# SYMPTOM MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE USING HIGH FREQUENCY AIRWAY OSCILLATIONS

Thesis submitted for the degree of Doctor of Philosophy at the University of Leicester

by

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# Symptom Management of Chronic Obstructive Pulmonary Disease Using High Frequency Airway Oscillations.

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**Introduction**

Dyspnoea and sputum retention are common problems in patients with Chronic Obstructive Pulmonary Disease (COPD). A High Frequency Airway Oscillating (HFAO) device offers respiratory muscle training and oscillatory mechanism with the aim of addressing dyspnoea and sputum retention, both common symptoms in COPD. The assessment of sputum clearance is challenging due to lack of reliable outcome measures. This thesis aims to assess the feasibility and clinical effectiveness of using a HFAO device in patients with COPD and assess the feasibility and responsiveness of the Lung Clearance Index as a surrogate measure for sputum clearance.

**Methods**

Three main study designs were undertaken to assess the above aims.

1. Systematic review to assess the effect of airway clearance devices on sputum clearance, exacerbation frequency and health related quality of life.
2. Single arm feasibility study to assess the use of HFAO device and LCI.
3. A randomised, double blinded, sham controlled trial to determine the clinical effectiveness of the HFAO device and the response of the LCI to an intervention.

**Results**

The use of the HFAO device is feasible in stable COPD however in a double-blind randomised controlled trial did not demonstrate statistically significant improvements when compared to the sham. There were favourable improvements in the multidimensional dyspnoea profile however this was not significant over the sham. The LCI offers promise in the assessment of sputum clearance, and whilst this worsened following the intervention, there were improvements in peripheral ventilation (measured by the $S_{acin}$).

**Conclusion**

The use of HFAO device does not improve dyspnoea in patients with stable COPD. There was no identified clinical responders' group however further research should focus on patients with frequent exacerbations. The LCI can be a valuable outcome measure in the assessment of sputum clearance when supplemented by the $S_{acin}$.

## Authors contributions

The author of this thesis contributed to the development of and execution of all phases of the studies. The protocol was developed alongside supervisors Professor Sally Singh and Dr Neil Greening. All participants were recruited and assessed by the author. Data was analysed by the author with support from supervisors. The blinding process for the TIDe study was completed by colleagues at the BRC in which the patient was randomised and device packaged and delivered to the patient. Benchmark data for the Aerosure device was performed by Dr Caroline Jolley from Kings College London and provided by Actegy LTD. Professor Salman Siddiqui and Dr John Owers-Bradley provided support in the analysis and interpretation of the Lung Clearance Index. Below list the publications that have occurred as a result of this thesis.

**Abstract publications**

Daynes, E., Greening, N., Singh, S. The use of High Frequency Airway Oscillations versus a sham to reduce dyspnoea in patients with Chronic Obstructive Pulmonary Disease. *ATS conference 2020.*

Daynes, E., Jones, A., Greening, N., Singh, S. The use of devices for airway clearance in patients with Chronic Obstructive Pulmonary Disease- Systematic review and meta-analysis. *ATS conference 2020.*

Daynes, E., Greening, N., Owers-Bradley, J., Siddiqui, S., Singh, S. The effect of high frequency airway oscillations on Lung Clearance Index when compared to a placebo device. *BTS Winter meeting* 2019.

Daynes, E., Greening, N., Owers-Bradley, J., Siddiqui, S., Singh, S. Correlations between the Lung Clearance Index measurements and spirometry in Chronic Obstructive Pulmonary Disease. *ERS International Congress* 2019

Daynes, E., Greening, N., Owers-Bradley, J., Siddiqui, S., Singh, S. Repeatability and comparisons of the LCI in stable Chronic Obstructive Pulmonary Disease. *ACPRC conference* 2019

Daynes, E., Soares, M., Greening, N., Owers-Bradley, J., Singh, S., Siddiqui, S. The feasibility and repeatability of the lung clearance index via multiple breath washout measurements in stable chronic obstructive pulmonary disease. *BTS Winter meeting* 2018

Daynes, E., Soares, M., Greening, N., Owers-Bradley, J., Singh, S., Siddiqui, S. Repeatability of multiple breath washout measurements in stable Chronic Obstructive Pulmonary Disease. *ERS International Congress* 2018

Daynes, E., Harvey- Dunstan, T., Greening, N., Singh, S. Is the use of a novel high frequency airway oscillating device feasible for the management of chronic obstructive pulmonary disease? *BTS Winter meeting* 2017.

Daynes, E., Harvey- Dunstan, T., Houchen-Wolloff, L., Singh, S. The Use of High Frequency Airway Oscillations in Chronic Obstructive Pulmonary Disease- A Pilot Study. *ATS conference* 2017.

**Full text publications**

Daynes, E., Greening, N., Owers-Bradley, J., Singh, S., Siddiqui, S. The feasibility of shortened multiple breath washout testing using sulphur hexafluoride in the assessment of patients with COPD. 2020 *submitted.*

Daynes, E., Jones., A., Greening, N., Singh., S. The use of Airway Clearance Devices in the management of Chronic Obstructive Pulmonary Disease- A Systematic review and meta-analysis of randomised controlled trials. 2020 *Annals of ATS (in press).*

Daynes, E., Greening, N., Siddiqui, S., Singh, S. A randomised controlled trial to investigate the use of high frequency airway oscillations as training to improve dyspnoea in COPD. *ERJ Open Res* 2019; 5.

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I will look back on this journey with fond memories and, in fact, I have had a pretty easy ride as far as PhD's go. I have you all to thank for that! As a token of my thanks, I will not make you read my thesis cover to cover, you know, unless you want to?!?

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## Glossary

ACBT Active Cycle of Breathing Technique

AD Autogenic Drainage

ATS American Thoracic Society

BMI Body Mass Index

CAT COPD Assessment Test

$C_{et}$ End Tidal Concentration of breath

CRQ Chronic Respiratory Questionnaire

COPD Chronic Obstructive Pulmonary Disease

ERS European Respiratory Society

$FEV_1$ Forced Expiratory Volume in 1 Second

FVC Full Vital Capacity

$FEF_{25-75}$ Forced Expiratory Flow 25-75%

GOLD Global institute for Obstructive Lung Disease

HADS Hospital Anxiety and Depression Scale

HFAO High Frequency Airway Oscillations

LCADL London Chest Activity of Daily Living

LCI Lung Clearance Index

LCQ Leicester Cough Questionnaire

MBW Multiple Breath Washout

MDP Multidimensional Dyspnoea Profile

MRC Medical Research Council

NICE National Institute of Clinical Excellence

PEP Positive Expiratory Pressure

PEEP Positive End Expiratory Pressure

$PI_{max}$ Maximal Inspiratory Pressure

$PE_{max}$ Maximal Expiratory Pressure

oPEP Oscillating Positive Expiratory Pressure

RV Residual Volume

$S_{acin}$ Acinar zone slope

$S_{cond}$ Conducting zone slope

$SF_6$ Sulphur Hexafluoride

TLC Total Lung Capacity

V/Q Ventilation perfusion

# 1. Introduction

## 1.1 Overview

Physiotherapists play an important role in the management of Chronic Obstructive Pulmonary Disease (COPD) with an emphasis on dyspnoea management and secretion clearance in both acute and stable disease. Whilst this is a well-established profession, the research in this area is scarce and dated. The use of positive pressure devices is amongst the vast treatment techniques respiratory physiotherapists utilise. In the United Kingdom, the provision of these devices is limited for numerous reasons. Firstly, the primary use of devices is to aid secretion clearance, and the definition of COPD frequently dismisses sputum retention as a symptom[1]. Mucus hypersecretion and retention affects 2.7-22% of the COPD population of which increases during periods of an exacerbation, however its usefulness in clinical diagnosis remains questioned[2]. Secondly, quantifying secretion clearance is difficult, with both objective and subjective measures remaining unreliable and difficult to interpret. Thirdly, the provision of devices is limited by its cost. Current guidelines state the use of devices can be considered in an exacerbation however its provision for long term sputum retention is not recommended[3]. Additionally, there are low cost alternatives such as breathing exercises that affect the provision of devices however, these are difficult to implement and requires a level of cognitive function and coordination that is often impaired in patients with COPD, particularly during an exacerbation[4].

A second device developed for COPD can also be used to improve respiratory muscle strength which has previously demonstrated improvements in dyspnoea and quality of life, however, its improvement over and above pulmonary rehabilitation is difficult to demonstrate and there is huge disparity in the research[5]. It is feasible that training to address secretion retention and dyspnoea in combination may lead to greater improvements in symptoms and health related quality of life compared to a control. The

Aerosure© by Revitive was designed as a duel functioning device for both respiratory muscle training, by way of flow resistance and, airway clearance by utilising oscillating positive expiratory pressure (oPEP). This aims to treat dyspnoea and secretion clearance, respectively. This device was designed for patients with respiratory diseases, including COPD however its use in the management of dyspnoea and secretion retention in patients with COPD is unknown.

As secretion clearance is difficult to quantify and apply meaning, the use of the Lung Clearance Index (LCI) may provide valuable insight. The LCI is measured via a multiple breath washout (MBW) which explores ventilation heterogeneity and is a measure of small airway disease. This measure could provide an objective marker of secretion clearance in COPD and strengthen the quality of physiotherapeutic evidence. The theoretical basis and application of this technique will be discussed in later chapters (chapters 1 and 3).

The initial part of this introductory section will explore the pathophysiology of Chronic Obstructive Pulmonary disease and its impact on symptoms and lung mechanics. Mucus hypersecretion and dyspnoea will be explored in detail and common treatment modalities for these clinical presentations. In order to understand the practical application of the LCI, lung heterogeneity will be explored.

## 1.2 Chronic Obstructive Pulmonary Disease (COPD)

### 1.2.1 Definition

COPD has been identified since 1679 when Bonet described 'voluminous lungs' in which, case studies had identified lung tissues as turgid, particularly from air[6]. Chronic cough and mucus hypersecretion became cardinal symptoms from the 1800's as identified by Badham[7]. Since then our understanding of COPD has continued to thrive[8]. In 1962 the American Thoracic Society committee on diagnostic standards defined the components of

Chronic Bronchitis and emphysema which have become the foundation for the modern definitions of COPD. Chronic bronchitis was historically defined by chronic cough lasting more than three months for at least two years whereas emphysema was pathologically described as enlarged alveolar spaces and loss of alveolar walls[9]. Since these classifications, the two diseases have been coined under the term "Chronic Obstructive Pulmonary Disease" or "COPD".

