. In future studies assessing the impact of COPD on HRQOL there should be more robust designs with RCT design.

1.2.3 Chest Imaging

Other diagnostic measures include imaging chest X-ray (CXR) which, in isolation, is not a definitive diagnostic test, however, it can be used to distinguish and exclude other possible differential diagnosis. CXR are used to assess clinical features such as hyperinflation and a flattened diaphragm (Theerakittikul, Hatipoğlu and Aboussouan 2014). Computer Tomography (CT) is a diagnostic test preferred, to identify emphysematous changes and categorizing the stage of the disease and sensitive to changes in COPD (Kumar 2009). A CT can identify bulla, bulla is a large air space created secondary to destruction of the alveolar septa and dilatation of the alveoli. Bulla is often susceptible to spontaneous pneumothorax whereby air enters the pleural space (Boren 1959).

1.2.4 Exercise Tolerance

In addition to imaging assessments of exercise capacity are also taken in patients with COPD. Progression of the disease leads to a reduction in exercise tolerance, increased dyspnoea, fatigue and respiratory muscle dysfunction all lead to reduce exercise capacity. Skeletal muscle wasting and, strength are both affected, specifically there is a reduction in the number of Type I muscle fibres which, are responsible for endurance and leads to a reduction in exercise capacity (Ambrosino 2002). From clinical experience it is the patient's ability to achieve simple activities of daily living such as walking to the shops, will be limited by shortness of breath. Exercise capacity can be assessed in several ways using a variety of measures. It may include the 6-minute walk test (6MWT) which, is a standardised test which is used in the clinical setting to assesses a patient exercise capacity.

As the disease progresses along with the patient's V/Q mismatch, there is also a change in the efficiency of skeletal muscle to utilise O_2 efficiently. The test involves the patient walking for 6 minutes, unassisted and the distance covered is then measured. The average distance walked is 500m for women and 580m for men (Talag and Wilcox 2008). The treatment itself evaluates physiological responses to of the cardiopulmonary vascular system, systemic response and skeletal metabolic responses. The test is more cost effective to complete compared to other methods of assessing exercise capacity such at cardiopulmonary exercise testing which involves specialist training and cost of equipment. 6MWT relies on the patients having to walk often a long a corridor measuring 30m in distance, it is relatively easy to perform and does not require training for the patient (American Thoracic Society 2002). Importantly this is a test of function and the patient's ability to complete basic tasks of daily living such as walking make this an ideal outcome measure to assess functional ability and exercise tolerance.

A sedentary patient is unlikely to reach maximal exercise capacity as this test allows patients to rest during the activity and does not require any additional equipment it therefore provides a more realistic idea of their level of exercise capacity to perform functional tasks (American

Thoracic Society 2002). There are many tests to measure exercise capacity in patients with diseases affecting pulmonary function, including cardiopulmonary exercise testing (CPET) and the shuttle walk test. CPET may be indicative when assessing the patient's requirements for oxygen during activity. However, the 6MWT is practical to use in a variety of clinical settings both in the community and in an acute setting. As all tests are open to a degree of variability, completing the test in a controlled environment should be completed always to minimise sources which would affect the reliability of the results. The test is both reliable and sensitive to change and therefore an ideal measurement to review both prognosis and the effect of treatment (Sciurba et al. 2003). It is a combination of reported clinical symptoms and diagnostic approaches which lead the diagnosis of COPD. Categorizing the patients has implications for their management plan.

1.2.5 Management of COPD

Exacerbations are related to poor outcomes and a reduction in LF, acute exacerbation of COPD (AECOPD) leads to disability and its frequency is directly linked to the survival of patients with COPD (Gunen et al. 2005). The clinical features of pathophysiology are complex and therefore challenging for diagnosis and management. The severity has a direct relation to the management of the disease. GOLD classification of COPD has helped to guide management of patients, more recently there has been a greater transfer of treatment based on their phenotypical presentation. What GOLD have done more recently is ascertain diagnosis not only degree of airflow limitation but in conjunction with risk of exacerbation and their co-morbidities (Lange et al. 2016). The objective of this management is to reduce exacerbation of COPD and prevent hospital admissions and therefore reduce the burden on health care systems. Optimal management of patients with COPD will include both pharmacological management and non-pharmacological management strategies. Standard therapy based on GOLD and NICE guidelines for assessment and management of adult

COPD. **Error! Reference source not found.** and **Error! Reference source not found.** demonstrate pharmacological and non-pharmacological approaches to management of COPD. In this systematic review the focus will be on the use of domiciliary NIV and its role in the management of COPD.

TABLE 5 PHARMACOLOGICAL MANAGEMENT OF COPD ADAPTED FROM (MORROW 2018)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

TABLE 6 NON-PHARMACOLOGICAL MANAGEMENT OF COPD (Morrow 2018)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

1.3 Non-Invasive Ventilation (NIV)

Mechanical ventilation was first mentioned as early as the 1800s where by the process of artificial respiration was introduced (Baker 1971). It is delivered by an oral nasal mask or nasal mask, NIV has been referred to as both Continuous Positive Airway pressure (CPAP) and Bi-level ventilation. CPAP is the delivery of one continuous pressure expiration and is used for the treatment on Type I respiratory failure (RF) where the primary problem is hypoxaemia. Bi -level ventilation provides two positive pressures on inhalation and exhalation is for the treatment of Type II RF. For this review NIV is referred to Bi-level ventilation. The principles are simple by delivering a pre-determined pressure on inspiration and expiration, it augments normal ventilation allowing for adequate gaseous exchange in patients with lung disease without the need for invasive techniques involving a tracheotomy or endotracheal rube. In an inefficient and ineffective ventilatory system, patients with COPD are at risk of AHRF because of a combination of pathophysiological changes. The physiological changes lead to inefficient ventilation a reduction in tidal volume and therefore an increase in P_aCO_2 and a reduction in P_aO_2, this is demonstrated following an ABG and is called Type II respiratory failure (RF).

The indication of NIV in an acute clinical setting will include a diagnosis of COPD or lung condition with the AHRF as determined by ABG **Table 7**. Patients should be in single system organ failure and have complete a course of 1 hour maximum medical management unsuccessfully before NIV is initiated (Davidson et al. 2016).

Table 7 Normal ABG Values and Type I RF and Type II RF adapted from (Davidson et al. 2016)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

As mentioned the aim of providing optimal therapy for patients with COPD is to reduce the incidence of exacerbations. NIV is used in the acute setting and has physiological effects because of IPAP and EPAP, which, help to reverse Type II RF **Table 8** summarises the physiological effects of NIV to improve ventilation and reverse hypercapnic respiratory failure.

Table 8 Physiological effects on NIV (Kallet 2015)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

1.4 Domiciliary NIV

Domiciliary NIV has many terms such as home NIV, long-term NIV and nocturnal NIV to name a few but the objective of long-term NIV in patients with COPD is to reduce hospital admissions and improve the patients QOL. The pathogenesis of COPD leads to an increase in P_aCO_2 and a reduction of P_aO_2 which becomes chronic hypercapnic respiratory failure (CHRF). Nocturnal hypercapnia occurs following hypoventilation, during sleep there are several physiological mechanisms which would not affect a normal health individual however, COPD patients who have an inefficient ventilatory system are at risk of reduction in respiratory function. During sleep there is a change of posture therefore putting the diaphragm at a mechanical disadvantage, there is increased upper airway resistance therefore a degree of obstruction, most importantly there is a reduction in ventilatory drive (Maranetra and Pain 1974). Peripheral and central chemo receptors detect a reduction in P_aO_2 and an increase in P_aCO_2 and hydrogen ions which result in an increase drive to breath. This stimulation is thought to be altered in COPD patients and because of V/Q mismatch and the Haldane effect by where haemoglobin has a great affinity to CO_2 and as minute ventilation is reduced in COPD patients there is greater retention of CO_2 (Abdo and Heunks 2012) therefore hypercapnia occurs. During sleep the process is exacerbated and as COPD progresses it leads to derangement of ABG and hospital admissions.

Figure 6 NIV interfaces (Nava, Navalesi and Gregoretti 2009)

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

From Top Left to bottom right names of interfaces. Nasal Mask, Nasal Pillows, Oropharyngeal mask, Hybrid, Hybrid without nasal pillows, Full face mask, Hood

Long-term nocturnal NIV can be beneficial in reducing P_aCO_2 in the blood, by providing a more efficient and effective ventilation mechanism to reduce P_aCO_2. Indications of long-term NIV are still poorly understood, there has been a recent survey completed to assess the indications and review practices among physicians looking after severe COPD patients (Crimi et al. 2016). Their web-based survey demonstrated that clinicians prescribe NIV with the perceived benefit of reducing hospital admissions, increasing patients QOL, reduce dyspnoea, improve exercise tolerance (ET) and LF. One other outcome that was anticipated was an increase in survival in patients in COPD. Indications for NIV however appeared diverse, the authors ranked in order of importance what the participants view was that on indicators for long-term NIV 3> admissions for HRF, failure to wean from NIV, P_aCO_2 of above 7.33Kpa, a P_aCO_2 6kpa > + hospital admissions, a P_aCO_2 6kpa > with desaturations, increased P_aCO2 with hypoxia. The main indication was severe hypercapnia with an inability to wean off NIV. This again is not a definitive indication for long-term NIV criteria the survey had a 42% response rate and the study was conducted across Europe to reflect the geographical variations in NIV prescription. The study was conducted using a purposive

sampling strategy, in which the 15 physicians shared details of their colleagues contact details to distribute the survey, this sample technique enabled them to be put into contact with experts in the field who would be able to answer the question the research question proposed (Parahoo 2016).

The survey by Crimi and colleagues (2016) highlight the varying practices across Europe, however the survey does much more by highlighting the differences in practice between approaches taken in NIV prescription. In contrast the survey does not show that there is benefit but more that it is a perceived benefit. The survey is based on expert and opinion and there is little known as to what pressures are best used for the prescription of domiciliary NIV and it is often left to the clinician's expertise as to what is the optimum pressure setting to use and therefore remains the question of what is the best settings to use in patients with COPD? The survey contributes to the theoretical concept of why practitioners clinically reason the prescription of domiciliary NIV to a population that systematic reviews (SR) and meta-analysis have demonstrated that there is no significant benefit for the treatment HRQOL and exacerbations compared to standard treatment (Becker et al. 2015, Dretzke et al. 2015, Dretzke et al. 2016, Kolodziej et al. 2007 **Table 9**). There is little definitive guidance as to the indications of NIV however the survey was able to highlight common practices amounts different clinicians, the author asked questions to investigated practices in ventilator modes, settings and interfaces **Figure 6** refers to the range of interfaces for patients.

1.5 Ventilator Settings

Different modes of ventilation are used in the clinical setting. Modes include pressure pre-set and volume assured, each may have different names dependent on their manufacturers branding and each setting or mode of ventilation may be used dependent on the presentations (Rabec et al. 2011) as new brands and developments in NIV continue there

have been the introduction of hybrid mode integrating volume with a predetermined parameter and back up rate with the patients spontaneous breath (Ekkernkamp et al. 2014) with each method has advantages and disadvantages. Volume assured (V_A) delivers a fixed volume during a given time and is guided by set parameters. The idea is that predetermined volume and flow rate to encourage ventilation. However airway pressure is determined by airway resistance and compliance this is not considered and therefore cannot guarantee the patients tidal volume and there is no attempt at compensation for leak (Rabec et al. 2011). Pressure pre-set generates airflow at a pre-determined pressure and therefore to maintain a pressure support. It can auto adjust to maintain a constant airway pressure support by maintain flow and therefore attempts to adjust if there is a significant leak of air at the mask. There are many advantages and disadvantages to each mode, pre-set pressure modes are increase the risk of damage to the airways called barotrauma. This Systematic review will focus on domiciliary NIV and management of COPD.

Chapter 2 Existing Systematic Reviews

Over the last 20 years there has been a growth of research into the effectiveness of NIV on patients with CHRF. Large Systematic Reviews (SR) and meta-analysis have investigated the effectiveness of NIV compared to standard treatment **Table 9** lists the characteristics of the systematic reviews. The results have not identified that NIV is superior treatment compared to standard therapy, yet the NIV is still a treatment choice for clinicians (Crimi et al. 2016) studies establishing the effect of NIV have used what can be considered as low-pressure ventilation and therefore have had a minimal effect on hypercapnia (Windisch et al. 2002).

In a systematic review by Kolodziej and colleagues (2007) in, which authors searched publications from 2001-2002 using both bibliographic databases and hand searching of journals they located 15 publications investigating the effect of NIV in severe COPD. The authors included both RCT's and Non RCTs, to examine the effect on respiratory function and health related outcomes such as dyspnoea, functional status HRQOL, exercise tolerance, morbidity and mortality. The authors narratively analysed comparator interventions and identified NIV compared physical activity, LTOT, and other modes of ventilation. In addition, the authors compared the length of follow up each trial that was conducted and narratively assessed and noted that there was great variation varying from 2 days to 5 years. They completed a meta-analysis on non RCTs comparing NIV to other treatments, there was a favourable effect on respiratory function including an improvement of P_aO_2 and a reduction of P_aCO_2. On appraisal of the review, the search was conducted between 2001 and 2003 there is no specific reasoning of why only over a 2-year period, in doing so the search year automatically rules out studies completed before which may have answered the question. The search identified 308 studies in total to be screened against inclusion and exclusion criteria. They had conducted a thorough search by hand searching

as well as electronic database searches therefore as recommended by the Cochrane collaboration (Higgins 2011) able to identify studies which may not have been identified by a database search alone (Cochrane Library 2017). Assessment of quality was completed by two separate reviews and therefore minimising the potential for bias by two people completing quality assessment (Parahoo 2014). As a result, there is minimised potential of selecting studies which would be more favourable to answer the question.

There were no studies identified from the authors search which investigated the effect of different NIV settings although this was not the primary aim as part of their systematic review, which was to compare NIV to different types of NIV, this may have been due to the limitation in search year. However, the findings from this review are further supported by two other SR conducted investigating the effect of NIV compared to standard treatment. Two SR completed in 2015 were completed examining the cost effectiveness of Domiciliary NIV compared to standard care in the treatment of patients with Domiciliary NIV by Dretzke and colleagues (2015) and Becker and colleagues (2015) both SR were Health Technology Assessments. Dretzke and colleagues (2015) completed in England whilst Becker and colleagues in Sweden. In a systematic review by Becker (2015) they aimed to answer two primary questions what the effect of NIV is compared to standard treatment and what is the effect of High intensity NIV (Hi-NPPV) compared to Low intensity NIV (LI-NPPV) on clinical outcomes and health related QOL outcomes. Their search included years 1980-2015 and bibliographic databases were searched including MEDLINE, PubMed, EMBASE, Cochrane library and HTA-databases, terms search were key words and Medical Subject Headings (MeSH). The title and abstracts were screened independently by two reviewers and discrepancies were discussed and resolved by third party. Full text articles were critically appraised by two independent reviewers against Grading Recommendation Assessment, Development and Evaluation (GRADE) system and a Swedish critical appraisal checklist as provided by the Swedish Council of Health Technology Assessment was used to assess the

quality of the paper and disagreements were resolved by consensus. In total 14 articles were included in the review of RCTs, Non RCTs and SR. Some of the studies identified had low certainty in assessment due to lack of blinding or no control group therefore increasing the risk of blinding in results. Including low quality publications, the results will affect the quality of the quality of the systematic review overall (Higgins 2008). Their results demonstrated that NIV compared to standard care may reduce mortality in COPD patients, improve HRQOL and improve dyspnoea with low certainty of evidence. There is little or no effect on patients who receive NIV compared to standard care on sleep quality, hospital admissions and exercise tolerance this is again with a low certainty of evidence.

Their second question assessed the effect of HI-NPPV compared to LI-NPPV, their search identified only one randomised cross over study completed by (Dreher et al. 2010) which, investigated the effect and therefore quality of recommendations based on this review are of extremely low certainty. As only one study identified there was no report on mortality and readmission rate. There is uncertainty in the effect on sleep quality, exercise tolerance, dyspnoea and reduction of P_aCO_2. Due to the limitation in evidence it is difficult to complete a conclusion from the review this review alone and therefore there is a need for further review and examination of the effect of pressure settings in NIV and this is further supported by Dretzke and colleagues systematic review and meta-analysis of the cost effectiveness of NIV compared to standard care in patients with end stage COPD.

Completed in the same year they searched electronic bibliographic databases between 1990-2014 and using a Markov Decision Model , which is a method of evaluating the healthcare cost in long-term conditions is varying disease states (Sculpher, Fenwick and Claxton 2000) and is a valid instrument to be used in this condition. In a study which identified 158 articles the results from the economic analysis demonstrated that there was a reduced risk on readmission in patients receiving NIV compared to those receiving standard treatment and this was supported by earlier economic analysis completed by Tuggey and

colleagues (2003), it is a disease specific systematic review however it may be possible to evaluate outcomes in long-term respiratory conditions such as cystic fibrosis where domiciliary NIV is used. In this study it demonstrated a wide range of NIV modes and pressure settings used in a variety of studies, from volume assured to higher pressure ventilation and prompts the question of what the optimum pressure or settings are used to have a greater patient benefit. As a sub category the authors investigated the effect of different setting of NIV in patients with end stage COPD. However, from their results they identified 3 studies which investigated the use of settings in NIV, due to the limit in studies identified and the heterogeneity in the outcome measures, length of intervention, numbers and study design the authors were unable to make any conclusions regarding the effect of pressure on NIV. Compared to Becker and colleagues (2015) this was a much larger review with no limitation on language and was able to identify more studies based in inclusion and exclusion criteria. The review was completed by more than one reviewer and minimising research bias. Studies were only included if they were of low risk bias and therefore this strengthens the quality of the systematic review. Dreher et al. (2010) was identified in both studies investigating the effect of pressure and therefore demonstrates at the time that there is further research needed to establish and effect.