Recent definitions by the Global Lung Initiative for Obstructive Lung Disease (GOLD) defines COPD as "a preventable and treatable disease with some significant extra-pulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterised by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with abnormal inflammatory response of the lung to noxious particles or gases"[10]. This definition characterises COPD by airflow limitation and encompasses smoking and noxious stimulus as a contributing factor in light of occupational dust and air pollutants research[11]. The phrasing of 'preventable' and 'treatable' allows for a more positive outlook for patients with this diagnosis. The Global Lung Initiative have also identified the need for early diagnoses and interventions. Spirometry should be used on all patients with suspected COPD; however, spirometry is not sensitive to early changes in the airways and often will appear normal in the presence of early lung disease. Additionally, general practice surgeries have access to spirometry equipment but may lack the ability to interpret these results which can hinder diagnosis[12].

It is predicted that 90% of COPD cases are caused by smoking in the UK and it is estimated that 25% of all smokers develop COPD[13]. It has been suggested that some people are more susceptible to the effects of smoking or other noxious stimulus such as occupational dust exposure. Predisposing factors includes gender and socioeconomic factors[14]. COPD affects more males than females, with 10% more males living with COPD in the UK, however this is likely due to exposure to risk factors rather than susceptability[15]. The socioeconomic gradient is greater than that of other disease populations, those from low to middle income

areas have an increased risk of mortality and symptoms, and a reduced lung function. This may be due to increased exposure to noxious stimuli such as smoking and occupational dust due to manual jobs. Education and income status greatly affects outcomes impacting on a patient's COPD management and access to healthcare[16].

### 1.2.2 Epidemiology

It is estimated that that 1.2 million people are living with a diagnosis of COPD- the second most common lung disease in the UK, after asthma[15]. This is an increase of 27% in the last decade with predictions of a continuous rise in diagnoses[15]. At present COPD is the fourth leading cause of mortality in the world and is expected to increase to third by 2020[17]. Currently, it is the fifth leading cause of years lost through disability which has increased from twelfth in 1990. The UK ranks twelfth for COPD mortality, with 210 per million deaths per year[18]. Whilst initiatives such as the smoking ban, and cigarette packaging regulations have reduced smoking incidences in the UK, the effects of this will not impact the incidence of COPD until much later. Increase prevalence of COPD may be a result of improved and early diagnosis and management, better understanding of causes and the aging population[17]. As a result, there is a need for management of debilitating symptoms such as breathlessness and further prevention strategies to reduce incidences.

The total annual cost of COPD to the NHS is estimated to be over £800 million in direct healthcare costs. It is estimated that a further £2.7 billion costs the economy in reduced productivity due to a loss of workdays. Improvement in management and effective treatments for patients with COPD is likely to result in fewer hospital admissions. A 5% reduction in admissions can save £15.5 million per year[19]. COPD causes a large burden on the healthcare system and the individual and therefore effective management is paramount. The NHS Long term plan outlines ambitions for the coming ten years and has acknowledged respiratory disease as a key priority and aims to tackle this burden in a

number of ways including enabling early diagnosis, expanding pulmonary rehabilitation services and encouraging self-management[20].

### 1.2.3 Diagnosis

A diagnosis of COPD is commonly based on symptoms and this is confirmed by spirometry results with considerations to associated risk factors[21]. A diagnosis of COPD should be considered in those over 35 years old who have had a long exposure to smoking or occupational dust hazards who present with one or more of the following symptoms: exertional dyspnoea, chronic cough, regular sputum production, frequent winter bronchitis or a wheeze. When suspected, post bronchodilator spirometry should be performed to diagnose and repeated to determine if patients show an exceptionally good response to treatment. Diagnostics should occur during stable disease and should be performed in the absence of a chest infection, or exacerbation. Spirometry is a measure of the large airways and is not a sensitive marker of small airway dysfunction, which often occurs before spirometry results indicates impairment. The Forced Expiratory Volume in 1 second ($FEV_1$) and Full Vital Capacity (FVC) are measured in spirometry and its ratio ($FEV_1$/FVC) is required to be below 0.7 to consider a diagnosis of COPD. Whilst guidelines reference a $FEV_1$/FVC value below 0.7, a patient's lower limit of normal is more accurate for diagnosis, given that lung function declines as a result of age. The use of 0.7 as a reference point is utilised in order to simplify diagnosis and encourage primary care practitioners to perform and interpret spirometry results leading to timely and accurate diagnosis and subsequently early interventions [10, 22]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) provides a classification of airflow obstruction severity as outlined in the table below (table 1.1).

*Table 1.1 Gold staging classification*

| GOLD Stage | COPD severity | $FEV_1$/FVC Ratio | $FEV_1$ Range |
|---|---|---|---|
| I | Mild | <0.70 | ≥80% of predicted normal |
| II | Moderate | <0.70 | 50%-79% of predicted normal |
| III | Severe | <0.70 | 30%-49% of predicted normal |
| IV | Very Severe | <0.70 | <30% of predicted normal or <50% of predicted normal with chronic respiratory failure present. |

*Table 1.1 GOLD Global Lung Initiative for Obstructive Lung Disease. COPD Chronic Obstructive Pulmonary Disease. $FEV_1$/FVC Forced Expiratory Volume in 1 second/ Full Vital Capacity Ration. $FEV_1$ Forced Expiratory Volume in 1 second.*

Spirometry should be performed by a competent healthcare professional (defined as Association of Respiratory Technology and Physiology ARTP accredited in the UK) and used in conjunction with a patient's history and presenting condition. It is estimated that up to 40% of COPD cases are misdiagnosed therefore rigorous diagnosis is paramount[23].

COPD has developed as a diagnosis replacing terms such as chronic bronchitis and emphysema, and instead differences are acknowledged through the presence of different phenotypes. It can be defined as a continuum of a disease leading to a wide variety of symptoms and physiological changes with a plethora of overlap. Due to variability in disease presentation and symptoms, recent GOLD guidelines categorise symptom severity of COPD with an alphabetical system[21]. This system utilises the modified Medical Research Council (mMRC) dyspnoea score and the COPD Assessment Test (CAT) for symptom severity. These measures are discussed further in Chapter 3.

| | | |
|---|---|---|
| ≥2 exacerbations or ≥ 1 leading to a hospital admission | C | D |
| 0 or 1 exacerbations (not leading to a hospital admission) | A | B |
| | mMRC 0-1<br>CAT < 10 | mMRC ≥ 2<br>CAT ≥ 10 |

*Figure 1.1 GOLD ABCD assessment tool*[21]

The use of the ABCD tool can be used in conjunction was the traditional GOLD staging, for example a patient with <30% $FEV_1$ predicted, one exacerbation and MRC 2 would be classified as a GOLD Stage IV B. Alternatively a patient with <30% $FEV_1$ predicted, one hospital admission in the previous 12 months and MRC 5 would be considered a GOLD stage IV D. This can provide greater insight into pathophysiology and symptoms of COPD which may better guide treatment.

### 1.2.4 Pathophysiological changes and clinical symptoms

Chronic Obstructive Pulmonary Disease (COPD) is characterised by an expiratory flow limitation with slow forced emptying of the lungs due to a combination of airway abnormalities and emphysematous changes[24]. Airflow limitation is progressive and not fully reversible leading to an associated abnormal inflammatory response caused by a lifetime of exposure to noxious particles or gases[25]. Pathological changes are primarily found in the proximal and peripheral airways, lung parenchyma and pulmonary vasculature. An increase in macrophages and lymphocytes, enlargement of submucosal bronchial gland, goblet cell metaplasia and ciliary dysfunction, can result in alveolar wall destruction and subsequently common symptoms such as dyspnoea and increased mucus production[25]. As a result of these changes individuals with COPD experience an adaptive immune response attributed to large antigen load associated with bacterial colonisation, frequent lower respiratory tract infections or potentially an autoimmune response. These pathogenic mechanisms can result in physiological changes such as mucus hypersecretion, ciliary dysfunction, airflow limitation, gas exchange abnormalities and systemic consequences.

Mucus hypersecretion and ciliary dysfunction contribute to symptomatic cough and difficulty expectorating, which in turn can increase the risk of respiratory infections. It is plausible that this can contribute to airflow obstruction, however the primary driver for this limitation is inflammation, narrowing, airway remodelling and inflammatory exudates in the small airways. Loss of elastic recoil occurs as a result of destruction to the alveolar wall, which can progressively lead to air trapping and resultant hyperinflation. This reduces inspiratory capacity and functional residual capacity approaches total lung capacity resulting in dyspnoea and exercise limitation, which are hallmarks of COPD[26].

Changes in lung structures and mechanics can lead to abnormalities in gaseous exchange. This is primarily caused by regional inequalities of ventilation and perfusion (V/Q) mismatch[27]. Emphysematous destruction of the pulmonary capillary bed increases the

physiological dead space. This is demonstrated by multiple inert gas washout techniques, in which those with an identified emphysematous phenotype display increased ventilation of poorly perfused lung units (high V/Q ratio) and an increased likelihood of hypoxaemia[28]. Conversely those with significant airway disease are more likely to demonstrate a low V/Q ratio, with heterogenous alveolar hypoventilation and substantial perfusion of under ventilated areas which consequents in a physiological shunt. COPD exacerbations often lead to deterioration of gaseous exchange. This is often due to an increased tissue consumption of oxygen with resultant decreased mixed venous return of oxygen tension, which is partially offset by an increase in cardiac output[28]. It has been identified that exercise may improve V/Q ratio in mild COPD patients due to improvement in the distribution of ventilation. Conversely, severe diseases V/Q mismatching and peripheral oxygen consumption is increased which can result in exertional dyspnoea[29, 30]. Longstanding hypoxaemia can contribute to the development of other comorbidities such as respiratory failure, type three pulmonary hypertension ("cor pulmonale") and therefore its management is essential[31].

The identification of phenotypes can develop our understanding of the complex physiology each patient may be exhibiting. The traditional classification of COPD relies solely on spirometry and fails to account for the complexity and heterogeneity of the disease. Phenotyping can identify single or combination disease attributes which can lead to tailored treatment and has been associated with clinically meaningful results. Current research has failed to identify specific subsets of patients that allows for generalisability as identified in a systematic review by Pinto et al (2015)[32]. Chronic bronchitis and emphysematous phenotypes are often referred to in the literature however this appears to have derived from previous definitions and diagnoses prior to the classification of the umbrella term COPD rather than based on rigorous research[32]. Whilst phenotyping may add value as a prognostic indicatory and as a strategy in physiotherapeutic management to assist with treatment priorities.

## 1.3 Breathing Mechanics

### 1.3.1 Physiology in Health

Breathing is controlled primarily in the brainstem at the medullary respiratory centre, pneumotaxic centre and alongside the apneustic centre. The medullary respiratory centre is responsible for respiratory rhythm which the apneustic centre is thought to contribute to also. The pneumotaxic centre can inhibit inspiration which shortens inspiratory time and increases respiratory rate. Voluntary control can be obtained in the cortex, typically hyperventilation is easy to achieve but hypoventilation is more difficult. Other parts of the brain such as the limbic system and hypothalamus can alter the pattern of breathing in response to emotions such as fear, rage and anxiety. Constant impulses are sent to the effectors, the muscles of respiration, which will be discussed later. There are several sensors involved in the control of ventilation; the central chemoreceptors surround the extracellular fluid and responds to change in the blood hydrogen levels. An increase in partial pressure of carbon dioxide diffuses into the cerebral spinal fluid and therefore releasing hydrogen ions to stimulate chemoreceptors[33]. There are peripheral chemoreceptors in the carotid arteries which respond to a decrease in partial pressure of oxygen and responds to arterial hypoxaemia. Pulmonary stretch receptors are found in the airway smooth muscle and increases expiratory time during exercise. Irritant receptors lie between the epithelial cells and the airways. These are stimulated by noxious gas, cigarette smoke, inhaled dust and cold air. Impulses travel up in myelinated fibres and causes bronchoconstriction and hyperpnoea. J-receptors are believed to have a role in dyspnoea although the exact mechanism is not known. They are situated in the alveolar wall close to the capillaries and result in rapid shallow breathing. The stimulation of these receptors ultimately controls how the respiratory centres react and sends the commands to the effectors, the muscles of respiration[34].

Breathing is a coordinated activity of the respiratory muscles to generate a sub-atmospheric pressure in order to produce ventilation. The primary driver for inspiration is the diaphragm, which is inserted into the lower ribs and supplied by the phrenic nerve (cervical segment 3, 4 and 5). Contraction of the diaphragm lifts the rib margins causing an increase in transverse diameter of the thorax. During tidal breathing the diaphragm descends approximately 1cm however on exertion this can increase to 10cm. The intercostal muscles cause an increase in lateral and anteroposterior diameter. The scalene and sternocleidomastoid muscles in addition to some small muscles in the face and neck (such as the alae nasi) can be used as accessory muscles of respiration. During quiet breathing these do very little, however can be utilised when breathing becomes laboured[33]. These muscles have a higher oxygen cost and are not designed for endurance, however are often relied on by patients with severe COPD[35].

Expiration is typically passive during quiet breathing in health as elastic recoil returns the chest wall back to its previous equilibrium. The elastic structures in the lung tissue and the surfactant that lines the alveolar wall ensures the chest wall returns to its original state without any effort. During voluntary hyperventilation, the abdominal muscles and intercostal muscles are recruited in coordination to ensure enough air is expired in preparation for the next inspiration. Rectus abdominas, internal and external oblique's, and the transverse abdominas, on contraction, increase the intra-abdominal pressure therefore pushing the diaphragm to its original domed position. The internal intercostal muscles pull inward and stiffen during training however research suggests that the intercostal's are more complicated than this account[36, 37].

The work required to move the lung and chest wall for ventilation can be calculated as pressure times by volume. The oxygen cost of quiet breathing is minimal at 5% to 10%. Voluntary hyperventilation can increase this cost to 30% however as breathing mechanics alter in lung disease this oxygen cost can increase further causing exercise limitation[38].

### 1.3.2 Breathing mechanics in COPD

The previous section explores breathing mechanics in the absence of respiratory disease however, pathophysiological changes and adjustments essential to maintain a functional breathing pattern, requires altered mechanics. The inability to maintain the required work of breathing in order to meet ventilatory demands results in severe dyspnoea, the body attempts to address this by causing anatomical and structural adaptations. Reportedly the most distressing symptom among patients with COPD is the feeling of "air hunger"[39]. This occurs when respiratory muscles are working near their capacity to meet the ventilatory demands[33]. Hypercapnic respiratory failure results when muscles can no longer provide sufficient ventilation to meet the metabolic demands. A combination of increased inspiratory resistance, increased elastane of the lung and chest wall, increased expiratory resistance, decreased gaseous exchange efficiency, extrinsic resistance and dynamic hyperinflation can all increase work of breathing within patients with COPD[33]. As a result, the muscles of respiration can become overworked or malfunctioning.

In healthy subjects the inspiratory resistance is relatively low. The effective resistance of the relaxed chest wall is caused by low pressure-volume hysteresis. This measured resistance is small in normal breathing and is largely a result of a loss in passive muscle. Pulmonary resistance is typically less than $1cmH_2O$[40]. In those with COPD there is an increased resistance. The causes of inspiratory resistance are well described and occurs as a result of long-term exposure to noxious gases and particles. The primary defence against this stimulus are the innate and adaptive immune and inflammatory response. Several mechanisms contribute to inspiratory resistance, by which: inflammation and oedema cause thickening of the bronchial mucosa; there is an increase in inflammatory infiltrate; hyperplasia of the mucus gland occurs; smooth muscle hypertrophy; inflammatory exudates and mucus impinges the airway lumen. Those who display a largely emphysematous picture have less mucosal inflammation and a greater destruction of small airways and loss of parenchymal attachments that stent the airways open and increases flow resistance[41]. The repair process remodels damaged tissue in an attempt to restore to its original state,

however, this often becomes fibrosed and inelastic. There is a strong correlation between thickening of the airway wall and the severity of COPD[41].

Some of the work performed by the respiratory muscles is stored as elastic potential. The elasticity of the respiratory system is defined by the change in inflating pressure divided by the change in volume. Exhalation is the result of a balance between the elastic recoil of the lungs prompting airflow and the airways limiting flow. Those with COPD experience a loss of elasticity in the wall of the small airways due to a reduction in the elastic tissue in the parenchyma and therefore require more active expiration. The absence of cartilage in the wall of the peripheral airways contribute further to loss of elasticity[42]. Changes in elastic properties effects the pressure generated during respiration. Under normal physiological conditions the respiratory muscles provide adequate power to create changes in pressure. The attainable end inspiratory and end expiratory volumes are determined by the pressure-volume relationship. Figure 1.2 demonstrates the pressure- volume relationship in normal lungs and in those affected by airway narrowing and emphysema. The lungs are most compliant between 20-80% of vital capacity. Patients with COPD experience changes in elastic recoil and will be breathing at a rate close to 80% of their vital capacity, on exercise the pressure required will fall outside of the optimum 20-80% range and therefore compliance is reduced[43]. Loss of elasticity can limit flow in patients with COPD and factors contributing to obstruction (discussed in later chapters) provide resistance and therefore expiratory flow is severely compromised[44].

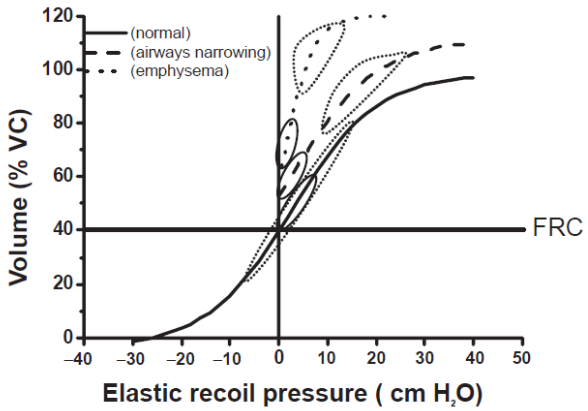



*Figure 1.2: Pressure-Volume relationship of the passive respiratory system of healthy individuals, those with airway narrowing and emphysematous (COPD) patients. Closed loops demonstrate tidal breathing at rest and dotted loops represent tidal breathing on exercise. FRC Functional Residual Capacity, VC Vital Capacity*[43]

Limitations in expiratory flow and increased resistance are critical due to the development of dynamic hyperinflation. Dynamic hyperinflation is the progressive over-inflation of the lungs during activity. When the inhaled tidal volume exceeds the volume exhaled, dynamic hyperinflation occurs. This temporary inequality leads to an increase in end-expiratory volume which increases expiratory flow rate. Dynamic hyperinflation is shown in figure 1.3[27]. The degree of expiratory flow limitation is dependent on the lung volume range in which the breathing occurs. Dynamic hyperinflation hinders breathing by decreasing inspiratory capacity of the chest wall and increasing elastic load of breathing, but also facilitates exhalation by increasing expiratory flow rates and therefore is essential for maintaining ventilation in the face of severe expiratory flow limitations[45]. It is estimated that during exercise the volume of dynamic hyperinflation is 350ml[46]. Dynamic hyperinflation is accompanied by dynamic intrinsic positive end expiratory pressure (PEEP). Dynamic PEEP represents a threshold load that must be overcome to initiate inhalation, and therefore increasing the work of breathing[46]. In addition, dynamic hyperinflation profoundly reduces the capacity of the inspiratory muscles to generate force and shorten, decreasing

the ventilatory reserve capacity and increasing the effort and sense of dyspnoea[45]. A recent study has also shown that dyspnoea perception can lead to dynamic hyperinflation as a result of increasing minute ventilation in an attempt to meet ventilatory demands in patients with COPD[47]. Therapeutic interventions to manage hyperinflation will be discussed further in this chapter.

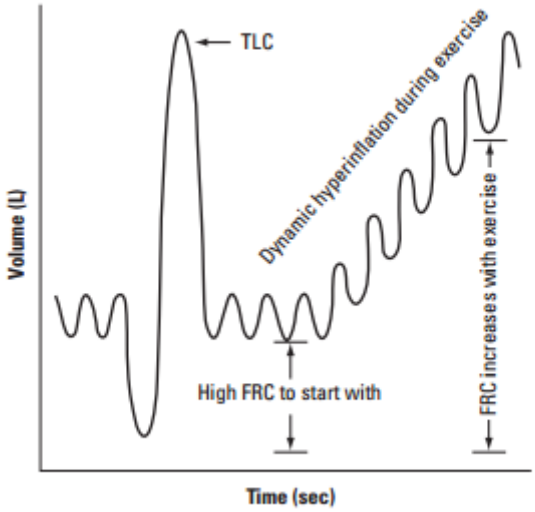



*Figure 1.3 Dynamic Hyperinflation in patients with COPD during exercise.*[27]

Individuals with COPD have diminished gas exchange efficiency of the lung which increases ventilatory requirements at rest and on exertion. Inhomogeneities of ventilation and perfusion result in an increased alveolar dead-space and therefore increases the ventilatory requirements in order to maintain normal levels of carbon dioxide and oxygen. Abnormalities in gas partial pressures can increase respiratory drive, and secondary air hunger if ventilation cannot meet the demands. Furthermore, an increase in ventilation will cause an increase in the volume of dynamic inflation in which patients may begin to retain carbon dioxide. Additionally, some individuals with COPD have a blunted response to high levels of carbon dioxide which can further worsen patient's symptoms[48]. This results in a phenomenon known as the hypoxic drive theory, in which a patient's respiratory drive is

determined by oxygen chemoreceptors as an alternative to carbon dioxide receptors, however this theory does not appear to have an evidenced premise[48]. High flow oxygen therapy has been demonstrated to induce hypercapnia in severe COPD but its exact mechanisms on chemoreceptors remain unknown[49]. Hypoxic pulmonary vasoconstriction is the most efficient way to alter V/Q ratios and improve gaseous exchange[48].