Importantly it must be noted that the search strategy for Dretzke and colleagues (2015) and (Kolodziej et al. 2007) was not directly designed to identify studies to analyse the effect of pressure on outcomes for patients with COPD, as it was not the primary aim of the original study but a sub-category. Becker and colleagues (2015) investigated the effect of non-invasive ventilation on clinical outcomes and directly asked the question in relation to NIV settings as their second and the effect of Hi-NPPV compared to LINPPV on clinical outcomes, although the search strategy designed to suit the first objective. As a result, studies may have been missed which did not directly address the question. To address the question of the effect of High-IPAP compared to low-IPAP on patients with COPD receiving

domiciliary NIV a SR search strategy must be designed to address the question. Windisch and colleagues have (2002) have discussed the use of High-IPAP with high back up rates with the aim of maximally reducing P_aCO_2 and aiming for normocapnia in patients with CHRF. Higher inspiratory pressures are thought to have a greater effect on VT by increasing inspiratory volumes and reducing leak from the NIV mask and improving compliance with patients COPD patients (Dreher et al. 2010). The physiological benefits are thought to be an improvement in FEV_1, exercise tolerance and QOL, (Duiverman et al. 2016). Budweiser and colleagues (2005) examined the effect of home ventilation on patients with COPD their objectives were to investigate the effect of long-term ventilation on patients with COPD. NIV works by reducing dynamic dead space to improve alveolar ventilation, their study used retrospective data of 42 patients using plethysmography which is an accurate way of measuring TLC, IC, RV. Inspiratory lung capacity was calculated as the difference between TLC and intra thoracic gas volume. NIV was set using either a face mask and patients were reviewed at 6 and 12-month follow ups as inpatients. The median daily application time was recorded to assess compliance and 6.1 hours and the mean IPAP was19.9CMH_20. The authors demonstrated that there was a reduction in lung capacity at different time periods. This was a retrospective exploratory design and as there is no control group there are other variable to consider in the reduction hyperventilation it does not demonstrate causality. There was a strong correlation between High-IPAP and reduction of P_aCO_2, however all patients were treated with standard pharmacological treatment including the use of bronchodilators and steroids which may have contributed to the reduction in at this is standard therapy used in the treatment of patients with COPD (Vogelmeier et al. 2017).

2.1.1 Why is this research important for patients?

From reviewing published literature there have been several questions raised regarding the effects positive pressure settings, Low-IPAP settings are thought to more effective in

reducing dyspnoea and maybe more favourable with synchrony of the patients breathing. Equally low-IPAP are thought to be less effective at reducing P_aCo_2 in patients with CHRF (Windisch et al. 2002). In both larger SR (Becker et al. 2015, Dretzke et al. 2015), they have been unable to conclude as to the most effective pressure settings to use in patients with COPD. A further study was conducted Dretzke and colleagues (2016) thought to be part of the original review in 2015. In which the results demonstrated similar findings to that of Dretzke and colleagues (2015) when investigating the clinical effect of domiciliary NIV in patients with COPD, therefore calling for further research in the area to address this issue.

Table 9 Characteristics of Systematic reviews

AUTHOR TITLE	POPULATION	INTERVENTION	COMPARATOR	METHOD	SEARCH SELECTION OF STUDIES	PRIMARY OUTCOMES	SECONDARY OUTCOMES	NUMBER OF STUDIES INCLUDED IN REVIEW	CONCLUSIONS
(Kolodziej et al. 2007) **SYSTEMATIC REVIEW OF NON-INVASIVE POSITIVE PRESSURE VENTILATION IN SEVERE STABLE COPD**	18≥ COPD with CRF FEV_1/FVC 50% P_aCO_2 >6.7 Mean Age 63	Bi-Level NIV h	Spontaneous breathing, sham ventilation LTOT exercise and different types of NIV.	Systematic Literature Review of RCT's Within subject crossover designs	Electronic Bibliographic database search and Hand search. Years 2001-2002 English language Two reviews scanned and assessed by two independent reviews	ABG Lung function Respiratory function	Symptom relief Functional status. Exercise Tolerance	15	No improvement in PaO2. In RCT's however improvement in non RCT's reduction PaCO2 in non RCTs no evidence of improved gas exchange in subgroup analysis No evidence to suggest an improvement in FEV1 No improvement in respiratory Muscle function Increase in VT No Improvement in Exercise Tolerance Improvement in dyspnoea Improvement in functional status No significant difference in mortality rate. There was little or no evidence to draw conclusions of the benefit on the potential

Continued page 1of 4

									benefits of higher pressure NIV settings Not possible to draw an overall conclusion of the cost effectiveness of NIV in the post hospital population No statistical significant difference in the in the effect of NIV and reduction hospital admissions
(Dretzke et al. 2015) **THE COST EFFECTIVENESS OF DOMICILIARY NIV WITH END STAGE CHRONIC OBSTRUCTIVE PULMONARY DISEASE: A SYSTEMATIC REVIEW AND ECONOMIC EVALUATION**	18≥ End stage stable COPD GOLD Stage III and IV	Bi-Level NIV	Standard treatment, different types of NIV	Systematic review and meta-analysis Review of RCT's, Non RCT's. Markov decision tool was used to assess the clinical effectiveness	Electronic Bibliographic database search, conference proceedings and clinical trial registers 1990-2014 No language Limitation Data extraction was performed by one reviewer, second review checked a proportion.	Mortality, QOL, adherence or discontinuation, number of exacerbations	Lung function, QOL, ABG's, exercise capacity (6MWT)	158	There was little or no evidence to draw conclusions of the benefit on the potential benefits of higher pressure NIV settings NIV may improve HRQOL NIV can Improve hypercapnia NIV has no significant effect on the reduction of hospital admissions.

Continued page 2 of 4

(**Becker et al. 2015)** **HOME MECHANICAL VENTILATOR TREATMENT FOR CHRONIC OBSTRUCTIVE PULMONARY DISEASE PATIENTS WITH CHRONIC HYPERCAPNIA**	COPD 18>	Bi-Level Ventilation, High or Low intensity High-Intensity ventilation	Standard treatment alone. Low intensity ventilation	Systematic review and meta-analysis	Electronic database search 1980-2015 English and Scandinavian Language	Mortality, HRQOL, sleep quality, exercise tolerance (6MWT) Exacerbation, dyspnoea.	HRQL, Sleep Quality, Exercise capacity (6MWT), dyspnoea	14	NIV compared to Standard treatment may reduce mortality. NIV compared to standard treatment may reduce mortality NIV may Improve HRQOL and dyspnoea No effect on sleep quality No effect hospitalisation, exacerbations No effect on the Exercise tolerance (6MWT)
(DRETZKE ET AL. 2016) **THE EFFECT OF DOMICILIARY NONINVASIVE VENTILATION ON CLINICAL OUTCOMES IN STABLE AND RECENTLY HOSPITALIZED PATIENTS WITH COPD: A SYSTEMATIC REVIEW AND**	18≥ End stage stable COPD GOLD Stage III and IV	Bi-Level NIV	Standard treatment, different types of NIV	Systematic review and meta-analysis Review of RCT's, Non RCT's.	Electronic Bibliographic database search, conference proceedings and clinical trial registers 1980-2014 No language Limitation Data extraction was performed by one reviewer, second review	Mortality, QOL, adherence or discontinuation, number of exacerbations	Lung function, QOL, ABG's, exercise capacity (6MWT)	31	NIV compared to Standard treatment improves hypercapnia, reduced. No evidence on survival of reduction in mortality in NIV compared to usual care alone. NIV may improve HRQOL. Not enough evidence comparing other forms of NIV.

Continued page 3 of 4

META-ANALYSIS		checked a proportion.

Continued page 4 of 4

Chapter 3 Aim

SR to date, investigating the effect NIV in addition of usual care have demonstrated there is no added benefit in terms on QOL and hospital admissions compared to usual care alone. It is believed that this may be due to patients not receiving adequate ventilator pressures (Windisch et al. 2002). However, there is published evidence demonstrating a greater effect on hypercapnia, reduced time to readmission and improvement in exercise tolerance. There is much published evidence on the effects of acute NIV on AHRF and recent RCT's evaluating the long-term benefits of NIV (Murphy et al. 2017). There is greater understanding into how NIV can have an impact on patients with COPD in AHRF. After several admissions for AHRF patients are considered for domiciliary NIV. There is published evidence in the field of acute NIV in AHRF which, suggest pressure settings to start with to allow for effective and efficient ventilation of patients and to reverse AHRF (Davidson et al. 2016).

SR have addressed the effect of domiciliary NIV compared to standard treatment for patients with COPD however investigating the effect of different pressures on NIV has not been successful due to the paucity of evidence. The reviews have attempted to answer the question in sub studies in their reviews however it given that it was not their primary aim it may have been that their search strategies were not designed to find and identify all studies to answer the question. The objective from this SR is to review the effect of High-IPAP on ABG's, LF, exercise tolerance, QOL and hospital admissions. The overall aim of the systematic review is to collate data from existing RCTs critically appraising the evidence and synthesising the finding to add to the growing body of evidence to provide a deeper understanding of how long-term ventilation benefits the patients and to identify if there are any potential risk to the patient. Greater understanding of the effects of different pressure settings it will help to promote admission free survival of patients with COPD, in tern it will

provide insight into what further research is required in the future to improve the provision of patient care.

3.1 Philosophical Underpinnings

Reaching new conclusion is research requires the application of a systematic and scientific approach, and so in intervention studies, understanding effectiveness of treatment modalities is important to demonstrate how efficient and effective a treatment modality is. More importantly in the NHS is the need to demonstrate that treatment modalities are sustainable in the long-term and much health and social care research is geared towards more of a creation of sustainable healthcare system in which to provide safe care to patients and the public (Department Of Health and Social Care 2015). Practitioners are bound, by their professional registration to provide evidence-based practice (EBP) however it is often with challenges of clinical practice in which, we require the need to put research into practice and a systematic search of available literature is required to form a solution or treatment which is supported by strong evidence. In this case the research question was formed based on the need to understand how to make home ventilation for patients safe, effective and efficient.

It is a challenge that healthcare practitioners face daily however, to gain understanding a systematic approach is needed to assess the truth behind results. After an important clinical question is asked there is systematic search of available and relevant evidence, critically reviewing the evidence for systematic bias and integrating evidence with clinical knowledge and then constructing an informed judgement as to the effect of a specific treatment. The search for knowledge and truth is often conducted according to a paradigm that is in line with the researchers worldview (Bryman 2016, Polit 2014). In quantitative studies there is both experimental which, is aimed at understanding the way in which an intervention works and observational where data is collected overtime without the introduction of an intervention

(Polit 2014). Quantitative research derives from a postpositivist paradigm and so there is the belief that human phenomenon can be objectified and such thought to be more rational and scientific than its counterpart of constructivism (Creswell 2014) As such is there is the belief that there is cause and effect, for example a patient develops COPD there is the scientific explanation is that the patient has had exposure to noxious stimuli. A positivist theorist would seek to find an answer by using deductive approaches (Parahoo 2014), in such isolating variables and introducing a control and therefore an attempt to minimise systematic bias (Hammersley 1996). In so the theory is in line with the ontological approach in which nature is explained by cause and effect relationships. Observational studies and experimental studies gather empirical data in a systematic and measurable way in which to explain a phenomenon. Their epistemological approach is to limit variables by ensuring control on measures is an attempt for the researcher to detach themselves from the world around them and minimise researcher bias.

SR are not empirical designs but seek to review empirical research to gather data. The nature of this review is to establish the effectiveness of a treatment modality. A systematic review of empirical evidence follows the paradigm of a positivists view as a systematic approach is applied to gather evidence to explain a phenomenon by assimilate and gain coherence (R. D. Riley, Higgins and Deeks 2011). From an ontological standing the research assesses which intervention is more effective in patients with COPD. From an epistemological view point, a systematic search of the literature and data collection from RCTs pool secondary data to assimilate knowledge to contribute to a greater understanding of how NIV works in patients with COPD.

3.2 PICO Components

Table 10 PICO components

Population	**Adult patients 18 > years or over with COPD with severe airflow limitation and as confirmed by lung function tests FEV/FVC ratio <70%. Patients must be stable who have required long-term NIV. Stable COPD would be defined as in the absence of acidosis on ABG, must not be receiving treatment as an inpatient for AHRF in an intensive care unit but it will include patients who have received NIV post hospitalisation for long-term management.**
Intervention	NIV in pre-set pressure, it is not to include the all mode of NIV such as volume assured mode or hybrid modes such as intelligent volume assured. In this context as the objective is to review patients on long-term oxygen the term domiciliary is referred to as treatment which includes long-term nocturnal ventilation. It is absent of the use of NIV delivered by tracheostomy. High-IPAP will include variations such as high intensity but this is to consider patients on a pressure pre-set mode of ventilation. After a review of the literature there is no absolute definition of what high pressure is. However, based on previous studies the definition for this review will focus on an IPAP ≥ $_{2}$0CMH_2O is to be considered as higher-pressure ventilation.
Comparator	Low-IPAP will be defined as patients receiving NIV in pre-set pressure mode and receiving a pre-set pressure of ≤19CMH_2O
Outcome	To gain a clear clinical picture of the effects of NIV, the following outcomes will be considered. Primary outcomes that will be assessed in this systematic review will include data on Lung function, the effect on arterial blood gases (P_aCO_2 and P_aO_2), FEV1 and FVC, compliance as reported by number of hours used and recorded on NIV. Secondary Outcomes include reports on QOL, exercise capacity, report of any adverse effects recorded.
Study Design	Randomised Control Trials, Randomised Cross Over Trials

Chapter 4 Methods

4.1 Inclusion Criteria/Exclusion Criteria

To identify studies which, will be suitable to answering the research question as broken down in **Table 10,** studies were assessed against a set of inclusion and exclusion criteria. RCT's have definitive inclusion and exclusion criteria of patients to include in an empirical study by assigning inclusion and exclusion criteria and ensures that studies identified are appropriate to answer the research question (Charrois 2015). It is important to plan and define the outcomes that are required to review the question a set of inclusion and exclusion criteria is required to allow boundaries to be set of the review (Higgins 2011, Parahoo 2014) **Table 11** demonstrates the criteria from which studies were selected based on eligibility criteria to address the outcomes of the systematic review.

4.2 Study Design

RCT's and SR were included the study designs are recognised as the top of the hierarchy of evidence, and this is due to the rigor at which they are designed to (Bryman 2016, Parahoo 2014). RCT's by design aim to eliminate confounding variables by providing a control group and attempts to minimise chance and establish that the intervention is the cause of any difference in results between groups (Polit 2014). SR were identified to hand search and identify further studies which may be relevant the systematic review objectives.

4.2.1 Population

For the outcomes of this review a search strategy was designed to be inclusive of the population, of stable hypercapnic COPD patients and intervention NIV. It is mentioned earlier that there is documentation in the literature of NIV from the 1929 in which, Drinker and Shaw (Drinker and Shaw 1929) discuss the use of an artificial respiration using a treatment

modality providing insufflation, however the routine use of NIV both in AHRF and long- term use of NIV has been in place since the 1990's (Elliott et al. 1990) it is for this reason that searches were designed to be inclusive of the years from January 1990 to December 2017. Both English language title and abstracts were scanned however only English language studies were included for assessment. This was because there was no translator on the team, but studies were not limited to country.

Studies were included adults 18≥ years who were diagnosed had a diagnosis of COPD with a GOLD standard group III-IV with and $FEV_1 \leq 0.7$. NIV is recommended for patients who are in the later stages of the diseases, are given with patients who are frequent exacerbators 3 or more admissions requiring the treatment of NIV for AHRF (Crimi et al. 2016). It is recognised that patients admitted for AHRF occur in the later stages of the disease(Riley 2013). Patients must be stable as defined as the absence of a cough and production of purulent sputum, no hospital admissions in the last 4 weeks to 3 months requiring NIV or intubation (Vogelmeier et al. 2017).

Studies were excluded if the population studied were diagnosed with OSA/OHS, NMD, unstable heart failure, pneumonia, pulmonary oedema or CWD. The reason for this is ensure that the population studies had a pure diagnosis of COPD which was causing HRF, Rebec and colleagues (Rabec et al. 2012) discuss NIV allows for a great variance in ventilator settings from different modes of ventilation. It is considered that high-IPAP has greater effect in patients who have CWD have greater response to volume assured modes and the fore any favourable results in a high pressure arm may be secondary to high-IPAP (Tuggey and Elliott 2006)

4.2.2 Intervention and Comparator

Domiciliary NIV is the use of NIV long-term use overnight in their own home and includes studies in which patients were already established on NIV at home.

High-IPAP will include variations such as high intensity (Windisch et al. 2002) but this is to consider patients on a pressure pre-set mode of ventilation. After a review of the literature there is no absolute definition of what high pressure is. However, based on previous studies the definition for this review will focus on an IPAP ≥ 20cmH_2O is to be considered as higher-pressure ventilation. NIV in pre-set pressure, it is not to include the all mode of NIV such as volume assured mode or hybrid modes such as intelligent volume assured pressure IVAP's. And a Low-IPAP will be considered as <19cmH_2O on assessment of evidence from (Windisch et al. 2002).

Studies were excluded if patients had any other form of NIV such as Via tracheostomy or received acute NIV or intubation in acute care setting for treatment of an AECOPD.

4.3 Primary Outcomes

1. Lung function, FEV1, as patient's lung function is severely impeded following the disease process and is an important marker in determining the treatment course for patients with COPD.

2.The effect on hypercapnia, derangement of PaCO2 are occur with progression of the disease and can be detrimental to the patient relating to respiratory failure.

3. Compliance as reported by number of hours used and recorded on NIV.

4.4 Secondary outcomes

1. HRQOL is severely affected in patients with COPD, there is much conflicting evidence into the effect of NIV on QOL and therefore would pose greater in sight to the effect of NIV on QOL. It was anticipated due to the variety of outcome measures for QOL in patients with COPD there was anticipation that data on this outcome would be heterogenous.

2. Exercise capacity in COPD as referred to in **Table 2**, is reduced because of impaired pulmonary function and a reduction in skeletal muscle strength. There is evidence to suggest that the use of NIV in patients with COPD improves exercise capacity as there is improved gaseous exchange and therefore the ability for skeletal muscle to uptake O2 and utilise. The 6MWT is the common used assessment tool for exercise capacity as recommended by GOLD and American Thoracic Society (2002). By assessing the effect on NIV on exercise capacity.

3. Reported adverse effects- NIV has a risk of positive pressure ventilation include pneumothorax, barotrauma, gastric reflux, haemodynamic instability, higher pressures have been reported to pose a risk of leak, asynchronous breaths, pressure ulcer secondary to complications associated with the mask (Gay 2009)

4.5 Study Identification

4.5.1 Literature search

Using key words relevant to the outcomes of this review a search strategy was created with in conjunction with a librarian at Coventry University. The search was an iterative process and was adapted to ensure that the most relevant studies were identified, a full list of searches including keywords used, their combination, dates of searches and results can be seen in **Appendix 4**.

The following electronic databases were searched between January 1990 and December 2017 in February 2018 the Cochrane Library and MEDLINE, CINAHL, AMED via EBSCO information services provided by Coventry University. The Cochrane Collaboration discuss that in SR of interventions, a variety of databases should be included, and MEDLINE should not be the only database searched (Higgins 2011). **Table 12** lists the databases included in the study each are representative of a variety of medical backgrounds and professional

disciplines and covers both published literature and unpublished literature such grey literature. A hand search of reference lists of existing SR was completed to identify additional studies, **Appendix 3** lists SR which were searched.

Once searches were complete they were then stored in RefWorks ProQuest (ProQuest Libraries 2017) under database headings. Through this reference management software deduplication was completed, however manual removal of duplicated was required to ensure that there no article was accounted for twice.

Table 11 Inclusion and exclusion of studies

Study selection criteria	Included	Excluded
Study design	RCT's crossover trials systematic reviews and meta-analysis	Narrative literature reviews, commentaries, Quasi experiments and observational studies,
Publication type	Full articles,	Abstracts alone, letters, conference proceeding, ongoing studies and reports.
Population	Adult Stable COPD GOLD III-IV	Studies on lung conditions such as, cystic fibrosis, bronchiectasis, OHS, unstable heart failure, obstructive sleep apnoea, Tb, chest wall deformity
Intervention	NIV High-IPAP compared to low IPAP in home setting or home use of NIV.	CPAP, V_A NIV, IVAPs NIV provided in acute setting, NIV via tracheostomy, NIV as treatment for AHRF.
Outcomes	Primary outcomes • FEV_1 • FVC • P_aCO_2 • P_aO_2 • pH • QOL • Compliance with treatment Secondary outcomes • Exercise capacity • Hospital admissions • Adverse events	QOL reports which are not disease specific to NIV. Studies which look only at these outcomes. • SNIPs, MIP, MEP • Cardiac outcomes • Imaging of lung function • Airway resistance, • Intubations, QOL, length of stay

FEV_1, Forced expiratory Volume 1 second, FVC, forced Vital Capacity, P_aCO_2, partial pressure carbon dioxide, partial pressure of oxygen, pH, potential hydrogens, QOL, Quality of life Nasal Inspiratory Pressure, MIP maximum inspiratory pressure, MEP, maximum expiratory pressure, OHS Obesity hypoventilation syndrome, CPAP continuous positive airway pressure, V_A volume assured, IVAP's intelligent volume assured pressure support, AHRF, acute hypercapnic respiratory failure

Table 12 Database search and specialism

Database search	Specialism
EBSCO -Allied and Complementary Medicine Database (AMED)	Medical database focuses on specialist allied to medicine including physiotherapists, occupational therapists Grey literature
Cochrane Library **Cochrane Central Register of Controlled Trials, Cochrane database of Systematic Reviews (CDSR), Cochrane central Register of Controlled Trials (CENTRAL), Cochrane methodology register (CMR), database or Abstracts of Effects (DARE), Heath Technology Assessment Database (HTA), NHS economic evaluation database (EED)**	Health care interventions RCTs and systematic reviews grey literature
EBSCO- National Library of Medicine's MEDLINE	Biomedical Literature RCTs, systematic reviews,
EBSCO -Cumulative Index to Nursing and Allied Health Literature (CINAHL)	Nursing and allied Health Literature Conference proceedings, RCTs and systematic reviews

4.5.2 Screening and Selection

One reviewer screened titles and abstracts for their relevance to the research question based on inclusion and exclusion. Once completed and full text articles were identified and obtained to include for review copies were obtained and stored on a USB. The study selection process and elimination of studies are displayed as the Preferred Reporting for SR Items for systematic reviews and Meta-Analysis (PRISMA) flow diagram (Shamseer et al. 2015).

4.5.3 Data extraction

was conducted using a form which was devised in Microsoft Word by one reviewer please see **Appendix 7**, the form was developed with the research question in mind. Continuous

data on the available outcomes were collected, the data collection form was not originally piloted. Data was collected on the patient characteristics, intervention, and comparator and available outcomes. any additional outcomes outside of the scope of this review were noted. Studies where assessed for potential sources of heterogeneity as it would make help to define the best approach to analyse the data. Mean difference, standard deviation and confidence intervals were extracted from each study on the available outcomes. The data was then tabulated, and characteristics were summarised from each study to determine appropriate way to synthesis data as can be seen in **Table 13**.

4.5.4 Assessment of Risk of Bias

The articles were assessed against the Cochrane Risk Bias tool for RCT's in Review Manager software 5 (RevMan 5)**Error! Reference source not found.**. The domains included from the tool were random sequence generation, allocation concealment, blinding of participant and personnel, incomplete data and selective reporting. Using the Cochrane handbook for guidance studies which had 3 or more domains as low risk were stratified as low risk study. If studies scored a total of 3 or more high risk with unclear they were classed as high-risk studies. The Critical Appraisal Skills Programme (CASP) tool for critical appraisal of randomised control trials was used to assess quality of RCT's (Critical Appraisal Skills Programme 2017). The two methods for assessment of quality of evidence were chosen as they are both accessible and provide appropriate prompts to ensure the right quality of the study is included in the systematic review. In a systematic review of critical appraisal tools completed by Zeng and colleagues (Zeng et al. 2015) they analysed the 21 critical appraisal tools CASP had a variety of assessment tools. CASP have a tool for RCTs and SR, the tool was developed for educational purposes and does not poses a scoring system, the tool considers the methodological quality and robustness of the research. The Cochrane risk bias tool for RCT's is recommended by the Cochrane collaboration, the tool provides a clear guide in which, assess the limitations of the studies

included in the review and therefore provide a more reliable conclusion in the systematic review (Higgins 2011)

4.5.5 Data Synthesis and Analysis

As recommended by the Cochrane Collaboration (Higgins 2011) and the Centre for Reviews and Dissemination (2009) a narrative synthesis and quantitative synthesis was undertaken to assimilate the results of this review. Study characteristics were tabulated, they were then reviewed, and a meta-analysis was completed on the outcomes where two or more studies were being reviewed in studies with close to similar methods. First an inverse variance, fixed effects meta-analysis was completed to review the standard mean difference, then a sensitivity analysis by removing low risk of bias studies and completing an analysis on high quality studies only. By completing a sensitivity analysis, it explores the robustness of the results, by assessing the degree at which results from studies with poor methodology effects the overall results (Centre for Reviews and Dissemination 2009).

A visual assessment of heterogeneity was assessed by reviewing overlap of confidence intervals for the effect size of each study. The potential clinical and methodological sources of heterogeneity include age of patients, time points of results taken, methods to assess LF, number of days on NIV and intervention characteristics, units of measurements may have a potential source of heterogeneity and adequate presentation of data. An assessment using the chi^2 test and p value was used to assess if there was any heterogeneity in the results a large p value was deemed as a significant level of heterogeneity. I^2 was used to quantify the amount of heterogeneity which is present, if $I^2 > 50\%$ was considered moderate heterogeneity (Higgins 2011) a random effects meta-analysis was completed if a sub-analysis was deemed appropriate.

A narrative approach was taken where only one study was identified or if the study if there was substantial heterogeneity was detected. The narrative approach was undertaken to summarise results between studies. Due to the small number of studies with a small sample size an assessment of publication bias using funnel plots was not appropriate (Lau et al. 2006)

4.5.6 Ethics

Ethics approval was sort from Coventry University research ethics committee and was deemed low risk of causing harm. The Health Research Authority research framework and (Health Research Authority 2018) that research should not be done to the patient, but is should be done with the patient for the patient in mind. It is quite a powerful statement and it challenges traditional practices where by research was conducted and the only involvement of the patient was as being a participant. As research culture has evolved and with ethical codes of conduct incorporated into legislation reporting, ethical considerations demonstrate a strong and robust approach to research.

4.5.7 Data protection

In a systematic review although this is not primary research it involves exploring data bases, the collection and storage of data and storing data and exploring primary research involving human participants. Therefore, measures needed to be taken to ensure that there is adequate authorisation to share data. To maintain confidentiality data was stored on a password protected computer and USB storage device. In line with the data protection act (Legislation.Gov.Uk 2005) it is planned that once the investigation is completed that it would be destroyed.

4.5.8 Funding

The systematic review was completed as part of an academic requirement from a Health Education England/ National Institute of Health and Research funded Master by research at Coventry University. There are no conflicts of interest and there all views stated are that of the authors. There were no addition costs to the NIHR for the completion of the project.

Figure 7 Flow Diagram depicting article selection

Some materials have been removed due to 3rd party copyright. The unabridged version can be viewed in Lancester Library - Coventry University.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Table 13 Characteristics of Randomised Control Trials

Characteristics of RCT's

Author, Year, Country	Study Design	Number of Participants, Length of follow up	Number lost to follow up with reason	Mean Age	Intervention Mean IPAP and Standard Deviation	Comparator	Primary Outcome	Secondary Outcomes	Other Outcomes
(Dreher et al. 2010) **Germany**	Single Centre, Randomised Controlled Cross over study No Blinding	17 6 Weeks	2 Refused LI-NPPV sequence 1 Refused not tolerant of LI NPPV 1 Stopped LI-NPPV at home despite tolerance	Not Recorded	HI NPPV Mean IPAP 28.6±1.9 MBAR	LI-NPPV Mean IPAP 14.6 ± 0.8MBAR	Nocturnal and daytime $PaCO_2$, FEV1, FVC	Exercise Capacity 6MWD, 6MWT Adherence Number of hours of NIV, HRQOL SRI SS	Dyspnoea Borg Dyspnoea scale
(Dreher et al. 2011) **Germany**	Single Centre Randomised Controlled Cross over study Investigator blinding	17 2 Nights	4 2 refused to sleep under LI-NPPV	63	Hi-NPPV Mean IPAP 29.2±3.9MBAR	LI-NPPV IPAP 14 MBAR Control setting	Nocturnal $PaCO_2$, PaO_2	HRQOL-Not Reported Adherence Not Reported, Hospital admissions not recorded	Sleep Quality Body Polysomnography Oxygen Desaturation Index
Duiverman et al. 2017 **Netherlands**	Single centre Randomised Cross over feasibility study No blinding	14 6 Weeks	2 Secondary to hypercapnia following establishment of LI-NPPV 1 refused to sleep under LI-NPPV	69	Hi-NPPV 23.6±3.1CMH20	LI-NPPV IPAP 15.5±1.1CM H_20	Daytime $PaCO_2$, PaO_2	HRQOL-SRI, Adherence No. hours on NIV, Exercise Tolerance not assessed, Number admissions not Recorded	Cardiac Output, Respiratory Muscle strength

LI-NPPV-Low Intensity Non-Invasive Positive Pressure Ventilation, HI-NPPV- High Intensity Non- Invasive Positive pressure Ventilation, $PaCO_2$- partial pressure Carbon dioxide, PaO_2-partial pressure Oxygen, FEV_1 - forced expiratory volume in 1 second, FVC-forced vital capacity, Mbar- millibar, CMH_2o- centimetres of water, HRQOL- health related quality of life, SRI SS-Serious respiratory insufficiency questionnaire sub scale, IPAP- Inspiratory Positive Airway Pressure

Chapter 5 Results and Findings

5.1 Summary of Results

During the search 1613 studies were identified after removal of duplicates from the listed databases, there were no additional studies identified from hand searching reference lists of systematic reviews. The PRISMA flow chart in **Figure 7** demonstrated the selection process for assessment of included studies in results. After screening titles and abstracts 6 studies were identified to review for text analysis, full text article was not available (Chen et al. 2011) despite a search by conducted by Coventry University Library therefore was not included and was excluded. A further two studies by Duiverman and colleagues (2017) and Schwarz, Magnet and Windisch (2017), were excluded due to methodology of literature review. Duiverman and colleagues (2017) compared high Intensity positive pressure compared to low intensity positive airway pressure in COPD patients however, 10 patients were assessed on four variations of HI-NPPV and LI-NPPV for only 15 minutes with spontaneous breath in between and was not and RCT design. The settings were randomly generated however, and each patient had a varying sequence of generation of pressure settings and was not a RCT. Schwarz and colleagues completed a narrative literature review of HI-NPPV compared to LI-NPPV there was no evidence of a systematic selection process of articles to include in the review therefore did not fit in the criteria, a summary of this can be found in **Appendix 1**, **Table 16**. Three randomised control trials were included in the systematic review and from hand searching no additional studies were identified from the systematic reviews that were not already located through database searching **Table 13** demonstrates the characteristics of the randomised control crossover trials.

5.2 Study Characteristics

5.2.1 Study population Participants

A total of 48 patients with a diagnosis of COPD GOLD stage III and IV were identified, all studies had the absence of MND, OSA/OHS, pneumonia, bronchiectasis and post TB sequalae. Participants were recruited with a $PaCo_2$ of >6.4 and had not displayed any signs of acute exacerbation of COPD. Participants were all described as having stable COPD managed with standard medical therapy or described usual care as inhaled bronchodilators, inhaled corticosteroids and LTOT. Studies were poor in reporting demographics however the average age was between 63 and 69 as described in the studies.

5.2.2 Intervention and comparator

All three RCT's had received domiciliary NIV established prior to recruitment to the study recruitment, one RCT included a patient who developed decompensated respiratory failure during their intervention and was subsequently withdrwarn from the study and not included in the final analysis. Intervention provided varied in length of time to follow up, Duiverman (2017) and Dreher (2010) had 6 weeks follow up compared to Dreher (2011) with a follow up of 1 night.

Protocol in which NIV was initiated included an overnight admission and NIV pressures were recorded in similar protocols and IPAP was increased until participants could tolerate IPAP of above 23CMH_2O. the lowest IPAP recorded was 14CMH_2O (14Mbar). Once patients tolerated settings they were discharged and returned for follow up. Dreher and colleagues (2011) acclimatised patients to high IPAP, patients then received the intervention before being switched to low IPAP.

5.2.3 Risk Of bias within studies

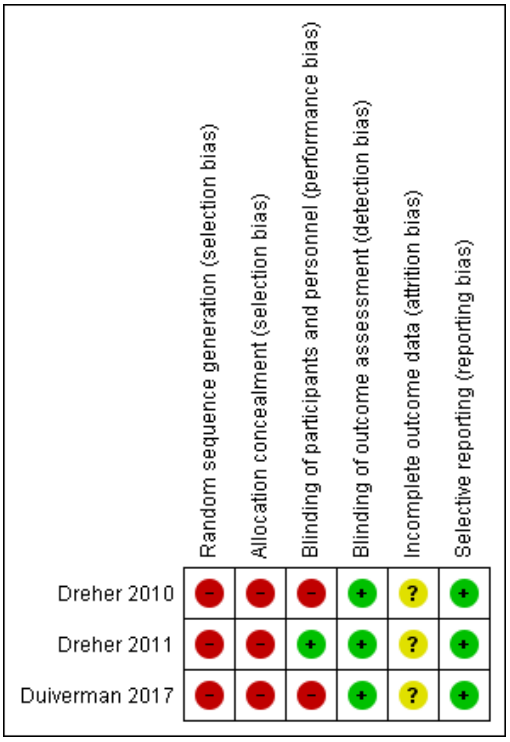
To review full quality assessment details and CASP tools on RCTs they are listed in **Error! Reference source not found.** and RCT's from assessment using the Risk Bas tool. **Figure 8** depicts the variation in quality in the domains of the risk bias tool of the included studies, all three studies were scored a high risk on random sequence generation, allocation concealment and blinding.

Blinding of participants and personnel risk bias for 2 RCTs was high, as there was no blinding reported, one trial reporting blinding of the assessor and scored low on this category. For the categories of blinding of outcome assessment two studies scored low and one study was unclear risk, outcomes used for the trials were objective measures and therefore unlike likely to be affected by bias. Therefore, objective outcomes such as ABG and ET are unlikely to be affected by bias. However, for studies that assessed subjective measures such as the Borg dyspnoea scale and the SRI scale there could have been affected by bias and therefore have an influence on the results.

For the category of incomplete data two trials scored an unclear risk and trial scored a high risk of bias secondary to lack of reporting subjects who had withdrawn from the trial and attrition bias due to the number of patients who had withdrawn from the studies.

All outcomes were reported as the study had discussed and therefore had a low risk of bias. Other factors considered in trials were carry over effect, as discussed patients were not naïve to NIV particularly HI-NPPV.

FIGURE 8:RANDOMISED CONTROL TRIALS INCLUDED IN SYSTEMATIC REVIEW



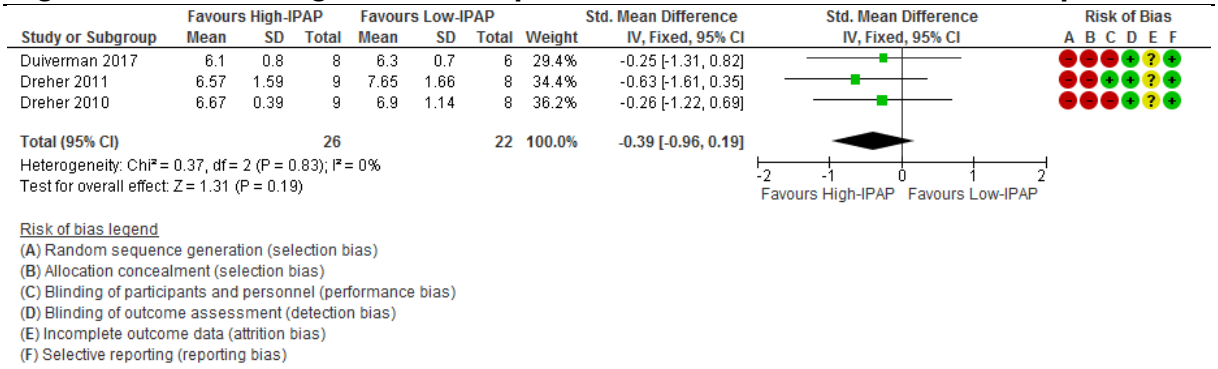
5.3 Primary Outcome

Results from a meta-analysis on $PaCO_2$, FEV_1 were completed, the results are as follows **Appendix 2** lists studies included in meta-analysis.