Changes to the chest wall such as obesity or hyperinflation can contribute to altered breathing mechanics of patients with COPD. These are known as extrinsic factors and can alter the position of the respiratory muscles and therefore reducing the efficiency of breathing. During hyperinflation the diaphragms and intercostal muscles are on a stretch and therefore are unable to generate the required pressure at this end of range[33]. These factors contribute to the mechanics of breathing and the individual's capacity to meet ventilatory demands.

The muscles of respiration are responsible for generating the pressure differences driving ventilation, and therefore weakness may be a clinically important feature in those with conditions affecting the respiratory system or respiratory drive. Respiratory muscle strength should be distinguished from lung function abnormalities and therefore should be measured independently Whilst respiratory muscle force has been demonstrated to be an important predictive factor for poor survival in COPD, this is not routinely assessed in the UK. Expiratory muscle weakness can lead to problems with speech and mucus frequency as a result of impaired cough efficiency, therefore this is a crucial outcome in assessing the impact of HFAO in COPD[50]. The changes in breathing mechanics require the muscles of respiration to work harder and as a result are often less efficient. As a result, patients utilise accessory muscles of respiration that have a higher oxygen cost and further increasing the work of breathing. Combined with changes in chest wall means the muscles of respiration may be weakened and are also required to work harder. This becomes even more evident on exertion.

### 1.3.3 Breathing response to exercise

Gaseous exchange demands of the lungs are increased during exercise. Typically resting oxygen consumption can rise from 300ml per minute to 3000ml per minute in relatively fit subjects[33]. This rise can also be seen in carbon dioxide exchange, which may become problematic for patients who suffer with carbon dioxide retention due to a blunted response to carbon dioxide. In order to meet these demands, diffusion capacity increases due to changes in the membrane and increased blood flow throughout the lung. Individuals with COPD have difficulties matching the demands of the ventilation due to the reasons discussed above, such as chest wall abnormalities and changes in gaseous exchange. During exercise dynamic hyperinflation can prevail and ultimately lead to premature exercise termination.

## 1.4 Dyspnoea

### 1.4.1 Causes and implications

It is estimated that 1.2 million people are living with a diagnosis of COPD, with predictions that incidences are increasing[13]. The common most complaint in COPD is dyspnoea which results in reduced exercise capacity and is frequently the main driver for seeking medical attention. Clear understanding of the underlying mechanisms of dyspnoea is necessary for its management within COPD. Dyspnoea is the result of a complex interaction of physiological, psychological, social and environmental factors. There are several sensory receptors located throughout the respiratory system considered responsible for the generation of dyspnoea however; there is no identified afferent receptor responsible for this sensation[34]. Dyspnoea can be considered in at least three distinct sensations, including air hunger, work and effort, and chest tightness[51]. It can be explored in two different dimensions, sensory and affective. Neuroimaging studies have suggested that neural

structures interpreting pain and dyspnoea may be shared, and therefore a neurophysiological and psychophysical approach must be utilised[34] .

### 1.4.1a Physiological causes of dyspnoea

There are several physiological factors that contribute to the sensation of dyspnoea. Sensory receptors detect changes in the respiratory system and respond accordingly. Chemoreceptors respond to pH, $pCO_2$ and $pO_2$ centrally and peripherally. Acute hypercapnia and hypoxia ($PaCO_2$ >6.0kpa, $PaO_2$ <8.0kpa) is thought to contribute to the sensation of air hunger and results in increase respiratory motor output. Metaboreceptors, located in the skeletal muscles, are believed to respond to local changes in the tissue environment. It is hypothesised that metaboreceptors are responsible for exercise induced dyspnoea however, increased ventilation occurs in the absence of hypoxaemia or hypercapnia and metabolic acidosis occurs relatively late during intense exercise. Little is known about vagal receptors and the contribution to dyspnoea however it is thought that these receptors monitor change in flow via the detection of temperature. It has been suggested that cool air stimulating these receptors can reduce dyspnoea however its mechanism remains unknown. Slowly adapting stretch receptors are found in the smooth muscle of the large airway and have been shown to reduce dyspnoea[34]. Conversely, rapidly adapting stretch reflex maintain inflation and deflation of the lungs and are activated by large number of mechanical and chemical irritants and as a result increases the sensation of dyspnoea. There are two kinds of C-receptors, juxta-pulmonary (J-receptors) and bronchial C-receptors. It is thought that these receptors respond to an increase in interstitial fluid outside the alveoli and contributes to exercise induced dyspnoea. Afferent signals in the joints, muscles and tendons of the chest project to the brain and contribute to the generation and modification of dyspnoea[33]. Vibration of the chest wall has been shown to activate muscle spindles and when activated outside of the respiratory cycle can increase the sensation of dyspnoea. Air hunger can be relieved by vagal afferents alone, thus the level of air hunger is a function of prevailing respiratory centre drive and inverse function of increased minute ventilation[26].

The neural pathways of dyspnoea are unknown and as it results in several distinct sensations it is likely to follow several pathways. Afferent information from respiratory muscles and vagal receptors are relayed in the brainstem and projected into the thalamic area. Neuroimaging studies have demonstrated that dyspnoea activates several distinct areas in the brain cortex, which is comparable to pain literature. That said, they do not necessarily follow the same pathways. There is a theory that suggests a mismatch between motor command and incoming afferent information. Campbell and Howell proposed that the inappropriateness of the length tension relationship of the respiratory muscles can trigger dyspnoea[52]. Under normal circumstances there is an appropriate relationship between respiratory muscle tension and the resultant volume or flow[52]. However, several studies have refuted this theory in high spinal cord injury paralysis[52]. This suggests that respiratory muscle contraction is not important in the generation of air hunger. The original theory has been developed and expanded to suggest dyspnoea is a result of dissociation between ongoing motor signals to the respiratory muscles and incoming afferent information[34]. This concept is difficult to prove since it is not easy to quantify the central respiratory activity and afferent feedback signals. Nevertheless experimental and clinical data support the theory of neuromechanical dissociation[34]. The central processing of dyspnoea is yet to be established and it is unclear if the identification of afferent and sensory dimensions of dyspnoea results in different cortical processing. It has been demonstrated in healthy subjects with induced air hunger have a strong activation of the anterior insular cortex[53]. Research suggests that the right posterior cingulate cortex may relate to the affective dimension of dyspnoea and the unpleasantness of dyspnoea is processed in the right anterior insula. All present studies have shown activation of the anterior insular cortex which indicates that unpleasant sensations produced by different respiratory challenges are processed in the same areas[34]. There is increasing evidence that the anterior insular cortex, which is also responsible for the interpretation of pain, acts as a centre of interception and plays a fundamental role in conscious awareness of unpleasant sensations[34]. This theory however ignores the contribution of psychological, social and environmental factors.

### 1.4.1b Psychological contributions

Dyspnoea is a subjective symptom and therefore is impacted by many other factors, including psychological state. There is a close relationship between dyspnoea and psychological functioning, with anxiety being a common symptom in respiratory diseases, however anxiety and dyspnoea does not directly correlate and therefore it is fair to assume that whilst this may be a contributor to dyspnoea, there is not a causal relationship[54]. Similarly, dyspnoea is a common symptom for psychiatric disorders such as panic attacks and agoraphobia supporting a relationship between psychological contributions to dyspnoea[55]. There has been a link between perceived intensity and distress in relation to dyspnoea and affective unpleasantness[55]. The affective dimension of perceived dyspnoea is specifically vulnerable to emotional wellbeing and may be influential in seeking medical attention. Studies have demonstrated that negative emotions decrease the accuracy of dyspnoea perception[56]. Patients with asthma have demonstrated higher incidences of dyspnoea during periods of negative mood[57]. Learning processes are also associated with the perception of dyspnoea alongside physiological pathways[55]. It is feasible that the learning pathway can become the main pathway in relation to dyspnoea and may result in inaccurate representation of this sensation. Continuous activation of neural pathways contributing to dyspnoea, may lead to a heightened response and sensitivity to dyspnoea, which is comparable to chronic pain literature[56]. Research surrounding psychological mechanisms of dyspnoea are scarce however is a crucial consideration in the management of COPD.

### 1.4.1c Social and environmental

Experiences of dyspnoea are shaped by social and environmental factors. This effects how patients understand their symptoms and when health seeking, and treatment is deemed appropriate. Dyspnoea is perceived differently amongst different disease population and is weighted by the underlying connotation of the symptom. For example, patients with cancer

had an association with mortality and prognosis whereas patients with COPD felt emotions of self-infliction[58]. External causes have an impact on patients control and responsibility. Medical cultures and distinct treatment approaches can influence perceptions. Some disease populations focus primarily on cure, whereas patients with COPD are less likely to seek medical attention in relation to dyspnoea due to the chronicity of the disease. As disease progresses the burden of dyspnoea increases, and as a result impacts quality of life and mood and therefore increasing the psychological influence of dyspnoea. Healthcare professional's responses to dyspnoea can impact the patients' perception of dyspnoea and is often ignored in the absence of physiological explanation[59]. Figure 1.4 demonstrates the interaction between physiological, psychological and functional impacts of dyspnoea. The breathing, thinking, functioning model acknowledges a variety of causes of dyspnoea that will vary between individuals with each one impacting on the other and contributing to the cycle of breathlessness.

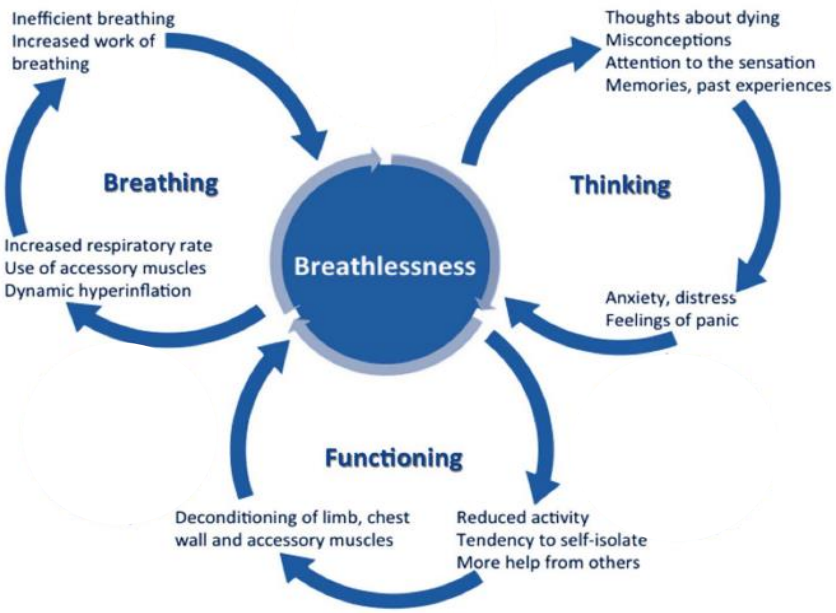



*Figure 1.4 Cycle of Breathlessness (adapted from Chin and Booth 2016[58]).*

### 1.4.1d Quality of Dyspnoea

Dyspnoea subsumes a variety of uncomfortable respiratory sensations and three primary descriptors have been acknowledged: air hunger, work of breathing and chest tightness. This division explores further the quality of dyspnoea and it is hypothesised that each sensation has a different afferent pathway[51]. Laboratory studies have isolated these sensations in order to gain deeper understanding however, it is likely that these symptoms occur together. It has been hypothesised that the perception of dyspnoea is independent of sensory intensity and rating scales do not make the distinction between quality and quantity therefore complicating assessment and data analysis. The exploration of multiple dimensions of dyspnoea may enable the translation from laboratory to clinical settings. The primary goal of understanding dyspnoea and its mechanisms is to adequately target treatment strategies[60]. There are a range of treatment strategies for dyspnoea that will be discussed in later sections. Treatment for this symptom is important for patients and therapists as it can be debilitating and impact on many aspects of a patient's life.

### 1.4.2 Effects of dyspnoea

Dyspnoea has been shown to impact on health-related quality of life and leads to an inability to perform daily tasks[58]. Patients frequently reduce their activities in order to avoid the unpleasant sensation of dyspnoea. Furthermore, the two may be closely related as both are measures of patient's perceptions and it has been discussed that an improvement in dyspnoea may lead to improvements of health-related quality of life. Anxiety and depression are prevalent within COPD and is associated with health-related quality of life[55]. Schneider et al demonstrated that the incidence of depression was 16.2 cases per 1000 person-years in patients with COPD compared to 9.4 cases per 1000 person-years within non-COPD control group. Furthermore, those with severe COPD were more likely to develop depression than that of the mild population[61]. A meta-analysis of 25 studies with long term follow up revealed that depression is likely to be bidirectional as depression may be both a

cause and a consequence of COPD[62]. The interrelationship between smoking, depression and/or anxiety and COPD are unclear though, associations between anxiety disorders and COPD appear to be largely explained by confounding factors such as previous smoking history and nicotine dependence[56]. However, these cross-sectional associations do not allow for inference of causality but identify a need for specifically designed trials. Further evidence suggests that low grade chronic inflammation mediates the association of depressive symptoms and pulmonary function[63]. Elevated levels of interleukin-6 and C-reactive protein were documented in both COPD and late-life depression[61]. Biological, behavioural and social factors may also contribute to physical disability and social isolation in COPD.

Furthermore, dyspnoea has a large impact of patient's exercise tolerance. Typically, COPD patients abstain from exercise due to dyspnoea and results in reduced exercise capacity. Disuse and inactivity are important pathogenesis of skeletal muscle dysfunction; however, this is exacerbated by systemic inflammation, malnutrition, corticosteroid use, hypoxia, aging and smoking[2]. Reduced limb strength in patients with moderate COPD contributes to poor exercise performance, increased dyspnoea and reduced quality of life. Lower limb muscle reduction is a powerful predictor of mortality in severe COPD patients[64]. Therefore, patients with COPD and symptomatic dyspnoea are likely to experience reduced quality of life, increased presence of anxiety and depression, decreased activity, exercise tolerance and muscle strength. In addition, patients with COPD develop other distressing symptoms such as cough or mucus hypersecretion.

### 1.4.3 Measures of dyspnoea

Measuring dyspnoea is challenging due to its complexity and as a result there are numerous tools that measure these different aspects. There are many questionnaires that assess dyspnoea that can be categorised into the breathing, thinking, functional model (figure 1.5)[58]. The most common is measuring severity of dyspnoea, such as the Borg breathlessness scale, which measures dyspnoea on a 0-10 Likert scale[65]. This tool can be

useful in assessing both baseline dyspnoea and in response to an activity or exercise. It is simple to administer and is supplemented with phrases to assist the interpretation as some patients find a numerical rating scale difficult. This tool can also be useful as a marker to assess how difficult patients are finding exercise and can be used to guide intensity. Other questionnaires such as the Multidimensional Dyspnoea Profile (MDP) also uses numerical rating scales to assess intensity however the MDP also assess types of dyspnoea sensations (such as work effort or concentration) and provides a sensory score and emotional score by assessing common emotional responses to dyspnoea (such as frustration and anxiety)[66]. The MDP is validated in respiratory conditions but there has been no exploration of sensitivity to change. There are some specific and non-specific assessments of the thinking aspect of dyspnoea. The COPD Anxiety questionnaire is a specific assessment of dyspnoea related anxiety however this is not widely used. The Hospital Anxiety and Depression scale is a generic measure of anxiety and depression that is validated in many disease groups, however, does not explore specifically dyspnoea related anxiety. The Chronic Respiratory Questionnaire (CRQ) measures functional responses to dyspnoea by asking patients to select activities that are making them breathless and scoring them from extremely breathless to none at all, which allows for individualised assessment of dyspnoea and is validated in patients with COPD[67]. Similarly, the Medical Research Council dyspnoea scale measures functional dyspnoea with five statements for patients to compare their breathlessness to, however this is not sensitive to change (Chapter 3, table 3.1)[68]. The London Chest Activities of Daily Living questionnaire explores common activities and how breathless they make the patient from not breathless to severely breathless[69]. This questionnaire also captures activities that patients are no longer able to do as a result of breathlessness, which is not captured in other questionnaires. There are a large number of questionnaires that assess dyspnoea that can be categorised into severity, functional and emotional assessments. The MDP covers the three categories of dyspnoea. Selection of questionnaires should be based on the aims of the study and validity of the questionnaires and it is difficult to compare when the desired intent differs. As of yet, there is no superior breathlessness questionnaire and therefore selection needs to be specific to the research question. Figure 1.5 can assist the selection of questionnaires based on the desired intent of

the assessment. Further explanation of questionnaires and their validity can be found in chapter 3.

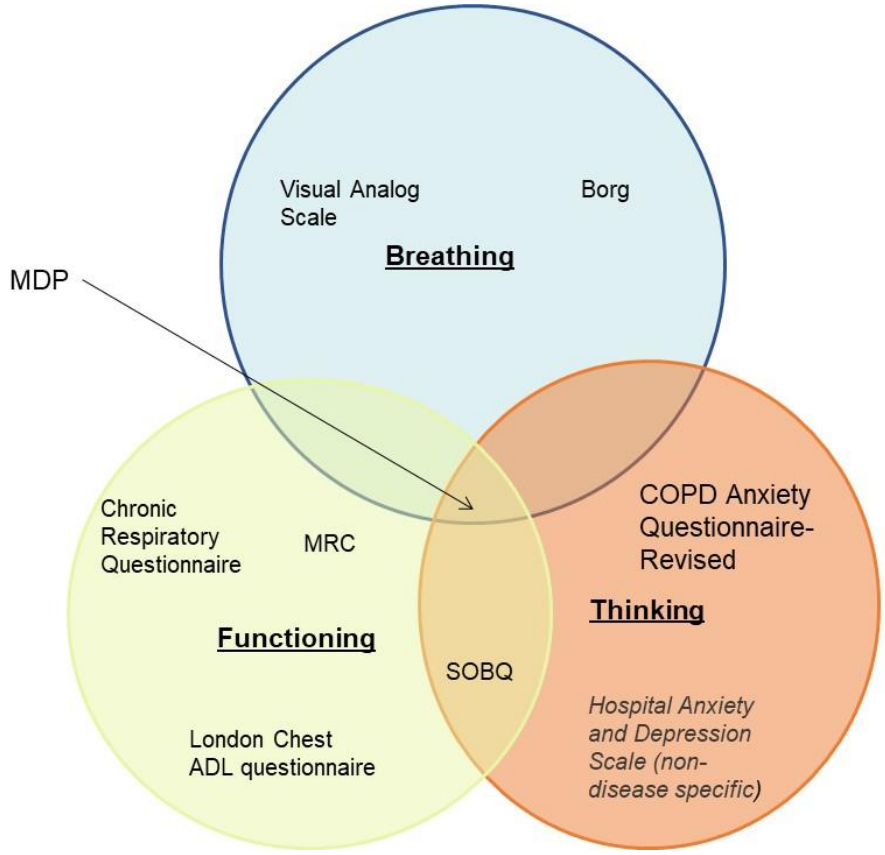



*Figure 1.5 Questionnaires assessing dyspnoea categorised into the breathing thinking functional model of breathlessness. ADL Activities of Daily Living, MRC Medical Research Council, SOBQ Shortness of Breath Questionnaire.*

## 1.5 Mucus Hypersecretion

### 1.5.1 Structure and Function of the Normal Airway.

Epithelial surfaces that encounter the outside environment are protected by mechanical or chemical barriers. Mucosal surfaces provide a mucus barrier as part of this protective mechanism[70]. Mucus layers vary widely however in the airway this is thin and mobile. There are two principle cell types in the pulmonary epithelium: ciliated and secretory. These secretory cells have been further categorised into subtypes (e.g. Clara, Goblet and Serous cells) however due to their structural, molecular and functional plasticity it is simplest to refer to them primarily as secretory cells. Secretory cells release mucins, immunodilatory molecules, protective molecules and antimicrobial molecules which are all incorporated into mucus[63]. Secretory cells are found in the first four generations of the airway and are not present in the terminal bronchioles.

Submucosal glands are found in the large airways and contribute to the secretion of mucins and liquids. In pathological states the volume of submucosal glands can increase to several times the normal volume[41]. The mucus gel layer consists of mucins, proteins, salts, lipids and cellular debris. This layer works as a solid physical barrier to most pathogens; however, this is readily penetrated by small viruses and hydrophilic capsids which has implications for infections. The production of mucin from secretory cells varies depending on health status, for example during allergic mucus metaplasia production can increase 40 to 200 times higher than normal. This also increased among asthmatics and smokers[71]. The regulation of mucin secretion is separate from mucin production. There is a continuous presence of low levels of ATP (Adenosine Triphosphate) in the airway surface liquid causing low activity of the secretory machinery, resulting in steady release of mucins providing a normal barrier of defence. When this is increased mucins accumulate intracellularly and secretion of a large number of granulated triggered, causing mucus hypersecretion. These are stored in a

dehydrated state and once hydrated swells to up to 300 times the size which results in airflow occlusion and contributing to airflow obstruction[63].

The mucus gel is propelled proximally by beating cilia, which collects and clears inhaled particles, pathogens and dissolved chemicals that may damage the lungs. Normal cilia beat 12 to 15 times per second, and the rate of clearance increases with hydration. The second mechanism for expulsion of mucus from the airway is coughing. Coughing is invaluable in secretion clearance, particularly in mucus hypersecretion, however, can commonly become a troublesome symptom and often exhaustive[72]. Coughing is effective only when sputum reaches the large airways/ throat and often additional techniques are required to assist the movement of sputum centrally to the throat. Excessive coughing prior to the sputum reaches the throat causes bronchoconstriction and limits the movement of sputum which can increase fatigue and thus effective strategies are vital.