5.3.1 Effect of High IPAP compared to low IPAP on hypercapnia

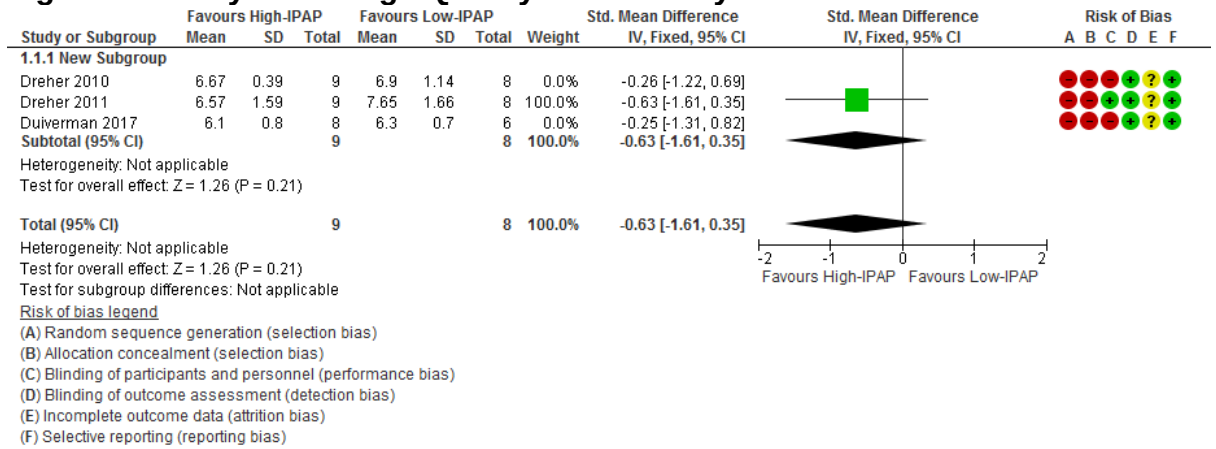
All 3 studies reviewed the effect of high-IPAP on hypercapnia with three studies, pooled data favoured high IPAP compared to low IPAP for reducing $PaCO_2$ with a standard mean difference with a reduction of P_aCO_2 by -0.39Kpa (95% CI [-0.96, 0.19]) no statistically significant difference (p=0.19) and results were homogenous (I^2=0%, p=0.83) as can be seen in **Figure 9** and **Figure 10**.

Figure 9 Effect of High-IPAP Compared to Low-IPAP on Reduction of paCO2



Units: Kilopascals (Kpa), SD- standard deviation, IV inverse variance, CI confidence Interval

Figure 10 Analysis on High Quality studies only



Units Kilopascals (Kpa), SD- standard deviation, IV inverse variance, CI confidence Interval

An analysis one high quality study demonstrated that results favoured high-IPAP with a reduction in P_aCO_2 a treatment effect of 0.63Kpa (95% CI - [-1.61, 0.32]) however there is no significant difference (p=0.21).

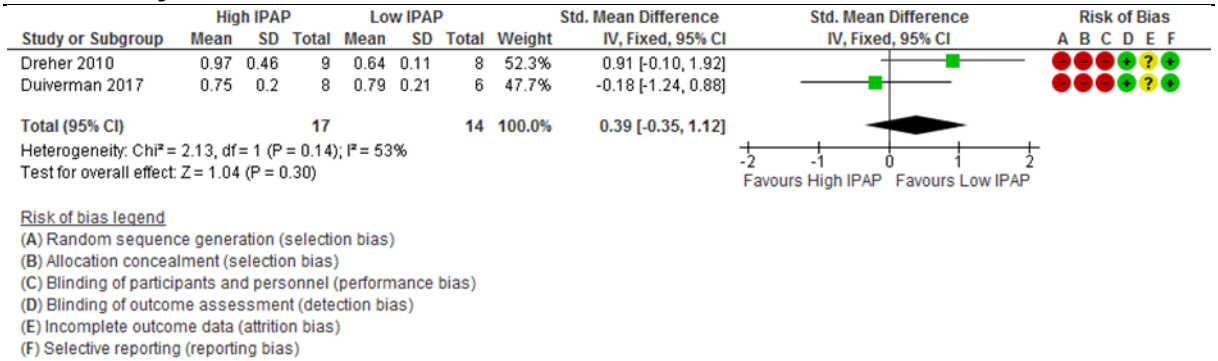
5.3.2 Effect of high IPAP versus low IPAP on FEV_1

Two studies were identified reviewing the effect of IPAP on FEV[1] Both studies were with a total of 31 participants. Results appear to favour low IPAP. On analysis of the results demonstrating that there was no significant difference (P= 0.30) in the effect of high-IPAP compared to low IPAP on FEV_1 however there was an improvement in FEV_1 with a mean

difference of 0.39l (95% CI [-0.35l, 1.12l]). There was evidence of moderate heterogeneity in results (I^2=53%, p=0.14).

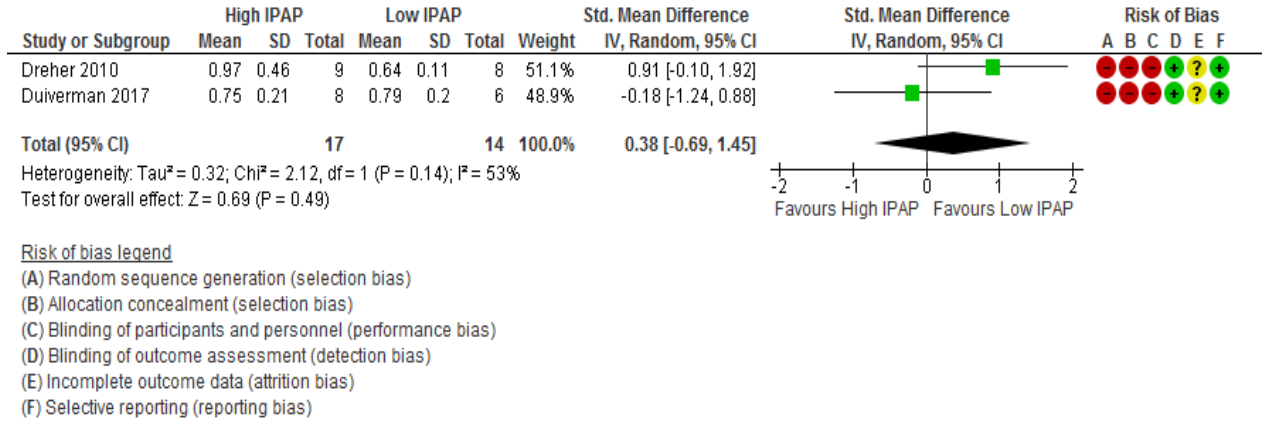
A random effects meta-analysis was completed to account heterogeneity, as can be seen in Figure 12, there was no statistically significant difference (p=0.49) (95% CI 0.38 [-0.69,1.45]) results were moderate heterogeneity (I^2=0% p=0.14) as can be seen in **Figure 11**.

Figure 11: Effect of High IPAP compared to low IPAP on FEV_1 Fixed effects meta-analysis



Units: litres (l) standard deviation, IV inverse variance, CI confidence Interval

Figure 12 Effect of High-IPAP Compared to Low-IPAP on FEV_1 Random Effects Meta-analysis



Units litres, SD- Standard deviation, IV inverse variance, CI confidence Interval

5.3.3 Effects of High-IPAP ventilation compared to Low-IPAP on exacerbation rates.

No study investigated the effect of pressure settings on exacerbation, Duiverman and colleagues (2017) discuss two patients were readmitted secondary to worsening hypercapnia when switched to the low-pressure intervention with a $PaCO_2$ increase to 10Kpa there are no further discussions on the follow up these patients to determine if this was secondary to an exacerbation.

5.3.4 Effect on adherence.

Two studies were found to investigate the effect on adherence both measure in number of hours however Duiverman and colleagues (2017) reviewed the median lengths of time on all patients who completed with a standard deviation compared to Dreher (2010) who recorded the mean length time completed for each period. Due to the differences in recording of data a meta -analysis was not completed. A median length of time on NIV for High-IPAP was 10.8hours compared to a mean of 7.7 hours spent on nocturnal NIV.

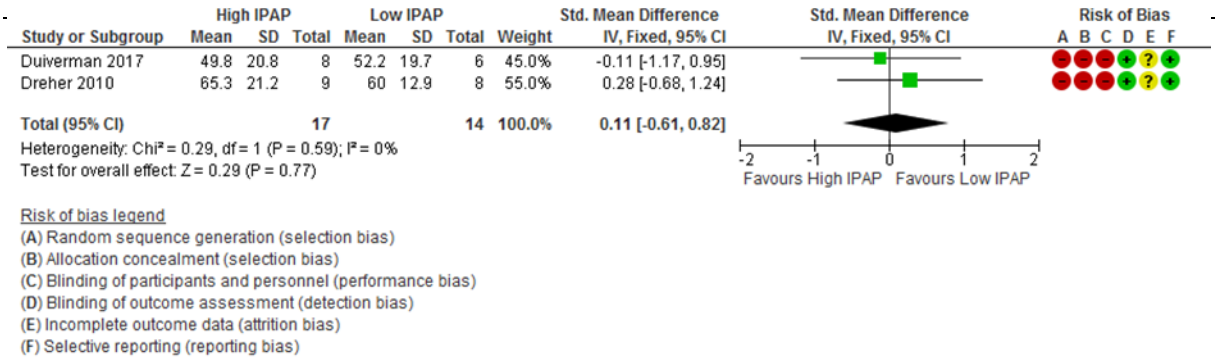
5.4 Secondary outcomes

A meta-analysis could only be completed on HRQOL, the results are as follows.

5.4.1 Effects on Health-related quality of life

Two studies analysed the effect of high-IPAP on the HRQOL Figure 12 with 6 weeks follow ups using the Serious Respiratory Insufficiency questionnaire. The results demonstrated that there was no significant difference between different settings and Health related quality of life (p=0.77) (95%CI 0.11 [-1.17,0.95]) there was no heterogeneity in results (I^2=0%, P=0.59).

Figure 12: Effect of high pressure compared to low pressure on the HRQOL



Standard deviation, IV inverse variance, CI confidence Interval

5.4.2 Effects of high-IPAP compared to low-IPAP on exercise tolerance

Table 14 Error! Reference source not found. illustrates that one RCT (Dreher 2010) investigated the effect on ET and recorded the six-minute walking distance, there was an increase in ET in both interventions with a between group difference of 14m, however it was not statistically significant (95%CI [-42m, 70m] p=0.58), the results were homogenous with (I^2=0%).

5.4.3 Reported adverse events

All three studies did not categorise serious adverse events, but, are discussed in terms of reasons for withdrawal, Error! Reference source not found. possible risks. Duieverman and colleagues (2017) discuss the increase in P_aCO_2 when switching from Hi- NPPV to Li- NPPV a rise of 10kpa is recorded in addition a participant who developed decompensated heart failure during the intervention. Dreher and colleagues (2011) report participants withdrawing to due to fear of asphyxiation.

Table 14 secondary Outcomes Exercise Capacity

Secondary Outcome Exercise Capacity						
Author, Year	Mean HI-PAP Standard Deviation BR (Supplementary O_2L/Min Standard Deviation)	Mean EPAP Standard Deviation	Mean LI IPAP	Mean LI EPAP	95% Confidence Interval between group difference After 6 weeks (M)	Comments
(Dreher et al. 2010)	28.6±1.9 Mbar BR 17.5±2.1 (2.2±0.8)	4.5±07Mbar	14.6±0.8 Mbar	4.0±0.7 Mbar	14 (-42- to 70) p=0.58	6MWT

Mbar- Millibar, 6MWT-6 Minute Walk test, LI-NPPV-Low Intensity Positive Pressure Ventilation, Kpa- Kilopascal, HI-NPPV-High Intensity Non-Invasive Positive Pressure Ventilation.

Table 15 Secondary Outcome reported Adverse events

Reported Adverse Events		
Author, Year	**Serious Adverse events recorded**	**Details**
(Dreher et al. 2010)	No	2 patients withdrew due to rise in dyspnoea secondary to switch from Li-NPPV to Hi-NPPV 1 withdrew secondary to intolerance of LI-NPPV settings
(Dreher et al. 2011)	No	4 patients withdrew due to refusal to sleep under lower pressures 2 following fear of asphyxiation to sleep under Li NPPV no report of the reasons behind withdraw of 2 participants
(Duiverman et al. 2017)	Yes	1 patient decompensated heart failure after 5 weeks in Hi-NIV arm, 2 patients did not tolerate the change from Hi-NPPV to lI-NPPV Rise in P_aCO_2 to 10Kpa

LI-NPPV-Low Intensity Positive Pressure Ventilation, Kpa- Kilopascal, HI-NPPV-High Intensity Non-Invasive Positive Pressure Ventilation, $PaCO_2$,

Chapter 6 Discussion

6.1 Summary findings

The primary objective of the systematic review was to analyse and synthesise available evidence on the effects of High-IPAP compared to Low-IPAP on specific patient outcomes who were receiving domiciliary NIV with a diagnosis of COPD to ascertain the most effective way to ventilate patients with home NIV. The review identified 3 RCTs, a meta-analysis was completed on outcomes where a minimum of two studies which investigated the same outcome. Forrest plots for outcomes (hypercapnia, lung function and quality of life) were completed and a narrative synthesis completed where there was only one study available. The results for the systematic review demonstrate that there was no significant difference between the effect of high-IPAP compared to Low-IPAP on hypercapnia, lung function and HROQL. There is paucity in evidence analysing the effect on exacerbation rate, exercise capacity and adverse effects of NIV. However, from reviewing the literature this is the first time a systematic review has directly addressed the question to establish the effect of high-IPAP ventilation compared to low pressure ventilation in COPD patients receiving domiciliary NIV. This review has highlighted that there is a gap in the evidence and therefore knowledge base in the effect of pressure settings on patients physiological and a clinical outcome

6.2 Primary Outcomes

All three studies were randomised open labelled cross over designs. As a result, this reduces the likelihood of a carryover effect (Cochrane 2011) which may have been an issue as there may have been carryover for the primary outcomes ($PaCO_2$ and $FEV_{1,}$). This method was discussed with a statistician at Coventry University to ensure the appropriate method was conducted and to ensure that each patient was not counted twice (Elbourne et al 2002)

6.2.1 Arterial blood gases

One of the possible advantages of high-pressure ventilation in patients with COPD included the reduction of P_aCO_2. On analysis on high quality study there was a reduction in P_aCO_2 which favour high-IPAP in (Vogelmeier et al. 2017) all three RCT's. Data suggests there is no significant difference (p=0.19) between the High-IPAP compared to low-IPAP on COPD patients receiving domiciliary NIV with a reduction of Paco2 a mean difference of -0.39Kpa (95% CI [-0.96, 0.19]). On sensitivity analysis, data suggest an improvement in PcO_2 the NIV is more favourable in patients who receive High-IPAP compared to low-IPAP however there is no significant difference. It is not yet fully understood the long-term physiological effects of the effect of NIV on hypercapnia. In all three-studies patient population were not naive to high-IPAP NIV and it may be possible that there was carry over effect upon entering the trial. It is not yet known how long the effects however with an increase in alveolar ventilation, there is greater gaseous exchange and a greater chance in reduction of P_aCO_2 (Borba Monteiro et al. 2012, Petersson and Glenny 2014). Although there is no statistically significant difference on sensitivity analysis due to the unknown long-term effects on dynamic hyperinflation.

NIV is hypothesised to reduce work of breathing (WOB) and airway resistance, this can improve respiratory muscle activity. The scope of this study did not seek to analyse the effect of High-IPAP compared to low-IPAP on the respiratory muscle function in patients. However, a recent study into the effect of HI-NPPV on participants respiratory muscle function, patients were exposed to four varying pressure sequences for 15minutes at a time and underwent electromyography to assess respiratory muscle activity (Duiverman et al. 2017) established that there was a decrease in respiratory muscle activity in patients who had a HI-NPPV compared to patients who had LI-NPPV. It demonstrated that NIV leads to respiratory muscle unloading and allows for greater control of the ventilation system

therefore an improvement in ventilation. It must be said however this study had a short follow up time on NIV and cannot be taken as long-term effects of ventilation on the respiratory muscles. Further studies in this area are needed to substantiate this theory.

There were limitations in data reporting on all RCT's, studies had incomplete reporting of baseline characteristics therefore this may lead to unreliable between group differences. There was Dreher and colleagues (2010) reported on the effect on P_aO_2 in which there was minimal effect on patients, however all patients had received supplementary oxygen. Due to the disease progression patients have a reduction in P_aO_2, under the BTS guidelines (Hardinge, Suntharalingam and Wilkinson 2015) oxygen LTOT can be prescribed to patients who are hypoxemic however it should be used appropriately as, COPD positions patients at a high risk of acidotic respiratory failure and it is important to control the flow of oxygen in patients receiving LTOT with a diagnosis of COPD and hypercapnic respiratory failure. Supplementary O_2 can also be of benefit for patients with HRF by stabilising P_aCO_2 (Stodart 2017) as it increases intrinsic PEEP a reduction in hospital admissions with NIV in combination with NIV compared to LTOT alone a result of stabilising P_aO_2 (Murphy et al. 2017) . Therefore, this is one variable that would require to be assessed in detail to ascertain that any change in P_aCO_2 was because of the higher pressures or higher pressure in combination with supplementary O_2.

6.2.2 Lung function

Data from the meta-analysis suggest that there is no significant difference between the effect of high-IPAP compared to low-IPAP on patients with COPD and their FEV_1 (p= 0.30) (95% CI 0.39l [-0.35l, 1.12l]). there was moderate heterogeneity in the results with I^2 53% p 0.14 with Dreher 2010 favouring low-IPAP and Duiverman (2017) favouring high-IPAP. Heterogeneity in the results could not be explained by a sensitivity analysis as they both

scored the same on quality of studies. A random effects meta-analysis was completed to assess for the differences in treatment effect. there was no statistically significant difference with a p value 0.39. The studies have wide confidence intervals due to the small sample of patients studied and therefore the results are less precise. Another explanation for the heterogeneity was one patient in Duiverman (2017) was admitted with severe hypercapnia prior to cross over and therefore there is a possibility that there was a reduction in FEV_1 preceding admission. LF has a significant decline as the disease progresses and there is a marked reduction in FEV_1 and FVC. 2 RCT's investigated the effect of pressures on LF and each demonstrated that there was an increase in FEV1 both RCTs, although there was an increase which was favourable towards higher pressure settings this increase was not a statistically significant differences between high-IPAP and Low-IPAP FEV_1 although an objective measure is not the only marker of lung volumes and there is no minimally important clinical difference to measure improvement and it suggested that a difference of between 100-140ml may be considered as an improvement Glabb and colleagues (2010). The measurements used to assess FEV_1 included the body plethysmography, this is an objective measure which is unlikely to be affected by the patient bias. It is said to be more accurate the assessment of patient's LF compared to spirometry (Wanger et al. 2005) and is a measure which is unlikely to be subjected to performance bias. As a widely used outcome measure of airflow limitation to establish treatment outcomes RCTs patients were categorised GOLD category COPD IV. There is a greater understanding of the pathogenesis of COPD in reviewing FEV_1 and FVC as an outcome, it will provide further information as to if NIV effect the progression of the disease, and longitudinal studies are needed to assess this phenomenon.