### 1.5.2 Pathology

Airway mucus is secreted by the goblet cells found in the superficial mucosa and the mucous glands in the sub-mucosa. These goblet cells decrease in number further into the bronchial tree until they disappear completely at the bronchioles. The mucosa acts as a line of defence and is a layer of columnar epithelial cells that are lined with cilia forming the mucociliary escalator. Airway mucus is part of the lungs innate immune function and traps particles, microorganisms and facilitates their clearance from the lungs. In normal airways, this is an efficient mode of defence however in mucin secretory cell hyperplasia and metaplasia there is an overproduction resulting in pathological consequences.

Mucus hypersecretion and chronic productive cough is a key feature in the chronic bronchitis phenotype. This is primarily caused by overproduction and hypersecretion of the goblet cells, as a consequence of tobacco smoke exposure, acute and chronic viral and bacterial infection or inflammatory cell activation of mucin gene transcription. In addition,

long term exposure to noxious stimulus i.e. tobacco smoke, harms the cilia leading to poor ciliary function and a reduced ability to clear secretions. Saetta et al shows that smokers with Chronic Bronchitis and airflow limitation have an increased number of goblet and inflammatory cells in the peripheral epithelium[73]. Goblet cell hypertrophy and hyperplasia occur in the large airway of habitual cigarette smokers and this hypertrophy results in increased epithelial mucin stores which are higher than healthy comparators. Patients with Chronic Bronchitis phenotype may also demonstrate acquired Cystic Fibrosis Transmembrane Conductance Regulator dysfunction and activation of the epidermal growth factor receptor. Oxidative stress as caused by cigarette smoking suppresses the Cystic Fibrosis Transmembrane Conductance Regulator in T84 cells and Calu-3 cells which is responsible for the appropriate diffusion of sodium across the membranes of the mucus, digestive enzymes, sweat and saliva. Changes in the diffusion capacity can cause an increased viscosity of the mucus contributing to mucus retention[74].

Mucus hypersecretion is estimated to be between 2.7%-22% among individuals with COPD[2]. This wide range could be explained by the varying definition of mucus hypersecretion or the inclusion of bronchiectasis. Excessive mucus affects important outcomes in COPD including lung function decline, health related quality of life and exacerbations including hospitalisation. It has been identified that those with the chronic bronchitis phenotype have an increased risk in respiratory-related and all-cause mortality[75]. However, Prescott et al reported that chronic mucus hypersecretion is a predictor of mortality from pulmonary infection but not in the absence of pulmonary infection[76]. Small airway mucus obstruction is characteristic of COPD even in the absence of excessive mucus expectoration. Airflow obstruction correlates with changes in mucin expression, increases in goblet cell size and number, occlusion of the small airway with mucus and expansion of the submucosal glands[2].

The mechanisms of mucus hypersecretion due to cigarette smoke is complex and not completely understood however adverse effects occur on the structure and function of the cilia, activation of the epidermal growth factors, decreased function of the Cystic Fibrosis

Transmembrane Conductance Regulator (CFTR) gene and proinflammatory affects that increase mucin production whilst decreasing hydration and clearance[74]. The identified toxins in cigarette smoke that are identified to directly affect mucin production are oxidative chemicals and organic compounds, particularly, acrolein as it potentially increases mucin production. Increased mucin production and decreased luminal liquid in COPD have deleterious consequences for airway health, including mucus stasis and airway infection. Approximately 25-50% of patients with COPD are colonised with infectious bacteria most commonly Haemophilus influenzae, Pseudomonas aeruginosa, Streptococcus pneumoniae, and Moraxella catarrhalis. This rate increases with disease severity and new strains are associated with exacerbations. This elicits airway inflammation and fibrosis which can lead to the development of scar tissue which is non contractile and therefore results in reduced lung function[63].

In addition to increased mucus production, there is a reduction in the ability to clear sputum due to pathophysiological changes. Cigarette smoke and other noxious stimuli affect the function of the cilia which become paralysed and unable to clear sputum in the direction of the mouth. This increased sputum can also lead to airway occlusion which will impact the clearance of sputum and can lead to plugging and affect ventilation in that area of the lung. Decreased ventilation to areas of the lung can lead to reduced peak expiratory flow and this in combination with reduced respiratory muscle strength can lead to weak and ineffective cough which will reduce the ability to clear sputum from the lungs[2].

The clinical consequences of mucus hypersecretion and mucus plugging is the mismatch between ventilation and perfusion which can further contribute to gaseous exchange abnormalities as discussed earlier (section 1.2.4). Compromised mucociliary clearance can encourage bacterial colonisation leading to frequent exacerbations and as a result accelerated lung damage and fibrosis leading to poorer outcomes[77]. The treatment of mucus hypersecretion has been challenging particularly without a full understanding of the

mechanisms however excess sputum can be managed and maintained through a range of therapies that will be discussed in later sections (section 1.7.3 and chapter 2).

### 1.5.3 Quality of life and functional limitations

Pathology leading to increased mucus production can also affect the function of the lungs. The ability to clear secretions is reduced due to poor ciliary function, reduced respiratory muscle strength and ineffective cough. The accumulation and inability to clear sputum can lead to increased severity of symptoms and subsequent functional decline. Dyspnoea severity has been associated with an increased risk of a diagnosis of chronic bronchitis phenotype which may be a result of increased smoking exposure[78]. Patients demonstrating mucus hypersecretion, or chronic bronchitis phenotype have demonstrated worse lung function, increased respiratory symptoms and more frequent exacerbations[78]. As a result, patients report a lower status of health-related quality of life than non-sputum producers. The presence of sputum and increased severity of symptoms can lead to reduced functional ability such as reduced activity and ability to perform activities of daily living. This can lead to reduced independence. This can have an effect of the ability of patients to perform airway clearance manoeuvres and becomes a viscous cycle of increased sputum and decreased ability to clear sputum. The discussion and management on secretion clearance in relation to quality of life is an area not well documented within COPD. Research among the Cystic Fibrosis population somewhat explores this however due to a huge variance in demographics results are non-transferable. There is a need for rigorous exploration of this topic and the importance to the patient.

### 1.5.4 Measures of sputum clearance

Historically the gold standard for measuring sputum clearance was sputum wet or dry weight. This requires the patient to expectorate secretions and for it to be accurately weighed which can present some difficulties. This relies on the patient expectorating all

secretions and not swallowing them. The weight will also include other fluids from the mouth and will not be an accurate representation of sputum in the lungs. This is labour intensive for both the patient and the researcher and can be inaccurate. The interpretation of these results is also difficult with an increased in sputum weight could mean better clearance or increased presence of sputum. Patient reported outcome measures are an alternative but are subjective and have a high variability. The most common questionnaires are the Patient Ease of Expectorating Questionnaire (PEQ) and the Breathlessness Cough and Sputum Score or COPD Assessment Test that are not specific sputum questions. Other alternatives to objectively assess sputum clearance are lung imaging. High Resolution Computed Tomography is common particularly in bronchiectasis, and has been shown to correlate with exacerbations in patients with Cystic Fibrosis[79]. Hyperpolarised $O_2$ MRI scans can assess ventilation changes that can be influenced by sputum and have been used to assess airway clearance devices in patients with COPD[80]. Two-dimensional gamma scintigraphy can be used to assess mucociliary clearance by the assessment of inhaled aerosols and combined anterior and posterior images. Similarly single photon emission computed tomography (SPECT) can use inhaled aerosols and a 360 degree gamma camera to assess mucociliary clearance[81]. Both techniques can assess regional and local lung deposition. Lung imaging techniques can provide objective assessment of mucociliary clearance which are invaluable but will subject the patient to radiology and are expensive techniques. This range of mucus clearance measurements makes synthesis of data difficult. Whilst imaging techniques may be considered the gold standard or most reliable they are typically costly and not widely available. Patient reported measures are inexpensive but come with a degree of variability. Other methods for measurements of sputum clearance can be indirect and assess ventilation heterogeneity as a surrogate for sputum clearance and are typically cheaper than lung imaging but may offer increased objectivity and reliability over patient reported outcomes.

## 1.6 Ventilation heterogeneity

### 1.6.1 Small airway function and obstruction

COPD is a combination of small airway disease and lung tissue parenchymal destruction. The relative contribution is variable between patients, however small airway disease is considered a major contributor to lung function in patients with COPD[41]. Small airways are typically described as less than 2mm internal diameter, which is inclusive of airways from the fourth to the fourteenth generation of branching. These airways lack cartilage and have a greater proportion of smooth muscles and fewer goblet cells in the epithelial layer. In healthy individuals, small airways contribute very little to airway resistance however Hogg et al pioneering research demonstrated the small airways as a major site of resistance in obstructive lung disease[41]. Small airway abnormalities in COPD are categorised by the presence of inflammation, fibrosis, and mucus plugging. These factors are found to be correlated with the severity of airflow obstruction as outlined by the Global initiative for Obstructive Lung Disease (GOLD) staging. GOLD staging is strongly correlated with airway wall thickening as a response to airway wall injury. The degree of luminal occlusion and the extent of the inflammatory response, as demonstrated by the number and magnitude of lymphocytes organised into follicles, were weakly correlated with disease progression. Bronchial obstruction and emphysema result in a non-uniform distribution and consequently ventilation inhomogeneity occurs. Spirometry is not a sensitive marker of disease progression and small airway dysfunction occurs long before spirometric changes are seen and thus there is a need for the measurement of small airway obstruction.

### 1.6.2 Lung clearance index

The Lung Clearance Index (LCI) is determined via the Multiple Breath Washout (MBW), and was developed in the 1950's by Robertson et al[82]. This technique is used to quantify ventilation heterogeneity and was initially described as a measure of nitrogen washout

using oxygen concentrate; however, this can be performed with other inert tracer gases such as helium or sulphur hexafluoride ($SF_6$). The theoretical underpinning of this test is based on the function of lung ventilation to maintain the physiological partial pressure of oxygen and carbon dioxide in the alveoli and thus the measurement should reciprocate this. Airway narrowing tends to be patchy due to factors such as mucus retention, inflammation and airway wall structural damage causing unevenness in ventilation[83]. The MBW measures the time that a molecule remains in the alveolar spaces. The washout rate is therefore dependent on the distribution of tidal breathing to the deeper pulmonary structures. The inert tracer gas is then washed out with room air and analysis focuses on of the efficiency and pattern in which the gas is washed out of the lungs during tidal breathing to further understand the function of the small airway. In cases of Nitrogen MBW, 100% oxygen is used to measure nitrogen washout. The replacement rate is defined as the ratio of the number of new molecules in the unit time to the number present at the end of expiration. Since its introduction, the LCI as measured by the MBW is becoming increasingly popular in research and slowly breaking into clinical practice particularly in the identification of early disease, Cystic Fibrosis and paediatric medicine.

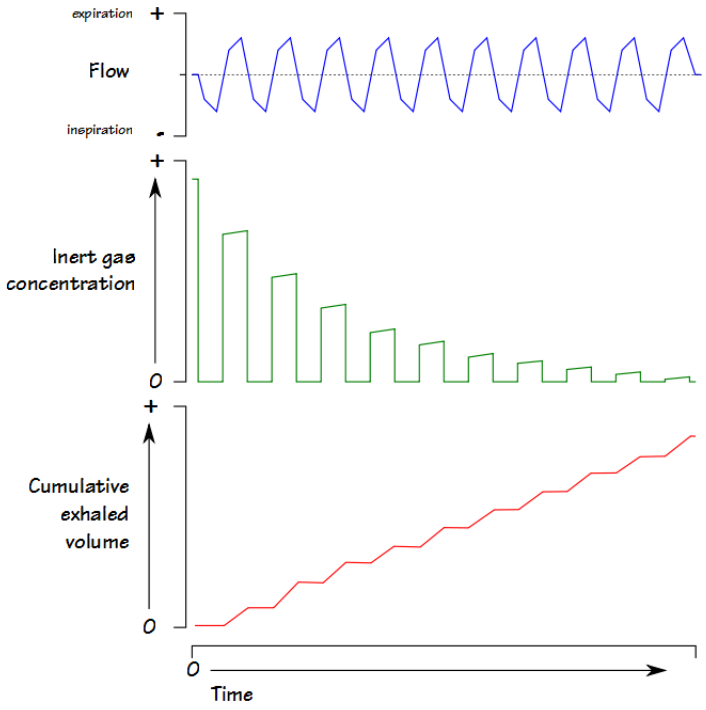



*Figure 1.6 Representation of the lung clearance index via multiple breath washout.*

The LCI is a calculation based on the cumulative expired volume and the full vital capacity. In the interest of reliability, the test is repeated in triplicate and the full vital capacity should be within a 10% variance for inclusion in the analysis. The washout is considered complete when the end tidal volume reaches 1/40$^{th}$ of the starting concentration. Figure 1.5 demonstrates the multiple breath washout test features of the cumulative exhaled volume and concentration of $SF_6$. The use of 1/40$^{th}$ of the starting concentration as an end point for the test is historic and represents the limits of operating rage of early nitrogen analysers. However there has been little movement of this reference point due to a compromise between losing sensitivity on a shortened test and an excessively protracted procedure[84]. The mechanism of ventilation homogeneity was pioneered by Paiva and Engel on the basis of mathematical modelling studies[85]. As air is inspired, it moves by bulk flow (convection) and as it reaches the distal airways gas diffusion increases. The point of equilibrium is

known as the convection-diffusion front, and this is thought to be the acinar entrance in healthy subjects. However, this varies slightly on the tracer gas used. As this measurement has developed, it is possible to calculate changes in both the small and the large airways, in addition to the anatomical dead-space. Results commonly report the conducting zone ($S_{cond}$) and the acinar zones ($S_{acin}$). Ventilation homogeneity occurs by two mechanisms: convection dependent inhomogeneity (CDI) referring to the unequal ventilation between relatively large lung units subtended by conducting airways with associated flow asynchronicity; and diffusion-convection-dependent inhomogeneity (DCDI) referring to asymmetries of airway volume or cross-sectional area occurring at the region of the convection diffusion front. Analysis of washout curves can also explore within breath analysis and can be separated into phases. Phase I represents the respiratory dead-space, which is not involved in gas mixing, phase II represents the arrival at the mouth of the first portions of alveolar air and phase III is the alveolar phase which represents purely alveolar air. Where there is a sharp increase at the end of phase III, this is labelled phase IV and represents the onset of airway closure in the basal lung segments (figure 1.6). An abnormal phase III slope is expected to be a result of CDI as DCDI would only be changed in the first five breaths. This is typically presented as $S_{cond}$ and $S_{acin}$ to represent the CDI and DCDI, respectively. Normal values of $S_{cond}$ and $S_{acin}$ are reported as 0.033 and 0.075 respectively which tend to increase with age. $S_{cond}$ is calculated at turnover 1.5 to 6 and is a calculation of the phase three slope versus ventilation. $S_{acin}$ is calculated from the first phase III slope minus the $S_{cond}$ times the turnovers of the first breath. As ventilation progresses, phase III slopes steadily increase, and therefore the $S_{cond}$ is a calculation of the mean of all phase III slopes in the washout test[86].

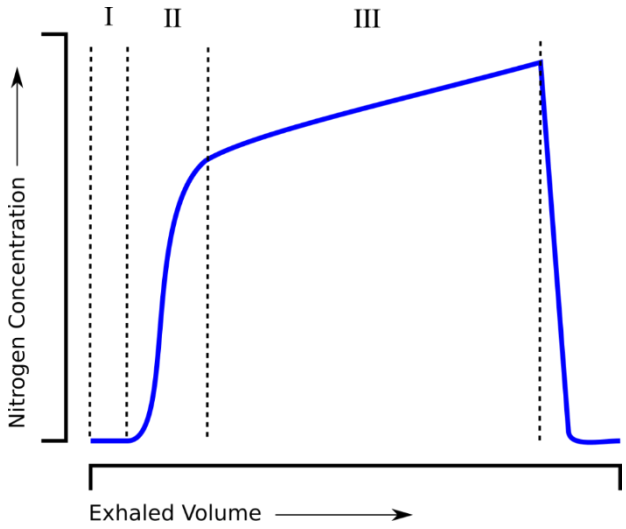



*Figure 1.7 Phased slope analysis*

The cited LCI for healthy subject's ranges between 6 and 7.5 (see table 1.2). The LCI is somewhat biased by variations in tidal volume, anatomical dead-space and FRC and therefore the ideal LCI is not a fixed value but is variable to account for these confounders. There is a variability among disease populations which is outlined in the table 1.2 below. Due to the simplicity of the technique, MBW tests are particularly useful in paediatric medicine which is reflected in the literature. Initially, research used relatively crude equipment developed in house, and whilst the research demonstrated abnormalities in gas mixing, the impact of this on clinical practice was not explored.

Research has become more robust since the development of a mass spectrometer to perform washouts using 0.2% $SF_6$. Research has demonstrated an elevation in LCI in a population of CF patients ages 3-18 compared to healthy controls[87]. It was also demonstrated that LCI is a more sensitive marker than $FEV_1$ in the detection of early diagnosis and disease severity. $FEV_1$ is often used as a marker of disease progression and an outcome measure for medical and physiotherapeutic research studies. These findings were confirmed with research demonstrating a higher LCI in patients with CF infective of pseudomonas aeruginosa, which is associated with poor prognosis[88, 89]. Further research has

confirmed these results with the inclusion of adults as well as children with CF [83]. Longitudinal studies have demonstrated the use of LCI as a marker of disease progression and demonstrated that LCI is the first measure to deteriorate compared with other spirometric techniques ($FEF_{50}$, FVC and finally $FEV_1$)[90]. Conversely, normal LCI in CF almost excludes the presence of abnormalities seen on HRCT[87] The LCI via MBW is well established within CF and can be used clinically and during research, however it has been suggested that LCI reproducibility declines with deteriorating LCI[83].

LCI has been utilised in the identification of asthma. Research has demonstrated and increased LCI that is reversed by bronchodilators that was not seen when compared with patients with CF[91]. Similarly, in a cohort of children with well controlled asthma, LCI was slightly elevated compared to aged matched healthy controls, however reversibility seen on $FEV_1$ was not demonstrated during LCI which suggests there is some degree of airway irreversibility in asthmatics[91]. Conversely, whilst the use of LCI has been useful in childhood asthma and adults and children with CF, the use during bronchiectasis is left to be desired. A study investigating the repeatability and responsiveness of LCI in a cohort of patients with bronchiectasis, demonstrated difficulties in obtaining repeatable results in acute and stable bronchiectasis, and was insensitive to medical management and physiotherapeutic techniques such as airway clearance and exercise[92]. This may be explained by the decreasing reproducibility with deteriorating LCI, or by the nature of increased coughing in bronchiectasis compromising the conductance of the test. Literature exploring the use of the LCI in a population of COPD patients is in its infancy. It has been demonstrated that the use of the LCI offers substantial promise within COPD and is comparable to CF research, however this is primarily within early airway disease[93]. Table 1.2 demonstrates the known ranges of LCI for different disease populations and healthy adults.

*Table 1.2 Reference values of the Lung Clearance Index in adults*

| | Gas | Healthy | Cystic Fibrosis | Asthma | Bronchiectasis |
|---|---|---|---|---|---|
| Fuchs 2006[94] | $SF_6$ | 7.21[0.26] | | | |
| Horsley 2008[95] | $SF_6$ | 6.7[0.4] | 13.1[3.8] | | |
| Singer 2012[96] | $N_2$ | 7.19[0.53] | | | |
| Verbanck 2012[86] | $N_2$ | 6.02[0.31] | | 6.26[0.42] | |
| Rowan 2014[97] | $SF_6$ | | | | 9.1[2.0] |
| Gonem 2014[84] | $SF_6$ | | | 8.20[1.48] | |
| Grillo 2015[92] | $SF_6$ | 7.36[0.99] | | | 11.91[3.39] |

*Table 1.2 $N_2$ Nitrogen, $SF_6$ Sulphur Hexafluoride*

LCI is advantageous over other measures of airway disease due to the simplicity of the test in relation to patient performance and burden. This test requires sustained tidal breathing which is not effortful for the patient. It is sensitive to small airway dysfunction, where spirometric tests are known to be insensitive. $FEV_1$ is insensitive to ventilation homogeneity and therefore LCI can fill this gap. LCI is particularly useful in diseases which are characterised by uneven small airway inflammation and obstruction such as CF, and as this test only requires tidal breathing it is ideal in the use of paediatric medicine. There is good intra and inter visit reproducibility and is more sensitive to changes to lung disease progression[93]. The normal values range is relatively small for a large age range, and as it is calculated using FRC in its formula, differences in gender and height are already accounted for. The main criticism of LCI surrounds the duration of the test. Where a wash-in and wash-out phase is required, those with mild diseases can expect the test to last five minutes and is then performed in triplicate. This may take twice as long for severe disease[83]. Treatments that may reduce mucus plugging might result in increased ventilated airways, which would paradoxically worsen (increase) LCI[83]. The use of the LCI in COPD has been explored in mild disease comparing nitrogen and $SF_6$ washout techniques. This demonstrated repeatability within 24 hours however longer-term duration and the impact of this exploration on severe disease was not explored[93]. Currently further research is necessary in the reproducibility of

LCI within the COPD population and its responsiveness to management techniques, particularly in relation to airway clearance.

## 1.7 Clinical management and treatment

Both dyspnoea and secretion management are key treatment priorities for all healthcare professionals in order to optimise treatment for respiratory patients and a reduction in costs. Firstly, this section will explore dyspnoea treatments that includes but is not exclusive to, pulmonary rehabilitation, respiratory muscle training and secretion clearance techniques. Secondly secretion management strategies will be discussed which can cover breathing techniques and devices.