6.2.3 Adherence

Two studies (Dreher 2010, Duiverman 2017) assessed adherence as an outcome however a meta-analysis could not be completed on secondary to the method of measurement and

recording of data. As a result, a meta-analysis could not be completed, to obtain the results required to complete a meta-analysis contact with the authors would have been beneficial however due to the time constraints of the project this was not feasible. It is reported that both studies participants were using on average more than 4 hours a day.

For NIV to have a greater effect on diurnal pattern there should be use of more than 4≥ hours or more (Masa and Corral-Penafiel 2014) on average patients were using NIV more than 9 hours. It is thought that higher pressures in COPD patients improves tolerability because of respiratory muscle unloading and by overcoming airway resistance (Windisch 2011). Murphy (2012) demonstrated in a small cross over trial that higher pressures in NIV are not only justified but also tolerable and patients were adherence to higher pressure ventilation >28cmh20.

It would be beneficial for further studies to review the impact of pressure on adherence to treatment. Technology such as the use of remote monitoring of patients in NIV may be implemented in further trials, providing information, on number of hours on NIV, tolerance of pressures and asynchronous events. In the future telemonitoring may be away of assessing and predicting if patients are at risk of an exacerbation by recording patient ventilator interactions, trends in a pattern of reduced tidal volumes, reduction in the number of hours on NIV and number of asynchronous activities. It may offer a solution into reducing hospital admissions in clinical practice and improve quality in care and practice (Arnal, Texereau and Garnero 2017).

6.3 Secondary Outcomes

6.3.1 Health related quality of life

Quality of life is severely diminished in COPD patient's, data from this systematic review demonstrate that there was no statistically significant difference in pressure and HRQOL

(p=0.77) with improvement in HRQOL favouring high-IPAP (95%CI 0.11 [-1.17,0.95]) results were homogenous (I^2 =0, p=0.59%). This is in support previous reviews which suggest NIV in combination with standardised care is not superior to standard care alone in terms of improving quality of life this supports findings. It is also supported by a previous study by Tissot and colleagues (2015) discuss long-term NIV in the elderly has little effect on patients HRQOL in a multicentre cohort study investigating the effect of NIV in the elderly. Upon entering the study their characteristics were recorded and were followed up 4 months after initiation and were then followed up routinely to assess their ventilator adherence which was assessed by mean ventilator usage. The cohort were split into two age groups >75 and ≤ 75. The following outcomes were reviewed, sleep quality, cognitive assessments, Medical outcome Survey Short form Health Survey (SF-36), with physical component summary and mental component summary scales and subscale. Their results demonstrate that there was some improvement at 6 months however compared to the elderly seem to have a less benefits in their QOL, however the study investigates QOL on elderly patients who have CHRF, with the SF-26, although valid in the use with patient with long-term conditions to analyse to determine the effect of treatment, it is not disease specific. The Severe Respiratory Insufficiency Questionnaire was valid for COPD a patient with severe chronic respiratory failure questionnaire is designed for use in patients with CHRF and particularly with the use of NIV (Windisch et al. 2008).

As discussed by Crimi and colleagues (2016) a perceived benefit of domiciliary NIV is to improvement in QOL however this systematic review has demonstrated is no significant difference between those who are ventilated with High-IPAP compared to patients who were ventilated with Low-IPAP. As QOL is an outcome measure which is used to determine clinical effectiveness and guide long term treatment for patients receiving domiciliary NIV, future trials should investigate the effect further.

6.3.2 Exercise tolerance

ET was recorded in one trial only (Dreher 2010) as a result no meta-analysis was completed. Result were tabulated **Table 20** and demonstrated that there was no significant difference exercise tolerance (95% CI 14 [-42-to 70] p=0.58), however it is difficult to define if any improvement in exercise capacity was attributed to a high-IPAP. During the 6-minute walk test an improvement of 54-80m needs to be seen to determine an improvement in exercise tolerance (Glaab, Vogelmeier and Buhl 2010). It is not discussed if patients were receiving pulmonary rehab or engaging in physical activity. Both GOLD and NICE discuss the benefits of pulmonary rehab and prescribed physical activity to increase patients HRQOL, improve dyspnoea, improve self-management and reduce exacerbations. Unfortunately, there are no details on the non-pharmacy management of these patients and this is therefore speculation that any increase in ET may be attributed due to an improvement in skeletal muscle strength due to an increase in physical activity. In an RCT investigating the effect of NIV and ET (van 't Hul et al. 2006) group were given IPAP of 10cmH_20 and the control group were exposed to IPAP of 5cmH_2o. Following an 8-week supervised outpatient exercise programme patient were assessed at baseline for their HRQOL using the SGRQ, shuttle walk test and a constant load cycle endurance performance test, they were then tested after the 8 weeks of intervention and results demonstrated a statistically significant improvement in their exercise endurance, there was improved walking distance there was however no difference in SGRQ score.

In future studies it could be suggested that this is investigated further, however after pulmonary rehab patients have an increase in ET as there would be a reduction in dynamic dead space and therefore adequate ventilation and perfusion allowing for a more efficient gaseous exchange (Salturk et al. 2015). If there is more efficient gaseous exchange there is an increase in the uptake of oxygen by the skeletal muscle. Recent studies into the effect of as an adjust in pulmonary rehab suggest there is a place for its use in improving dyspnoea

and allowing patients to exercise longer (Puhan et al. 2011) In a systematic literature review by Corner and Garrod (2010) discussed the benefits of NIV in addition to pulmonary rehab, in which they concluded, NIV may increase exercise intensity in moderate to severe patients however the validity and reliability of evidence is questionable.

On the available study there is evidence suggesting that there is no significant improvement in exercise tolerance and high-IPAP. Further studies are required to enhance understanding of this this outcome.

6.3.3 Exacerbation

No study recorded exacerbation or readmission rates. It is reported in Duiverman (2017) that two patients were admitted secondary to a rise in PCO_2 of >10Kpa when patients received NIV in the low-IPAP treatment arm, however there are no further details provided to ascertain if this was secondary to exacerbation of COPD. Murphy and colleagues (2018) have demonstrated a improvement in time to readmission for patients receiving domiciliary NIV, LTOT and standard medical therapy compared to medical therapy alone. Murphy and colleagues (2018) predominantly used pressures median >28CMH20 during this trial and this relatively high IPAP may be attribute to the improvement in time to readmission. Further studies are required to investigate this phenomenon as there is no detailed data available to analyse. As a result, no conclusion could be drawn for this outcome as there no studies were identified.

6.3.4 Adverse Events

There was limited discussion on adverse events out of the three randomised open labelled cross over trials. **Table 14** displays serious adverse events recorded resulting in hospital admissions for Duiverman (2017) two patients were admitted secondary to an increase in

their PaCO2 and one patient was admitted following decompensated heart failure. They could be considered as an adverse event by WHO definition as an untoward medical occurrence during a clinical investigation (World Health Organization Quality Assurance and Safety of Medicines Team 2002). Reporting of adverse events in clinical trials are poor, however it is vital to report any adverse events are particularly for practitioners to consider treatment is beneficial and harms (Schulz, Altman and Moher 2010). Due to the poor reporting and follow up it is not possible to ascertain whether the increase in PaCO2 was a result of poor follow up or due to a reduction in pressure or a possible sign of a deterioration in disease status or possible AECOPD. One explanation for the increase in $PaCO_2$ is possibly due to not achieving the desired MV, resulting in asynchronous breath which increase the load on respiratory muscles in pressure <19CMH_2O (D. R. Hess 2011) therefore inadequate gaseous exchange leading to an increase in PaCO2 both in spontaneous breathing and NIV overnight (Tuggey and Elliott 2006).

It is also noted that Dreher and colleagues (2011) report that two patients were lost at cross over they did not want to sleep under low-IPAP as they reported the feeling of asphyxia. The feeling of asphyxia is normally associated with placement of an interface such as a oronasal face mask (Gay 2009) **Figure 6**. It is an interesting finding and patients withdrew from the trial following this fear. It is noted that there were no serious adverse events however it also not discussed what procedures were in place to safeguard patients against serious harm.

There is not enough detailed data evident to assess adverse events, there is paucity in the studies as to what is classed as an adverse event, whether there was a measurement for adverse events and how an adverse event was identified and document. Further studies should be conducted in this area to assess the effect of NIV pressures and adverse events.

6.3.5 Generalisability

In relation to the scope of the review question, it asked a specific question which was aimed to assess individuals who were receiving NIV as an additional form of management for COPD. There were limitations in the inclusion and exclusion criteria as discussed, studies identified as a result were limited to English language as a result participant were from western European countries who followed GOLD (2017) standard of care guidelines. The average of age of participants ranged from 63 and 67 with an FEV_1, <0.7 this is a typical presentation of patients with end stage COPD.

NIV is recommended in NICE guidelines (2010) and GOLD (2017). The results from this review are applicable to patients from this demographic for patients with end stage COPD GOLD stage 4 classification where domiciliary NIV is accessible. The results are specific to patients with COPD, other long-term respiratory condition (CWD, OHS, OSA, and NMD) where patients may suffer from chronic hypercapnic respiratory failure should use these results with caution as respiratory pathologies may require different ventilatory modes, settings (Rabec 2011) and further investigations should be carried out to assess the applicability of the results to other respiratory conditions.

6.3.6 Sensitivity analysis

The sensitivity analysis on analysing the effect on hypercapnia was completed to assess the effect of the robustness of the studies on the results (Cochrane 2011). On sensitivity analysis there was no significant difference between the effect of High-IPAP compared to Low-IPAP. This demonstrates that there was no influence on the quality of the trial on the results. However, the confidence intervals were wide, and this is largely due to the relatively small quantity of patients that were sampled, therefore although there is a more favourable outcome towards high-IPAP there it cannot be said with certainty, despite pooling of data

together, as demonstrated in the meta-analysis. Further studies are required with a large sample of patients.

6.3.7 Limitations of the study

As with all studies there are limitations, the search strategy was conducted in conjunction with an experienced librarian. To ensure that there was an effective database search was completed the search was conducted in collaboration with the subject librarian as to the best way to construct search syntaxes to ensure relevant studies were accounted for and advice sought on the bibliographic databases to utilise. In the involvement of systematic reviews, they are becoming more valuable and involved in health care research. In a scoping review Spencer and Eldredge (2018)to assess the role of librarians in a systematic review they concluded that there are up to 18 roles where the librarian can perform in a systematic review and in health research, they include planning the search, citation management, reporting and documenting in adherence to PRISMA format and de-duplication of records. Two roles identified in this review for which could be used in the future is for librarians in developing the protocol which was not previously considered and using technology and analytical tools for predicting the amount to references for a systematic review. The search was based on key words designed to detect studies relevant to the systematic review question. MeSH were not used and therefore there may have been articles not identified form search strategy which was completed. This is a limitation in the search strategy and as a result this may not a fully exhaustive search key words were used and if the study was to be completed again MeSH Headings would be ideally placed to ensure all relevant articles are identified.

Electronic databases were searched for English language studies in the following electronic databases available through the Coventry University EBSCO information services and

Cochrane which were accessible. Articles and abstracts which were unavailable were acquired through the Coventry University library. The Cochrane Library, MEDLINE and CINHAL and AMED were bibliographic databases searched there are many other databases which could be searched and Lam and McDarmid (2016)discuss that the number of databases searched in systematic review and meta-analysis has increased. However time constraints were a limiting factor in this case, however it thought that MEDLINE, the Cochrane library of systematic review which includes CENTRAL and CINHAL are sufficient enough to identify published and unpublished literature (Higgins 2011).

As the construction of the search was limited to English language only this may have been a limiting factor as studies which were written in another language were included in the review. This is often a common challenge in SR, systematic review teams conduct the review and with grants they may provide funding for an addition of a translator and therefore would be able to include studies in different languages, introducing language bias. In limiting languages there was a restriction to more western culture and as noticed the studies identified were European, therefore it would be likely that there may be minimal variation in management and diagnosis of patients with a diagnosis of COPD however it is beyond the scope of this review to identify the individual management practices of COPD patients in each country. But all trials refer to use of GOLD diagnosis and management of COPD guideline and therefore the approaches may have minimal or no variation therefore making conclusions generalizable to practice in the UK which, is important when making decisions in health care.

In addition to searching electronic databases hand searching was completed of identified systematic reviews to identify any additional trials not identified during the electronic database search. One other limitation of the review was that screening, selection data extraction, critical appraisal and evidence synthesis was conducted by a single reviewer, and

therefore it is subject to the scope of the authors knowledge and could be considered a source of bias. However, a systematic approach was taken in the approach was taken to answer the research question.

The initial time plan had changed and amendments were made to ethics in order to allow for a change of databases to be included in the search of the Cochrane library, initially a search of academic search complete was considered however it would have identified literature such as university thesis and conference posters and some clinical academia literature, but, would not have been adequate for the question posed in the systematic review, it was a learning curve and highlighted the importance of ensuring the right databases are searched for the question asked.

The data collection form was modelled based on literature and with consideration of the expected outcomes, however the form was not preliminary tested to establish the adequacy of function, in future studies it is recommended that data collection forms are tested on a few studies to identify that they are adequate in obtaining the data required (Evelina Tacconelli 2010). One limitation in data collection was simply that there was data which was not recorded, in some cases there was no baseline characteristics or reported in the trials and therefore could not be recorded in the form. What was also not considered in data collection was the recording of nocturnal and daytime $PaCO_2$ it was not anticipated that both measurements were taken and therefore was not accounted for in the data collection form. It is not believed that this would affect the results as data which is not reported on was a result of the studies not investigating outcomes.

Other methods of assessing the quality of evidence include the Grading of Recommendation Assessment and Development and Evaluation (GRADE) (Guyatt et al. 2008)which, would be

appropriate to use in when making recommendations for use in health. Guyatt and Gordan (2008) discuss the advantage of the GRADE system for making recommendations is there is a transition from quality of evidence to strength of recommendations and although both the Cochrane Risk Bias tool and the GRADE system are both used in SR and health technology assessments, GRADE provides a clear interpretation of what is a strong recommendation compared to a weak recommendation. If this systematic review was to be conducted again GRADE would be recommended as a method to make recommendations.

The CASP tool was used to appraise the evidence, as discussed it is both easy to use and accessible (Zeng et al. 2015). Although originally designed for use for educational purposes it is used in systematic reviews (Katrak et al. 2004). It is often discussed that only 50% of studies are published (Howes 2017) and studies are likely to be published if they have a statistically significant result. Due to the relatively small number of trials identified publication bias was not formally assessed with funnel plots. It is just as important to highlight areas of research which may not have had a favourable outcome (Lineberry et al. 2016).

6.4 Future Works

One of the key messages that was highlighted during this process is, further research is required in this area to gain greater understanding. Research which favours positive results are most likely to be published however there is much to be gained from research where there is no statistical significance and the future recommendation is to set about a new area for research. The length of follow up in each study was short and with 6 weeks follow up and in one study patients were followed up the following day, there not all outcomes necessary were reported and the protocol for NIV however it was dependent on the question asked, there was minimal or no blinding in the trials discussed. It was beyond the scope of this review to assess the effects of volume assured mode compared to pressure pre-set, and this is an area that would be with exploring in the future. A future RCT should be focused on the

long-term effects of High-IPAP compared to COPD patients with CHRF, to explore both the clinical effects and the physiological effects of long-term NIV.

A longitudinal multi centre RCT should be designed analysing the effect of High-IPAP, however it may not be practical to assess as a cross-over trial to lower pressures but, in fact a comparator may be assessing the effect of aiming for desired V_T or using V_A settings. Outcomes to consider are LF, dyspnoea, HRQOL, ABG, hospital admission, ET and adherence. The length of time required for follow up would be over a year to 24 months with intervals of 3 months, 6 months, 12 months and 24 months. This will allow for data to be collected on time to readmission or death and create a greater understanding on the longitudinal effects of mortality and morbidly. It may then be possible to perform a cost analysis to completed based on collected data. Another factor would be to apply a mixed methods approach to establish the lived experiences of COPD patients receiving domiciliary NIV, this will provide a holistic view of the management of patients. The design of the trial should collaborative approach with patients and public.

It was beyond the scope of this systematic review to analyse the physiological effect of NIV on the heart, however located one study reviewing patients with heart failure was identified it was an interesting find there appeared to be no detrimental effect of the high pressure NIV on the heart in patients with heart failure in patients with COPD The RCT demonstrated that it is feasible to investigate this phenomenon and future trials should also be encouraged to investigate this effect in long-term studies, especially when previously theories suggest that an increase in positive pressure leads to haemodynamic changes.

Chapter 7 Conclusion

This is the first systematic review completed which has a sole aim to assess the effect of pressure on patients with a diagnosis of COPD with CHFRF receiving Domiciliary NIV. The aim would be to create recommendations as to what settings would be best when prescribing NIV to patients with COPD in doing so making an impact to patient's long-term management. To answer this question following a design of a protocol and a systematic search of the literature, a total of 3 randomised control crossover trials were identified.

Following quality assessment and critical appraisal of studies a meta-analysis was performed on outcomes where two or more studies identified were performed on the (hypercapnia, FEV_1 and HRQOL). A narrative synthesis was completed on outcomes where only one study completed and assessment. From the outcomes there was no statistical difference in the effect of High-IPAP compared to Low-IPAP on patients $PaCO_2$, FEV_1, and HRQOL although results favoured high-IPAP. There was not enough data provided to conduct a meta-analysis on adherence a primary outcome and further studies are required to assess this further to understand what drives patient's compliance with NIV.

There was no data on outcomes for exacerbation rate and poor reporting on adverse effects of different pressures. The possible risks identified include a rise in hypercapnia fear of asphyxiation when switching to low-IPAP, however there is not enough information provided. When prescribing NIV there should be careful consideration as to which pressures are tolerable and just when prescribing NIV for domiciliary use. The review has identified that further research is needed in this area to ascertain if there is a more efficient and effective method to ventilate our patients and to ensure to improve their outcomes.

References

Abdo, W. F. and Heunks, L. M. A. (2012) 'Oxygen-Induced Hypercapnia in COPD: Myths and Facts'. *Critical Care (London, England)* 16 (5), 323

Ahmed, M. S., Neyaz, A., and Aslami, A. N. (2016) 'Health-Related Quality of Life of Chronic Obstructive Pulmonary Disease Patients: Results from a Community Based Cross-Sectional Study in Aligarh, Uttar Pradesh, India'. *Lung India: Official Organ of Indian Chest Society* 33 (2), 148-153

Albert, R. K., Spiro, S. G., and Jett, J. R. (2012) *Clinical Respiratory Medicine* [online] 4. ed. edn. Philadelphia: Mosby/Elsevier

Albert, R. K., Spiro, S. G., and Jett, J. R. (2008) *Clinical Respiratory Medicine*. 3. ed. edn. Philadelphia: Mosby/Elsevier

Ambrosino, N. (2002) 'Pulmonary Rehabilitation Programs: Outcomes in Patients with Chronic Obstructive Pulmonary Disease'. *Disease Management & Health Outcomes* 10 (9), 535-542

American Thoracic Society (2002) 'ATS Statement: Guidelines for the Six-Minute Walk Test'. *American Journal of Respiratory and Critical Care Medicine* 166 (1), 111

Aminoff, M. J. (2014) Aminoff's Neurology and General Medicine. Fith Edition edn. San Diego, CA, USA: Elsevier Science

Arnal, J., Texereau, J., and Garnero, A. (2017) 'Practical Insight to Monitor Home NIV in COPD Patients'. *Copd* 14 (4), 401-410

Baker, A. B. (1971) 'Artificial Respiration, the History of an Idea'. Medical History 15 (4), 336-351

Becker, H., Bossios, A., Daxberg, E., Eriksson, M., Hemlin, M., Jivegård, L., Persson, J., Svedmyr, S., and Sjögren, P. (2015) *Home Mechanical Ventilator Treatment for Chronic Obstructive Pulmonary Disease Patients with Chronic Hypercapnia (Structured Abstract)* [online] available from <http://onlinelibrary.wiley.com/o/cochrane/clhta/articles/HTA-32016000605/frame.html>

Booth, S. (2006) *Dyspnoea in Advanced Disease*. 1. publ. edn. Oxford [u.a.]: Oxford Univ. Press

Borba Monteiro, M., Cortozi Berton, D., Fontoura Moreira, M. Â, Saldanha Menna-Barreto, S., and Zimermann Teixeira, P. J. (2012) 'Effects of Expiratory Positive Airway Pressure on Dynamic Hyperinflation during Exercise in Patients with COPD'. *Respiratory Care* 57 (9), 1405-1412

Boren, H. G. (1959) 'Pulmonary Emphysema'. *Medical Clinics of North America* 43 (1), 33-52

Branson, R. D. and Gentile, M. A. (2010) 'Is Humidification always Necessary during Noninvasive Ventilation in the Hospital?...Including Discussion with Gay PC, MacIntyre NR, Borg U'. *Respiratory Care* 55 (2), 209-216

Bryman, A. (2016) *Social Research Methods* [online] Fifth edition edn. Oxford: Oxford University Press

Budweiser, S., Heinemann, F., Fischer, W., Dobroschke, J., and Pfeifer, M. (2005) 'Long-Term Reduction of Hyperinflation in Stable COPD by Non-Invasive Nocturnal Home Ventilation'*. Respiratory Medicine* 99 (8), 976-984

Carlucci, A., Pisani, L., Ceriana, P., Malovini, A., and Nava, S. (2013) 'Patient-Ventilator Asynchronies: May the Respiratory Mechanics Play a Role?'*. Critical Care (London, England)* 17 (2), R54

Carron, M., Freo, U., BaHammam, A. S., Dellweg, D., Guarracino, F., Cosentini, R., Feltracco, P., Vianello, A., Ori, C., and Esquinas, A. (2013) 'Complications of Non-Invasive Ventilation Techniques: A Comprehensive Qualitative Review of Randomized Trials'*. BJA: British Journal of Anaesthesia* 110 (6), 896-914

Centre for Reviews and Dissemination (2009) Systematic Reviews [online] available from <https://www.york.ac.uk/crd/guidance/> [31st September 2017]

Critical Appraisal Skills Programme 2018 CASP Randomised Control Trials. [2018] available from <https://casp-uk.net/casp-tools-checklists/> [Apr 25, 2018]

Charrois, T. L. (2015) 'Systematic Reviews: What do You Need to Know to Get Started?'. The Canadian Journal of Hospital Pharmacy 68 (2), 144

Chen, H., Liang, B., Xu, Z., Tang, Y., Wang, K., Xiao, J., Yi, Q., Sun, J., and Feng, Y. (2011) 'Long-Term Non-Invasive Positive Pressure Ventilation in Severe Stable Chronic Obstructive Pulmonary Disease: A Meta-Analysis'*. Chinese Medical Journal* 124 (23), 4063-4070

Chojnowski, D. (2003) "GOLD' Standards for Acute Exacerbation in COPD'*. Nurse Practitioner* 28 (5), 26-37

Cochrane Library (2017) *Cochrane Library* [online] available from <http://www.cochranelibrary.com> [2 December 2017]

Corner, E. and Garrod, R. (2010) 'Does the Addition of Non-Invasive Ventilation during Pulmonary Rehabilitation in Patients with Chronic Obstructive Pulmonary Disease Augment Patient Outcome in Exercise Tolerance? A Literature Review'*. Physiotherapy Research International* 15 (1), 5-15

Creswell, J. W. (2014) *Research Design*. 4. ed., internat. student ed. edn. Los Angeles, Calif. [u.a.]: SAGE

Crimi, C., Noto, A., Princi, P., Cuvelier, A., Masa, J. F., Simonds, A., Elliott, M. W., Wijkstra, P., Windisch, W., and Nava, S. (2016a) 'Domiciliary Non-Invasive Ventilation in COPD: An International Survey of Indications and Practices'*. Copd* 13 (4), 483-490

Crimi, C., Noto, A., Princi, P., Cuvelier, A., Masa, J. F., Simonds, A., Elliott, M. W., Wijkstra, P., Windisch, W., and Nava, S. (2016b) 'Domiciliary Non-Invasive Ventilation in COPD: An International Survey of Indications and Practices'*. Copd* 13 (4), 483-490

Davidson, A. C., Banham, S., Elliott, M., Kennedy, D., Gelder, C., Glossop, A., Church, A. C., Creagh-Brown, B., Dodd, J. W., Felton, T., Foëx, B., Mansfield, L., McDonnell, L., Parker, R., Patterson, C. M., Sovani, M., and Thomas, L. (2016) 'BTS/ICS Guideline for the Ventilatory Management of Acute Hypercapnic Respiratory Failure in Adults'. *Thorax* 71 Suppl 2 (Suppl 2), ii35

Dempsey, J. A. and Smith, C. A. (2014) 'Pathophysiology of Human Ventilatory Control'. *European Respiratory Journal* 44 (2), 495-512

Department Of Health and Social Care (2015) *The NHS Constitution for England - GOV.UK* [online] available from <https://www.gov.uk/government/publications/the-nhs-constitution-for-england/the-nhs-constitution-for-england> [Apr 14, 2018]

Dreher, M., Ekkernkamp, E., Walterspacher, S., Walker, D., Schmoor, C., JH, S., Windisch, W., Dreher, M., Ekkernkamp, E., Walterspacher, S., Walker, D., Schmoor, C., Storre, J. H., and Windisch, W. (2011a) 'Noninvasive Ventilation in COPD: Impact of Inspiratory Pressure Levels on Sleep Quality'. *Chest* 140 (4), 939-945

Dreher, M., Storre, J. H., Schmoor, C., and Windisch, W. (2010) 'High-Intensity Versus Low-Intensity Non-Invasive Ventilation in Patients with Stable Hypercapnic COPD: A Randomised Crossover Trial'. *Thorax* 65 (4), 303-308

Dretzke, J., Moore, D., Dave, C., Mukherjee, R., Price, M. J., Bayliss, S., Wu, X., Jordan, R. E., and Turner, A. M. (2016) 'The Effect of Domiciliary Noninvasive Ventilation on Clinical Outcomes in Stable and Recently Hospitalized Patients with COPD: A Systematic Review and Meta-Analysis'. *International Journal of Chronic Obstructive Pulmonary Disease* 11, 2269-2286

Dretzke, J., Blissett, D., Dave, C., Mukherjee, R., Price, M., Bayliss, S., Wu, X., Jordan, R., Jowett, S., Turner, A. M., and Moore, D. (2015) 'The Cost-Effectiveness of Domiciliary Non-Invasive Ventilation in Patients with End-Stage Chronic Obstructive Pulmonary Disease: A Systematic Review and Economic Evaluation'. *Health Technology Assessment (Winchester, England)* 19 (81), 1-246

Duiverman, M. L., Windisch, W., Storre, J. H., and Wijkstra, P. J. (2016) 'The Role of NIV in Chronic Hypercapnic COPD Following an Acute Exacerbation: The Importance of Patient Selection?'. *Therapeutic Advances in Respiratory Disease* 10 (2), 149-157

Duiverman, M. L., Huberts, A. S., Eykern, L. A., Bladder, G., and Wijkstra, P. J. (2017) 'Respiratory Muscle Activity and Patient-Ventilator Asynchrony during Different Settings of Noninvasive Ventilation in Stable Hypercapnic COPD: Does High Inspiratory Pressure Lead to Respiratory Muscle Unloading?'. *International Journal of Chronic Obstructive Pulmonary Disease* 12, 243-257

Duiverman, M. L., Maagh, P., Magnet, F. S., Schmoor, C., Arellano-Maric, M. P., Meissner, A., Storre, J. H., Wijkstra, P. J., Windisch, W., and Callegari, J. (2017) 'Impact of High-Intensity-NIV on the Heart in Stable COPD: A Randomised Cross-Over Pilot Study.'. *Respiratory Research* 18, 1-12

Ekkernkamp, E., Kabitz, H., Walker, D. J., Schmoor, C., Storre, J. H., Windisch, W., and Dreher, M. (2014) 'Minute Ventilation during Spontaneous Breathing, High-Intensity Noninvasive Positive Pressure Ventilation and Intelligent Volume Assured Pressure Support in Hypercapnic COPD'. *Copd* 11 (1), 52-58

Elliott, M. W., Steven, M. H., G D Phillips, and M A Branthwaite (1990) 'Non-Invasive Mechanical Ventilation for Acute Respiratory Failiure' 300, 358-360

ES, K. and HW, F. (2001) 'Current Management of Primary Pulmonary Hypertension'. *Drugs* 61 (13), 1945-1956

Faner, R., Rojas, M., Macnee, W., and Agustí, A. (2012) 'Abnormal Lung Aging in Chronic Obstructive Pulmonary Disease and Idiopathic Pulmonary Fibrosis'. *American Journal of Respiratory and Critical Care Medicine* 186 (4), 306

Fernández-Villar, A., Soriano, J. B., and López-Campos, J. L. (2017) 'Overdiagnosis of COPD: Precise Definitions and Proposals for Improvement'. *British Journal of General Practice* 67 (657), 183-184

Fischer, B. M., Voynow, J. A., and Ghio, A. J. (2015) 'COPD: Balancing Oxidants and Antioxidants'. *International Journal of Chronic Obstructive Pulmonary Disease* 10, 261-276

Flesch, J. D., MD and Dine, C. J., MD (2012) 'Lung Volumes'. *Chest* 142 (2), 506-510

Gay, P. C. (2009) 'Complications of Non-invasive Ventilation in Acute Care'. *Respiratory Care* 54 (2), 246-258

Gentile, M. A. (2011) 'Cycling of the Mechanical Ventilator Breath'. *Respiratory Care* 56 (1), 52-60

Gordon H. Guyatt, Andrew D. Oxman, Gunn E. Vist, Regina Kunz, Yngve Falck-Ytter, Pablo Alonso-Coello, and Holger J. Schünemann (2008) 'Rating Quality of Evidence and Strength of Recommendations: GRADE: An Emerging Consensus on Rating Quality of Evidence and Strength of Recommendations'. *BMJ: British Medical Journal* 336 (7650), 924-926

Gruffydd-Jones, K. and Loveridge, C. (2011) 'The 2010 NICE COPD Guidelines: How do they Compare with the GOLD Guidelines?'. *Primary Care Respiratory Journal : Journal of the General Practice Airways Group* 20 (2), 199-204

Gunen, H., Hacievliyagil, S. S., Kosar, F., Mutlu, L. C., Gulbas, G., Pehlivan, E., Sahin, I., and Kizkin, O. (2005) 'Factors Affecting Survival of Hospitalised Patients with COPD'. *European Respiratory Journal* 26 (2), 234-241

Hammersley, M. (1996) *Social Research* [online] Reprinted edn. London <>: Sage Publ

Hardinge, M., Suntharalingam, J., and Wilkinson, T. (2015) 'Guideline Update: The British Thoracic Society Guidelines on Home Oxygen use in Adults'. *Thorax* 70 (6), 589-591

Health Research Authority (2018) *UK Policy Framework for Health and Social Care Research* [online] [04 March 2018]

Hess, D. R. (2011) 'Patient-Ventilator Interaction during Noninvasive Ventilation'. *Respiratory Care* 56 (2), 153-167

Hess, M. W. (2017) 'The 2017 Global Initiative for Chronic Obstructive Lung Disease Report and Practice Implications for the Respiratory Therapist'. *Respiratory Care* 62 (11), 1492-1500

Higgins, J. P. T. (2011) *Cochrane Handbook for Systematic Reviews of Interventions* [online] available from <http://www.cochrane-handbook.org/> []

Higgins, J. P. T. (2008) *Cochrane Handbook for Systematic Reviews of Interventions* [online] []

Hillas, G., Perlikos, F., Tsiligianni, I., and Tzanakis, N. (2015) 'Managing Comorbidities in COPD'. *International Journal of Chronic Obstructive Pulmonary Disease* 10, 95-109

Howes, M. 2017*Publication Bias and Clinical Trial Outcomes Reporting*. [-06-12T08:00:50+00:00 2017] available from <https://www.centerwatch.com/news-online/2017/06/12/publication-bias-clinical-trial-outcomes-reporting/> [May 3, 2018]

Jones, P. W., Brusselle, G., Dal Negro, R. W., Ferrer, M., Kardos, P., Levy, M. L., Perez, T., Soler-Cataluña, J. J., van der Molen, T., Adamek, L., and Banik, N. (2010) 'Health-Related Quality of Life in Patients by COPD Severity within Primary Care in Europe'. *Respiratory Medicine* 105 (1), 57-66

Kallet, R. H. (2015) 'A Comprehensive Review of Prone Position in ARDS'. *Respiratory Care* 60 (11), 1660-1687

Katrak, P., Bialocerkowski, A. E., Massy-Westropp, N., Kumar, S., and Grimmer, K. A. (2004) 'A Systematic Review of the Content of Critical Appraisal Tools'. *BMC Medical Research Methodology* 4 (1), 22

Kerstjens, H. (2004) 'The GOLD Classification has Not Advanced Understanding of COPD'. *American Journal of Respiratory and Critical Care Medicine* 170 (3), 212-213

Kolodziej, M. A., Jensen, L., Rowe, B., and Sin, D. (2007) 'Systematic Review of Noninvasive Positive Pressure Ventilation in Severe Stable COPD (Structured Abstract)'. *European Respiratory Journal* 30 (2), 293-306

Kumar, P. J. (2009) *Clinical Medicine* [online] 7., rev. ed. edn. Edinburgh: Saunders

Lam, M. T. and McDiarmid, M. (2016) 'Increasing Number of Databases Searched in Systematic Reviews and Meta-Analyses between 1994 and 2014'. *Journal of the Medical Library Association : JMLA* 104 (4), 284-289

Lange, P., Halpin, D. M., O'Donnell, D. E., and MacNee, W. (2016) 'Diagnosis, Assessment, and Phenotyping of COPD: Beyond FEV'. *International Journal of Chronic Obstructive Pulmonary Disease* 11 Spec Iss, 3

Legislation.Gov.Uk (2005) *Data Protection Act 1998* [online] available from <https://www.legislation.gov.uk/ukpga/1998/29/pdfs/ukpga_19980029_en.pdf> [20 December 2017]

Lineberry, N., Berlin, J. A., Mansi, B., Glasser, S., Berkwits, M., Klem, C., Bhattacharya, A., Citrome, L., Enck, R., Fletcher, J., Haller, D., Chen, T., and Laine, C. (2016) 'Recommendations to Improve Adverse Event Reporting in Clinical Trial Publications: A

Joint Pharmaceutical Industry/Journal Editor Perspective'. *BMJ (Clinical Research Ed.)* 355, i5078

Loveridge, C. (2009) 'A National Strategy for COPD -- Opportunity Or Threat?'. *Practice Nurse* 38 (1), 38-45

Maranetra, N. and Pain, M. C. (1974) 'Ventilatory Drive and Ventilatory Response during Rebreathing'. *Thorax* 29 (5), 578-581

Masa, J. F. and Corral-Penafiel, J. (2014) 'Should use of 4 Hours Continuous Positive Airway Pressure Per Night be Considered Acceptable Compliance?'. *European Respiratory Journal* 44 (5), 1119-1120

Mason, J. K., McCall Smith, A., and Laurie, G. T. (2011) *Law and Medical Ethics* [online] 8. ed. edn. New York: Oxford University Press

Mertz, M., Kahrass, H., and Strech, D. (2016) 'Current State of Ethics Literature Synthesis: A Systematic Review of Reviews'. *BMC Medicine* 14 (1)

Moher, D., Liberati, A., Tetzlaff, J., and Altman, D. G. (2009) 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement'. PLoS Medicine 6 (7), e1000097

Morrow, R. (2018) 'New GOLD Standard in COPD Guidelines'. *World of Irish Nursing & Midwifery* 26 (1), 55-56

Murphy, P. B., Brignall, K., Moxham, J., Polkey, M. I., Davidson, A. C., and Hart, N. (2012) 'High Pressure Versus High Intensity Noninvasive Ventilation in Stable Hypercapnic Chronic Obstructive Pulmonary Disease: A Randomized Crossover Trial'. *International Journal of Chronic Obstructive Pulmonary Disease* 7, 811-818

Murphy, P. B., Rehal, S., Arbane, G., Bourke, S., Calverley, P. M. A., Crook, A. M., Dowson, L., Duffy, N., Gibson, G. J., Hughes, P. D., Hurst, J. R., Lewis, K. E., Mukherjee, R., Nickol, A., Oscroft, N., Patout, M., Pepperell, J., Smith, I., Stradling, J. R., and Wedzicha, J. A. (2017) 'Effect of Home Noninvasive Ventilation with Oxygen Therapy Vs Oxygen Therapy Alone on Hospital Readmission Or Death After an Acute COPD Exacerbation: A Randomized Clinical Trial'. *JAMA: Journal of the American Medical Association* 317 (21), 2177-2186

Nava, S., Navalesi, P., and Gregoretti, C. (2009) 'Interfaces and Humidification for Noninvasive Mechanical Ventilation...Including Discussion with Keenan SP, Hill NS, Kacmarek RM, Hess DR, Epstein SK and Mehta S'. *Respiratory Care* 54 (1), 71-84

Neil Lineberry, Jesse A Berlin, Bernadette Mansi, Susan Glasser, Michael Berkwits, Christian Klem, Ananya Bhattacharya, Leslie Citrome, Robert Enck, John Fletcher, Daniel Haller, Tai-Tsang Chen, and Christine Laine (2016) 'Recommendations to Improve Adverse Event Reporting in Clinical Trial Publications: A Joint Pharmaceutical Industry/Journal Editor Perspective'. *BMJ : British Medical Journal (Online)* 355, i5078

NICE (2010) *Chronic Obstructive Pulmonary Disease in Over 16s: Diagnosis and Management* [online] available from <https://www.nice.org.uk/guidance/cg101> [21 December 2017]

Openstax, C. *Anatomy & Physiology - OpenStax CNX* [online] available from <https://cnx.org/contents/FPtK1zmh@6.27:u67b9E14/The-Process-of-Breathing> [May 24, 2018]

Parahoo, K. (2014) *Nursing Research : Principles, Process and Issues* [online] 3rd edn. Basingstoke: Palgrave Macmillan. available from <http://replace-me/ebraryid=11314518>

Petersson, J. and Glenny, R. W. (2014) 'Gas Exchange and Ventilation-Perfusion Relationships in the Lung'*. European Respiratory Journal* 44 (4), 1023-1041

Polit, D. F. a. (2014) *Essentials of Nursing Research : Appraising Evidence for Nursing Practice* [online] 8th edition. International edition.. edn. Philadelphia: Philadelphia : Lippincott Williams & Wilkins

Public Health England (2015) *Chronic Smoking-Related Lung Disease Blights Over 1 Million Lives in England - GOV.UK* [online] available from <https://www.gov.uk/government/news/chronic-smoking-related-lung-disease-blights-over-1-million-lives-in-england> [Mar 23, 2018]

Puhan, M. A., Gimeno-Santos, E., Cates, C. J., and Troosters, T. (2016) 'Pulmonary Rehabilitation Following Exacerbations of Chronic Obstructive Pulmonary Disease'. in *The Cochrane Library*. ed. by Anon: John Wiley & Sons, Ltd

Rabec, C., Langevin, B., Rodenstein, D., Perrin, C., Leger, P., Pepin, J., Paul Janssens, J., and Gonzalez-Bermejo, J. (2012) 'Ventilatory Modes. what's in a Name?...Chatburn RL, Volsko TA, Hazy J, Et Al. Determining the Basis for a Taxonomy of Mechanical Ventilation. Respir Care 2012;57(4):514-524'*. Respiratory Care* 57 (12), 2138-2139

Rabec, C., Rodenstein, D., Leger, P., Rouault, S., Perrin, C., and Gonzalez-Bermejo, J. (2011) 'Ventilator Modes and Settings during Non-Invasive Ventilation: Effects on Respiratory Events and Implications for their Identification'*. Thorax* 66 (2), 170-178

Reddy, R. M. and Guntupalli, K. K. (2007) 'Review of Ventilatory Techniques to Optimize Mechanical Ventilation in Acute Exacerbation of Chronic Obstructive Pulmonary Disease'*. International Journal of Chronic Obstructive Pulmonary Disease* 2 (4), 441

Rennard, S. I. (2012) *Chronic Obstructive Pulmonary Disease* [online] . Philadelphia, Pa: Saunders

Rikxoort, E. M. v. and Ginneken, B. v. (2013) 'Automated Segmentation of Pulmonary Structures in Thoracic Computed Tomography Scans: A Review'. Physics in Medicine and Biology 58 (17), R220

Riley, J. (2013) 'Acute Decompensated Heart Failure: Diagnosis and Management'*. British Journal of Nursing* 22 (22), 1290-1295

Riley, R. D., Higgins, J. P. T., and Deeks, J. J. (2011) 'Interpretation of Random Effects Meta-Analyses'*. Bmj* 342 (7804), 964-967

Royal College of Physicians (2017) *Royal College of Physicians* [online] available from <https://www.rcplondon.ac.uk/news/copd-report-highlights-concerning-levels-hospital-readmissions-patients-england> [21 December 2017]

Salturk, C., Karakurt, Z., Takir, H. B., Balci, M., Kargin, F., Mocin, O. Y., Gungor, G., Ozmen, I., Oztas, S., Yalcinsoy, M., Evin, R., Ozturk, M., and Adiguzel, N. (2015) 'Comparison of Exercise Capacity in COPD and Other Etiologies of Chronic Respiratory Failure Requiring Non-Invasive Mechanical Ventilation at Home: Retrospective Analysis of 1-Year Follow-Up'. *International Journal of Chronic Obstructive Pulmonary Disease* 10, 2559-2569

Schulz, K. F., Altman, D. G., and Moher, D. (2010) 'CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomised Trials'. *Journal of Clinical Epidemiology* 63 (8), 834-840

Schwarz, S. B., Magnet, F. S., and Windisch, W. (2017) 'Why High-Intensity NPPV is Favourable to Low-Intensity NPPV: Clinical and Physiological Reasons'. *Copd* 14 (4), 389-395

Schwarz, S. B., Magnet, F. S., Schönhofer, B., and Windisch, W. (2017) 'Home Mechanical Ventilation - Concepts and Therapy Recommendations]'. *Deutsche Medizinische Wochenschrift (1946)* 142 (16), 1197-1204

Sciurba, F., Criner, G. J., Lee, S. M., Mohsenifar, Z., Shade, D., Slivka, W., and Wise, R. A. (2003) 'Six-Minute Walk Distance in Chronic Obstructive Pulmonary Disease: Reproducibility and Effect of Walking Course Layout and Length'. *American Journal of Respiratory and Critical Care Medicine* 167 (11), 1522-1527

Sculpher, M., Fenwick, E., and Claxton, K. (2000) *Assessing Quality in Decision Analytic Cost-Effectiveness Models: A Suggested Framework and Example of Application* [online] . Cham: Adis International. available from <http://www.ingentaconnect.com/content/adis/pec/2000/00000017/00000005/art00005>

Shaw, L. A. and Drinker, P. (1929) 'An Apparatus for the Prolonged Administration of Artificial Respiration'. *Journal of Clinical Investigation* 8 (1), 33-46

Shujaat, A., Minkin, R., and Eden, E. (2007) 'Pulmonary Hypertension and Chronic Cor Pulmonale in COPD'. *International Journal of Chronic Obstructive Pulmonary Disease* 2 (3), 273

Siafakas, N., Vermeire, P., Pride, N., Paoletti, P., Gibson, J., Howard, P., C. Yernault, J., Decramer, M., Higenbottam, T., S. Postma, D., and Rees, J. (2018) *Optimal Assessment and Management of Chronic Obstructive Pulmonary Disease* [online] [Mar 30, 2018]

Spencer, A. J. and Eldredge, J. D. (2018) 'Roles for Librarians in Systematic Reviews: A Scoping Review'. *Journal of the Medical Library Association* 106 (1)

Stodart, K. (2017) 'A Champion of Respiratory Care at Home'. *Kai Tiaki Nursing New Zealand* 23 (5), 13-14

Talag, A. A. and Wilcox, P. (2008) 'Clinical Physiology of Chronic Obstructive Pulmonary Disease'. *BC Medical Journal* 50 (2), 97-102

Theerakittikul, T., Hatipoğlu, U., and Aboussouan, L. S. (2014) 'Hyperinflation on Chest Radiograph as a Marker of Low Adherence to Positive Airway Pressure Therapy in the Overlap Syndrome'. *Respiratory Care* 59 (8), 1267-1274

Tissot, A., Jaffre, S., Gagnadoux, F. '. '., Levaillant, M., Corne, F. '. '., Chollet, S., Blanc, F. c., Goupil, F. c., Priou, P., Trzepizur, W., and Magnan, A. (2015) 'Home Non-Invasive Ventilation Fails to Improve Quality of Life in the Elderly: Results from a Multicenter Cohort Study'. *Plos One* 10 (10), e0141156

Tuggey, J. M. and Elliott, M. W. (2005) 'Randomised Crossover Study of Pressure and Volume Non-Invasive Ventilation in Chest Wall Deformity'. *Thorax* 60 (10), 859-864

Tuggey, J. M., Plant, P. K., and Elliott, M. W. (2003) 'Domiciliary Non-Invasive Ventilation for Recurrent Acidotic Exacerbations of COPD: An Economic Analysis'. *Thorax* 58 (10), 867-871

Tuggey, J. M. and Elliott, M. W. (2006) 'Titration of Non-Invasive Positive Pressure Ventilation in Chronic Respiratory Failure'. *Respiratory Medicine* 100 (7), 1262-1269

van 't Hul, A., Gosselink, R., Hollander, P., Postmus, P., and Kwakkel, G. (2006) 'Training with Inspiratory Pressure Support in Patients with Severe COPD'. *European Respiratory Journal* 27 (1), 65-72

Vogelmeier, C. F., Criner, G. J., Martinez, F. J., Anzueto, A., Barnes, P. J., Bourbeau, J., Celli, B. R., Chen, R., Decramer, M., Fabbri, L. M., Frith, P., Halpin, D. M. G., Victorina López Varela, M., Nishimura, M., Roche, N., Rodriguez-Roisin, R., Sin, D. D., Singh, D., Stockley, R., Vestbo, J., Wedzicha, J. A., and Agusti, A. (2017) 'Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report'. *Respirology*

Vos, T., Flaxman, A., and Naghavi, M. (2012) 'Years Lived with Disability (YLDs) for 1160 Sequelae of 289 Diseases and Injuries 1990-2010: A Systematic Analysis for the Global Burden of Disease Study 2010'. *Lancet* 380 (9859)

Wanger, J., Clausen, J. L., Coates, A., Pedersen, O. F., Brusasco, V., Burgos, F., Casaburi, R., Crapo, R., Enright, P., van der Grinten, C P M, Gustafsson, P., Hankinson, J., Jensen, R., Johnson, D., MacIntyre, N., McKay, R., Miller, M. R., Navajas, D., Pellegrino, R., and Viegi, G. (2005) 'Standardisation of the Measurement of Lung Volumes'. *European Respiratory Journal* 26 (3), 511-522

Weindling, P. (2001) 'The Origins of Informed Consent: The International Scientific Commission on Medical War Crimes, and the Nuremburg Code'. *Bulletin of the History of Medicine* 75 (1), 37-71

Windisch, W. (2011) 'Non-invasive Positive Pressure Ventilation in COPD'. *Breathe* 8 (2), 114-123

Windisch, W., Storre, J. H., Sorichter, S., and Virchow, J. C. (2005) 'Comparison of Volume- and Pressure-Limited NPPV at Night: A Prospective Randomized Cross-Over Trial'. *Respiratory Medicine* 99 (1), 52-59

Windisch, W., Vogel, M., Sorichter, S., Hennings, E., Bremer, H., Hamm, H., Matthys, H., and Virchow, J., J C (2002) 'Normocapnia during nIPPV in Chronic Hypercapnic COPD Reduces Subsequent Spontaneous PaCO2'. *Respiratory Medicine* 96 (8), 572-579

Windisch, W., Budweiser, S., Heinemann, F., Pfeifer, M., and Rzehak, P. (2008) 'The Severe Respiratory Insufficiency Questionnaire was Valid for COPD Patients with Severe Chronic Respiratory Failure'. *Journal of Clinical Epidemiology* 61 (8), 848-853

World Health Organisation (2017) *World Health Organization * [online] available from <http://www.who.int/mediacentre/factsheets/fs315/en/> [14 December 2017]

World Health Organization. Quality Assurance and Safety of Medicines Team (2002) *Safety of Medicines : A Guide to Detecting and Reporting Adverse Drug Reactions : Why Health Professionals Need to Take Action*.: Geneva : World Health Organization. available from <http://www.who.int/iris/handle/10665/67378>

World Medical Association (2013) 'World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects'. *Jama* 310 (20), 2191-2194

Zeng, X., Zhang, Y., Kwong, J. S. W., Zhang, C., Li, S., Sun, F., Niu, Y., and Du, L. (2015) 'The Methodological Quality Assessment Tools for Preclinical and Clinical Studies, Systematic Review and Meta-analysis, and Clinical Practice Guideline: A Systematic Review'. *Journal of Evidence-Based Medicine* 8 (1), 2-10

Appendices

Appendix 1 Studies Excluded at Full Text with Reason

Table 16 Table of Studies Excluded from Full Text with Reason

Author, Year	Title	Reason for exclusion	Comment
(Schwarz et al. 2017)	Why High-Intensity NPPV is Favourable to Low-Intensity NPPV: Clinical and Physiological Reasons	Excluded on methodology	Narrative Literature review
(Chen et al. 2011)	Long-term non-invasive positive pressure ventilation in severe stable chronic obstructive pulmonary disease: a meta-analysis	Unable to Locate Full Text article	Unable to assess from abstract alone, full text article not available
(Duiverman et al. 2017)	Respiratory muscle activity and patient-ventilator asynchrony during different settings of non- invasive ventilation in stable hypercapnic COPD: does high inspiratory pressure lead to respiratory muscle unloading?	Excluded on methodology	Case Controlled Study design, patients were assessed in 15-minute intervals, exposed to 4 variations of settings

Appendix 2 Studies included in Meta-Analysis

Table 17 Table of studies in Meta-Analysis

Author, Year	Title	Method	Reason for inclusion
(Dreher et al. 2010)	High-intensity versus low-intensity non-invasive ventilation in patients with stable hypercapnic COPD: a randomised crossover trial	Randomised Control Cross Over Trial	Met inclusion criteria on study design, patient population, intervention, outcome, comparator
(Dreher et al. 2011)	Non-Invasive ventilation in COPD: impact of inspiratory pressure levels on sleep quality	Randomised Control Cross Over Trial	Met inclusion criteria on study design, patient population, intervention, outcome, comparator
(Duiverman et al. 2016)	Impact of high-intensity non-invasive ventilation on cardiac function in stable hypercapnic COPD: a randomised cross-over trial	Randomised Control Cross Over Trial	Met inclusion criteria on study design, patient population, intervention, outcome, comparator

Appendix 3 Identified Systematic Reviews

Table 18 Systematic Hand Searched

Author, Year	Title	Method	Reason for inclusion
(Becker et al. 2015)	Home mechanical ventilator treatment for chronic obstructive pulmonary disease patients with chronic hypercapnia	Systematic Review	Met inclusion criteria on study design, population, intervention, comparators and outcomes
(Dretzke et al. 2015)	The Cost-effectiveness of Domiciliary Non-Invasive Ventilation in Patients with end stage chronic Obstructive pulmonary disease: a systematic review and economic evaluation	Systematic Review and Meta-Analysis	Met inclusion criteria on study design, population, intervention, comparators and outcomes
(Dretzke et al. 2016)	The effect of domiciliary non-invasive ventilation on clinical outcomes in stable and recently hospitalized patients with COPD: a systematic review and meta-analysis	Systematic Review and Meta-Analysis	Met inclusion criteria on study design, population, intervention, comparators and outcomes

Appendix 4 Search Strategy

Database CINAHL (EBSCO)
search strategies run on the 22/02/2018

ID	**Date of Search** **22/02/2018**	**Results**
S1	TX “Non-Invasive Ventilation” or “NIV” or NPPV or “Non-Invasive Positive Pressure Ventilation” Or “NPPV” or “Bi-PAP”	7314
S2	S1 and TX “domiciliary NIV” or “Home NIV” or “Nocturnal NIV” “Long Term Ventilation”	3248
S3	S1 AND S2 AND TX “Pulmonary Disease, Chronic Obstructive” or “COPD” or “Chronic Obstructive Pulmonary Disease” or “Chronic Obstructive Pulmonary Disorder”	1457
S4	S1 AND S2 AND S3 AND Limits English Language, 1990-2017	1432

Database AMED (EBSCO)

Search strategies run 20/92/2018

ID	**Date of Search**	**Results**
S1	TX “Non-Invasive Ventilation” or “NIV” or NPPV or “Non-Invasive Positive Pressure Ventilation” Or “NPPV” or “Bi-PAP”	88
S2	S1 and TX “domiciliary NIV” or “Home NIV” or “Nocturnal NIV” “Long Term Ventilation”	7
S3	S1 AND S2 AND TX “Pulmonary Disease, Chronic Obstructive” or “COPD” or “Chronic Obstructive Pulmonary Disease” or “Chronic Obstructive Pulmonary Disorder”	2
S4	S1 AND S2 AND S3 AND Limits English Language, 1990-2017	2

Cochrane library

Search Strategy Run 21/2/2018

Id	Date of Search 21/2/2018	Results
#1	"Non-Invasive Ventilation" or "NIV" or NPPV or "Non-Invasive Positive Pressure Ventilation" Or "NPPV" or "Bi-PAP" (Word variations have been searched)	1507
#2	#1 and Domiciliary NIV or Home NIV or Long-Term Ventilation or Nocturnal Ventilation (word variation have been Searched)	391
#3	#1 AND #2 AND Pulmonary Disease, Chronic Obstructive or COPD or Chronic Obstructive Pulmonary Disease or Chronic Obstructive Pulmonary Disorder (Word variations have been searched)	180
#4	#1 and #1 and #3 until December 2017, English language studies	180

MEDLINE (EBSCCO)
Search Strategies run 20/02/2018

Id	Date of Search	Results
S1	TX "Non-Invasive Ventilation" or "NIV" or NPPV or "Non-Invasive Positive Pressure Ventilation" Or "NPPV" or "Bi-PAP"	6615
S2	S1 and TX "domiciliary NIV" or "Home NIV" or "Nocturnal NIV" "Long Term Ventilation"	715
S3	S1 AND S2 AND TX "Pulmonary Disease, Chronic Obstructive" or "COPD" or "Chronic Obstructive Pulmonary Disease" or "Chronic Obstructive Pulmonary Disorder"	279
S4	S1 AND S2 AND S3 AND Limits English Language, 1990-2017	214

Appendix 5 Critical Appraisal frame work for Randomised Control Trials

Table 19 Critical appraisal (Dreher et al. 2011)

CASP Criteria for Randomised control trial	Dreher et al. 2011)	Comments
Did the trial address a clearly focused issue?	Yes	Patients hypercapnic respiratory failure, albescence of lung pathology neuromuscular, chest wall deformity, Overlapping OHS, bronchiectasis, bronchial Carcinoma or post Tb Sequalae, pCO2> 50mmhg. Patients not included if they were unstable AHRF and with as defined as possessing 2 signs, purulent sputum, C-reactive protein >5mg/dl changes in chest x-ray, received NIV in the last 3 months or any form of ventilation Intervention- Hi -NPPV Comparator- li-NPPV Outcomes- lung function, ABG, polysomnography, overnight oximetry to measure O2 desaturations index (ODI) ≥4% and number of desaturations per night <90% the largest decrease was recorded, ECG electrooculograms, digastric electromyogram, finger probe Sao2, EEG polygraph, total sleep time (TST), sleep efficiency measured by TST divided by time spent in bed, arousals were defined as the appearance of EEG of an α wave 3-15 seconds in duration. Sleep measured by 30 second epochs. Physiological outcomes were reported on.
Was the assignment of patients to treatments randomised?	Yes	Patients were randomized as reported however no detail on allocation concealment, randomization sequence generation. Therefore, risk of bias due to inadequate randomization reporting
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	All patients who completed the trial were accounted for, at risk of subject attrition bias due to withdrawal of patients in the LI-NPPV to Hi NPPV sequence. Four patients withdrew >20% of patient population no power calculation was completed. Reasons for withdrawal accounted for in flow diagram unlikely to affect results due to power calculation to determine how many participants would be required. Patients were analyzed in both the groups they were in and between group differences were reported. 2 refused to sleep under LI-NPPV due to fear of asphyxia there is no report of why the remaining 2 dropped out therefore there is inadequate follow up. No details however on follow up of these patients to safeguard from harm. Due to open labeled study design patients were aware of which treatment sequence they would be on may have affected the decision of the patient however due to lack of information on follow up this is purely speculation.

Continued 1 of 3

Were patients, health workers and study personnel 'blind' to treatment?	Yes	Investigator completing assessment of outcome measures for sleep assessment was blinded to ventilator setting and subjective evaluation, however it is unlikely to have influence by researcher or participant due to the outcome measures used. Therefore, reduces the risk of researcher bias
Were the groups similar at the start?	Can't Tell	There is minimal information provided on baseline statistics however age is reported however number of males to females is not. Information on baseline characteristics such as age, BMI, IPAP and EPAP settings were provided however appears to be a variation in FEV_1 SD 11.2 and BMI standard deviation 5.5. The varying distribution of FEV_1 and BMI may suggest that there is one patient in the Obese category and therefore cannot out that that patient did not have a greater effect from increase pressure as patients with higher BMI's require high pressures to ventilate more efficiently. However, this is speculation due to the minimal information on characteristic.
Aside from the experimental intervention were the groups equally treated	Yes	There is no appearance of favourable treatment, patients were all treated as per protocol.
How large was the treatment effect and how precise were the estimate of treatment effect		P value for all groups P>.05 Mean between group difference P_aCO_2– 6.4(95% CI -10.9 to 1.8 p value 0.1) No difference in sleep quality mean difference -3.0 (95% CI, -10.0 to 3.9, P-value 0.36) HCO_3 -1.8 (95% CI -3.1 to -0.50 P value 0.013) pH 0.025 (0.004 to 0.0046, P -value 0.25) paO2 2.5 (-4.7 to 9.8 P value 0.46) small sample quite large confidence limits, statement calculation to access number needed for clinical significance estimate 13 patients. Larger samples would provide more accurate confidence limits.
Can the results be applied to the local population or in your context?	No	Small sample, all received high pressure NIV prior to treatment as they were previously set up and therefore exposed to NIV prior to treatment. However, patients were in the same GOLD category IV and receiving standard medical therapy there is no discussion as to the details of the treatment plan. Short duration in terms of follow up unable and may be open performance bias as patients were assessed in laboratory environment. Unable to assess the long-term effects of the intervention due to the short duration of time. Study also completed in Germany and unsure of their practices or guidelines of management and domiciliary NIV.
Were all clinically important outcomes considered?	No	No measure of: HRQOL, Lung function post treatment, Exercise capacity, number of exacerbations, leak. However, provided the short duration of time unable to discuss the effects at length on the listed outcomes. There is no detail of tolerance overnight, and considering this is investigating the effect of sleep, it would be a useful outcome to assess the length of time patient was on continuous NIV.
Are the benefits worth the harms and costs?	No	Issue not addressed in the published report. The study protocol seems similar to a previous study completed in 2010 by the same author, could be a following study however this is not confirmed. Based on the study protocol, the duration of the study completed, the small sample, the design and the dropout rate, the results, although, add to the body of knowledge of NIV on sleep there are multiple systematic flaws in the published study which may influence the results.

Continued 2 of 3

Other considerations of carry over effects, due to cross over designs and to factor in that patients had been exposed to NIV previously. Authors address this with and ANOVA however it is currently unknow the long-term effects of NIV and although there is a statistical analysis clinically this is difficult to rule out. What is known is that there is an improvement on NIV regardless of the pressure given.

They discuss humidification, both nasal and oronasal masks, the oronasal masks are better at coping with high pressure ventilation that nasal mask, could be the reason for improved ventilation.
Humidification improves gaseous exchange therefore may influence the results.

Continued 3 of 3

Table 20 Critical Appraisal (Dreher et al. 2010)

CASP Criteria for Randomised control trial	(Dreher et al. 2010,)	Comments
Did the trial address a clearly focused issue?	Yes	Population- Adult, diagnosis of COPD, GOLD stage, IV, stable COPD with chronic hypercapnic respiratory failure, albescence of lung pathology neuromuscular, chest wall deformity, Overlapping OHS, bronchiectasis, bronchial Carcinoma or post Tb Sequalae, $PaCO_2$> 50mmhg. Patients not included if they were unstable AHRF and with as defined as possessing 2 signs, purulent sputum, C-reactive protein >5mg/dl changes in chest x-ray, received NIV in the last 3 months or any form of ventilation Intervention- Hi -NPPV Non- Invasive ventilation Comparator- li Non- invasive ventilation Outcomes- lung function peak inspiratory mouth occlusion pressure, ABG, Exercise capacity 6MWT, Dyspnoea, dyspnoea during walking using Borg dyspnoea scale, HRQL using severe respiratory insufficiency questionnaire. Pneumotachograph used for ventilatory measurements, compliance as assessed by ventilator count Physiological and clinical outcomes are reported on
Was the assignment of patients to treatments randomised?	Yes	Patients were randomized as reported however no detail on allocation concealment, randomization sequence generation. Therefore, risk of biais due to inadequate randomization reporting
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	All patients who completed the trial were accounted for, at risk of subject attrition bias due to withdrawal of patients in the LI-NPPV to Hi NPPV sequence. Four patients withdrew >20% of patient population no power calculation was completed. Reasons for withdrawal accounted for in flow diagram unlikely to affect results due to power calculation to determine how many participants would be required. Patients were analyzed in both the groups they were in and between group differences were reported. 2 Due to intolerance of NIV before entering period 2 on li NPPV 2 During period 1 LI before follow-up due to intolerance of Li NPPV 1, 1 patient stopped at home despite tolerance of Li NIV No details however on follow up of these patients to safeguard from harm. Due to open labeled study design patients were aware of which treatment sequence they would be on may have affected the decision of the patient however due to lack of information on follow up this is purely speculation.

Continued 1 of 3

Were patients, health workers and study personnel 'blind' to treatment?	No	No blinding of researcher, patient or due to nature of the treatment may not be possible to blind researcher however possibility to blind those completing the outcome measures as to which sequence. Due to nature of objective measures for outcome, it is unlikely to affect the result, may have effect however the SRI score as QOL been a subjective measure.
Were the groups similar at the start?	Can't Tell	Minimal information on baseline characteristics, only given because of the patients included in the measurement. Therefore, unable to assess, it does however state that they were of GOLD standard IV and FEV1 and the similar disease state. 9 Men and 4 women were accounted for men, Sex differences between- women have a reduced FEV1/FVC, increased incidences of women compared to men.
Aside from the experimental intervention were the groups equally treated?	Yes	All patients were exposed to treatments for the same length of time, follow up was completed after 6 weeks. All patients had had NIV prior to the investigation on long term Hi NPPV therefore there may have been some carryover effects, no evidence of any favourable treatment to one group over the other.
How large was the treatment effect and how precise were the estimate of treatment effect?		Primary Outcomes nocturnal PaCo2 mean value at 1.00h and 4.00h at follow up visit Secondary outcomes, daytime PaCO2 determined at day time PaCO2, HCO3, ling function, PI Max, Dyspnoea after 6MW, 6MWD SRI scale, and compliance. Analysis of Variance was completed to compare the means with treatment, period and randomized sequence effects size estimated as 95% CI tested on a two-side level of 0.05. Kolmogorov-Smirnov test to test for variation in means. CI are large due to the small sample. T-test was performed using separately for all patients.
Can the results be applied to the local population or in your context?	Can't tell	Small sample, of patients who were not naive to NIV. The population included were COPD and due to minimal detail of baseline characteristics unable to determine if the patients were similar. RCT performed in a single centre in Germany, which have their own set of guidelines on the use of domiciliary NIV in patients with CHRF further trials would be needed to assess the applicability to the UK health care systems in the UK requiring larger samples.
Were all clinically important outcomes considered?	No	The scope of the review did not assess for readmission and exacerbations. It would have been beneficial to assess pressure settings have an influence of patient's readmission and exacerbation rate. No data was provided on P_aO_2 and this may be because all patients had a supplementary O2 provided for them may have been enough to create a normalized PaO_2. It is not discussed as to the effect of different interfaces however analysis would shed light on the effect of pressures and efficiency of ventilation, reported some patients had nasal masks or oronasal mask, further analysis of which patient had which interface may have shed light into the tolerance of NIV
Are the benefits worth the harms and costs?	Yes	It is likely after a drop-in pressure from 28 to 14 that there would be a significant influence on hypercapnia and a reduction of tolerance in patients with COPD and therefore may cause more harm than good. However, it was a randomized control trial which adds to the body of knowledge and information of the potential benefits for higher pressure NIV. As the first study of it kind it has addressed an issue on ventilation and demonstrates the need for further RCT's in this area. Appears that the outcome measures were not anything that would be considered as extra analysis and therefore could be not subjecting the patient to any extra cost. The length of time taken to establish patient on NIV which they were

Continued 2 of 3

already established on may be considered as an extra burden on the patient however there is no detail if patient received compensation for their time.

Ethical approval was sought from the Institutional Review board for human studies at albert Ludwig University

Table 21 Critical Appraisal (Duiverman et al 2017)

CASP Criteria for Randomised control trial	(Duiverman et al. 2017)	Comments
Did the trial address a clearly focused issue?	Yes	Patient hypercapnic respiratory failure, absence of lung pathology neuromuscular, chest wall deformity, Overlapping OHS, bronchiectasis, bronchial Carcinoma or post Tb Sequalae, pCO2> 50mmhg. Patients not included if they were unstable AHRF and with as defined as possessing 2 signs, purulent sputum, C-reactive protein >5mg/dl changes in chest x-ray, received NIV in the last 3 months or any form of ventilation Intervention- Hi -NPPV Comparator- li-NPPV Outcomes- lung function, ABG, polysomnography, overnight oximetry to measure O2 desaturations index (ODI) ≥4% and number of desaturations per night <90% the largest decrease was recorded, ECG electrooculograms, digastric electromyogram, finger probe Sao2, EEG polygraph, total sleep time (TST), sleep efficiency measured by TST divided by time spent in bed, arousals were defined as the appearance of EEG of an α wave 3-15 seconds in duration. Sleep measured by 30 second epochs Physiological outcomes were reported on
Was the assignment of patients to treatments randomised?	Yes	Patients were randomized as reported however no detail on allocation concealment, randomization sequence generation. Therefore, risk of bias due to inadequate randomization reporting
Were all of the patients who entered the trial properly accounted for at its conclusion?	Yes	All patients who completed the trial were accounted for, results at risk of subject attrition bias due to withdrawal of patients in the LI-NPPV to Hi NPPV sequence. Four patients withdrew >20% of patient population no power calculation was completed. Reasons for withdrawal accounted for in flow diagram unlikely to affect results due to power calculation to determine how many participants would be required. Patients were analyzed in both the groups they were in and between group differences were reported. 1 patient developed decompensated heart failure whilst on the HI-NPPV treatment arm and underwent a procedure 2 patients developed hypercapnia with P_aCO_2 above 10Kpa No details however on follow up of these patients to safeguard from harm.

Continued 1 of 3

		Due to open labeled study design patients were aware of which treatment sequence they would be on may have affected the decision of the patient however due to lack of information on follow up this is purely speculation.
Were patients, health workers and study personnel 'blind' to treatment?	No	No blinding of researcher, patient or due to nature of the treatment may not be possible to blind researcher however possibility to blind those completing the outcome measures as to which sequence. Due to nature of objective measures for outcome, it is unlikely to affect the result, may have effect however the SRI score as QOL been a subjective measure.
Were the groups similar at the start?	No	Noted difference not in stage of disease in COPD, but in variations in cardiac involvement. For this baseline characteristics were not averaged in fact they were given independence due to the small sample.
Aside from the experimental intervention were the groups equally treated?	Yes	All patients were exposed to treatments for the same length of time, follow up was completed after 6 weeks. All patients had had NIV prior to the investigation on long term Hi NPPV therefore there may have been some carryover effects, no evidence of any favourable treatment to one group over the other.
How large was the treatment effect and how precise were the estimate of treatment effect?		There is some information provided on baseline statistics however age is reported however number of males to females is not. Information on baseline characteristics such as age, BMI, IPAP and EPAP settings were provided however appears to be a variation in FEV1 SD 11.2 and BMI standard deviation 5.5. The varying distribution of FEV1 and BMI may suggest that there is one patient in the Obese category and therefore cannot out that that patient did not have a greater effect from increase pressure as patients with higher BMI's require high pressures to ventilate more efficiently. However, this is speculation due to the minimal information on characteristic. Large treatment effect as seen may be due to small sample Mean between group difference was taken for P_aCO2 -2.8 (95% CI -6.6 to 1.00) FEV_1 0.00 (95% CI 0.11to 0.010) SRI-SS -2.9 (95% CI -8.0-2.0)
Can the results be applied to the local population or in your context?	Can't tell	Small sample, of patients who were not naive to NIV. The population included were COPD and due to minimal detail of baseline characteristics unable to determine if the patients were similar. RCT performed in a single centre in Germany, which have their own set of guidelines on the use of domiciliary NIV in patients with CHRF further trials would be needed to assess the applicability to the UK health care systems in the UK requiring larger samples.
Were all clinically important outcomes considered?	No	The scope of the review did not assess for readmission and exacerbations. It would have been beneficial to assess pressure settings have an influence of patient's readmission and exacerbation rate. No data was provided on P_aO_2 and this may be because all patients had a supplementary O2 provided for them may have been enough to create a normalized PaO_2. It is not discussed as to the effect of different interfaces however analysis would shed light on the effect of pressures and efficiency of ventilation, reported some patients had nasal masks or oronasal mask, further analysis of which patient had which interface may have shed light into the tolerance of NIV
Are the benefits worth the harms and costs?	Yes	It is likely after a drop-in pressure from 28 to 14 that there would be a significant influence on hypercapnia and a reduction of tolerance in patients with COPD and therefore may cause more harm than good. However, it was a randomized control trial which adds to the body of knowledge and information of the potential benefits for higher pressure NIV.

Continued 2 of 3

As the first study of it kind it has addressed an issue on ventilation and demonstrates the need for further RCT's in this area.
Appears that the outcome measures were not anything that would be considered as extra analysis and therefore could be seen as not subjecting the patient to any extra cost. The length of time taken to establish patient on NIV which they were already established on may be considered as an extra burden on the patient however there is no detail if patient received compensation for their time.

Ethical approval was sought from the Institutional Review board for human studies at albert Ludwig University

Appendix 6 Data Extraction

Data Extraction Form **Study Details**				
Citation and Year			Date of data extraction	
Country/ language				
Number of participants at Start of Recruitment				
Number End of recruitment				
Number of participants lost to follow up and reason				
Mean Age				
Number of Males				
Number of females				
Number of recruiting centres				
Where the participants matched at baseline	Yes/No/Unsure			
Number of patients randomised				
Details of intervention			Additional details of intervention	
Group	1	2		
Description of Intervention				
Mode of Administration	Inpatient or Outpatient	Inpatient or Outpatient		
Mean IPAP				
Mean EPAP				
Details of follow up				
Were any other outcome measures taken during the study and details of the measures				Additional outcomes
Adverse Events recorded If so full details				
Inclusion Criteria				
Exclusion Criteria				
Other Variables to consider				

$PaCO_2$		Baseline				Follow intervention				Change in following intervention			
Time Point	Intervention Group	Number of participants	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												

Adherence in hours

		Baseline				Follow intervention				Change in following intervention			
Time Point	Intervention Group	Number of participants	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												

		Baseline				Follow intervention				Change in following intervention			
Time Point	Intervention Group	Number of participants	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												

FEV_1		Baseline				Follow intervention				Change in following intervention			
Time Point	Intervention Group	Number of participants	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval	Number	Mean	Standard Deviation	Confidence interval
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												
	1												
	2												

Appendix 7 Gantt Chart