### 1.7.1 Pulmonary Rehabilitation

Pulmonary rehabilitation is the gold standard treatment strategy for individuals with COPD[98]. This is a multidisciplinary programme of care, utilising physiotherapists, nurses, dieticians, occupational therapists and doctors in order to individually tailor and optimise each person's physical and social performance and autonomy. The National Institute for Clinical Excellence (NICE) and British Thoracic Society (BTS) have developed guidelines for the development and implementation of pulmonary rehabilitation and the quality of programmes are assessed using the ongoing national COPD audit programme. Programmes should be a minimum of six weeks in duration of bi-weekly supervised sessions. Supervised training sessions should be individually tailored, prescribed, progressive exercise training including both aerobic and resistance training and include a defined structured education programme[3, 98, 99, 100]. Pulmonary rehabilitation has been shown to improve quality of life, reduce respiratory symptoms; including dyspnoea, increase exercise tolerance and improve independence[101]. Whilst pulmonary rehabilitation has no direct effect on lung function, it can prevent exacerbations and hospitalisations which have been demonstrated to reduce lung function. Patients with COPD that complete pulmonary rehabilitation demonstrate an

improvement in exercise tolerance, dyspnoea and lower rates of hospitalisations. This can also impact on survival rates[102]. The effect of pulmonary rehabilitation has a significant effect on survival for patients that complete the course comparatively to those who drop out[103]. This result is amplified if the patient achieves an improvement of 50m on the incremental shuttle walking test[104]. In order to increase patients attendance and access to pulmonary rehabilitation and to reduce barriers, online and home based programmes have been developed which demonstrate improvement in patient outcomes[105].

### 1.7.2 Respiratory Muscle Training

Respiratory muscle training is a technique that aims to improve function of the respiratory muscles through specific exercise training. It applies basic principles of exercise to improve respiration including strength, endurance and overload training, however considerations are necessary due to an inability to adequately rest the muscles of respiration. Evidence suggests that respiratory muscle training causes physiological adaptations. Techniques of respiratory muscle training can improve breathing endurance and increase diaphragm thickness[106]. During tidal breathing a person uses between 10-15% of their total lung capacity which can be increased with respiratory muscle training. Research amongst healthy subjects have demonstrated improvements in whole body endurance capacity and short duration high intensity time trial performance after specific respiratory muscle training[107, 108, 109]. Whilst this is a very popular technique amongst athletes in addition to their normal training, evidence for an ergogenic effect remains somewhat controversial[110]. It has been shown that inspiratory muscle training can increase constant power and cycling time trial performance in cyclists, which may be explained by an increase in anaerobic work capacity as a result of the physiological changes that occur from training[110]. The use of athlete literature has provided a theoretical underpinning of respiratory muscle training which may be applied to population groups who suffer from abnormal dyspnoea such as asthma, bronchitis and COPD. Research remains ambiguous but predominantly prioritises inspiration. Recently, there has been a growing interest in expiratory or combined respiratory muscle training. There a different methods of respiratory muscle training which

includes, normocapnic hyperpnoea, resistive or threshold training, expiratory muscle training and endurance training. The application of respiratory muscle training is growing in popularity despite the variability of the literature. It has been suggested by NICE that it may be useful in COPD, however this is currently not recommended in the UK[3].

Normocapnic hyperpnea is a method of respiratory muscle training aimed at strengthening respiratory musculature by accelerated deep breathing with controlled oxygen saturation of the blood. It has been demonstrated that four weeks of normocapnic hyperpnea can improve respiratory muscle strength, exercise capacity and endurance[111]. This has been directly correlated with quality of life[112]. Training uses a handheld unit with a pouch and base station, a two-way piston valve connected to a rebreathing bag which permits a constant isocapnic end tidal $CO_2$ fraction to be maintained[112]. The rebreathing bag is adjusted to 50-60% of a patient's vital capacity. The frequency can be adjusted to a patient's maximal voluntary ventilation, which can be calculated from their $FEV_{1.}$ These changes allow for training to be performed at their target ventilation. Normocapnic hyperpnea has been demonstrated as an effective treatment for COPD to improve respiratory muscle strength, ventilatory pattern and thoracoabdominal coordination, which results in improved oxygen saturations. This improves the perception of dyspnoea, exercise capacity and quality of life[112, 113]. This training has been demonstrated to improve respiratory muscle endurance and is a feasible home-based treatment[113]. Training tends to be aimed at 50-60% vital capacity however differences occur in training durations, ranging from 4-8 weeks. This research is limited by the inability to provide a convincing sham intervention. Research has compared normocapnic hyperpnea to breathing exercises or a control group receiving no intervention, which therefore may overestimate the benefit of this training. Normocapnic hyperpnea offers thoracoabdominal retraining which is not available from other forms of respiratory muscle training and may be a useful adjunct particularly in those with dysfunctional breathing as it offers both inspiratory and expiratory training.

Threshold inspiratory muscle training is performed using a handheld device, which provides titrated constant resistance throughout inspiration. The device is typically set at 30-50% of a patient's maximal inspiratory pressure and training can vary from five to ten breaths per set (for three sets). Patients must meet the set pressure in order to open the one-way valve and allow inspiratory flow. The pressure required to open the valve is increased over time as the patient sees an improvement[114]. Additionally, a tapered flow resistive device has been developed, to provide resistance tapered to the pressure generated throughout the breath profile, in which the peak workload would be the same, but this is tapered throughout the patients flow and patients demonstrate a higher work rate when using a tapered flow resistive device when compared to manual threshold loading[115]. Comparatively devices can be flow resistive, in which the pressure received is dependent on the flow the patient can generate. These devices are not able to set a resistance and therefore training is dependent on the patient increasing their flow rate in order to increase resistance. Gosselink has explored the literature in a systematic review and meta-analysis and demonstrated a statistically significant increase of inspiratory muscle strength of 13cm$H_2O$ [CI 0.72-1.25] compared to a control or sham group in a pooled cohort of 430 patients with COPD. There were no observed differences between threshold loading and resistive training. Subgroup analysis of those demonstrating inspiratory muscle weakness demonstrated no significant differences compared to those without inspiratory muscle weakness. It also appears that differences in training protocol did not influence improvements of $PI_{max}$. Additionally patients demonstrated a significant improvement of 32m and 85m in exercise capacity, as measured by the six and twelve-minute walking distance respectively after an inspiratory muscle training programme (varied intensities)[116]. Improvements were greater in those receiving inspiratory muscle strength training compared to resisted endurance training (using normocapnic hyperpnoea techniques). Dyspnoea was measured via the Borg score, transition dyspnoea index and chronic respiratory questionnaire. Significant improvements were noted in all three outcome measures. This was not increased with the addition of a general exercise programme which suggests that inspiratory muscle training is beneficial as a standalone treatment. Similarly, there was a significant improvement in quality of life as

measured by the Chronic Respiratory Questionnaire and Saint Georges Respiratory Questionnaire[116].

The use of inspiratory muscle training via threshold or resistive training demonstrated significant improvements in muscle strength, dyspnoea, exercise capacity and quality of life, however studies were commonly underpowered, and the use of a sham group was inconsistently applied. Patients with a clear inspiratory muscle weakness showed greater improvements in exercise capacity, dyspnoea and quality of life, particularly when applied as an adjunct to a general exercise training programme[116]. This research is further supported by the significant increase in the proportion of type I fibres and the size of type II fibres (fast and slow twitch fibres respectively) in the external intercostal muscles[117]. The use of IMT as an adjunct to pulmonary rehabilitation did not demonstrate additional benefits in the six-minute walking distance however did improve dyspnoea during cycle endurance testing. Therefore, inspiratory muscle training is an effective treatment modality in COPD with a greater improvement in those demonstrating inspiratory muscle weakness, however this is rarely applied within the UK. The current NICE guidelines state that inspiratory muscle training may be a useful adjunct to pulmonary rehabilitation however further research is needed to explore this and to identify a subgroup of patients that may benefit[3].

Expiratory muscle strength and endurance are commonly impaired in COPD and therefore it seems sensible to train these specifically, however literature primarily explores inspiratory muscle training. Expiratory muscle weakness contributes to a reduction in exercise capacity. Research has demonstrated the feasibility of expiratory muscle training within COPD, however improvements in dyspnoea were unconvincing. Improvements in expiratory muscle strength do not appear to translate to direct patient benefits, in a small study of 23 participants[118]. Evidence is overwhelmingly in favour of inspiratory muscle training, comparatively to expiratory muscle training, however there is a discrepancy in the volume and reliability of the literature[119]. There is scope for combined respiratory muscle training,

though research has demonstrated no additional benefit of combining inspiratory and expiratory training, and it appears that the benefits are solely the result of inspiratory muscle training[118].

Research in respiratory muscle training is inconsistent and therefore its application to clinical practice is difficult. Studies investigating respiratory muscle training favour the muscles of inspiration and has been demonstrated to improve dyspnoea, exercise capacity and quality of life. Whilst expiratory muscle training improves expiratory muscle strength there appears to be no translation into patient benefits. Combined respiratory muscle training is feasible but offers no additional benefit to inspiratory muscle training alone. Most literature is underpowered and whilst some utilise a sham intervention, this is inconsistent. The training protocols vary greatly however there appears to be no differences in the benefits seen. The lack of rigorous and unanimous evidence means respiratory muscle training has not been recommended by the COPD NICE guidelines[3].

### 1.7.3 Mucociliary Clearance

Mucociliary clearance is a common treatment strategy for respiratory physiotherapists in the management of COPD and other respiratory conditions alike. Airway clearance techniques utilise external applications of forces to aid the clearance of pulmonary secretions from the lungs. Treatments typically combine a number of techniques which can be categorised into the following: manual techniques, breathing exercises, positive expiratory pressure devices and mechanical devices applied externally to the chest wall. These interventions manipulate lung volumes, gas flow and pulmonary pressure to transport sputum. A combination of these factors exerts shearing forces onto the sputum and air liquid interface, resulting in energy transfer shifting secretions in the direction of the mouth. Abnormal secretion production can lead to airway obstruction, predisposing the patient to infection and inflammation, and therefore it is important to manage excess mucus efficiently in order to reduce the rate of disease progression. There is some evidence

to support beneficial effects of airway clearance techniques on mucus clearance, sputum volume and dyspnoea in patients with COPD[120].

The Active Cycle of Breathing Technique (ACBT) is the most common breathing exercise used to target sputum clearance among respiratory patients with copious secretions (typically more than 10ml per day). ACBT will consist of three key components devised into a cycle with adjuncts as assessed on an individual basis. ACBT will include breathing control, thoracic expansion exercises and the forced expiratory techniques at its core[121]. Breathing control techniques are developed to relax the airways and reduce bronchial constriction by way of abdominal breathing, this technique is interspersed between the remaining techniques. Thoracic expansion exercises encourage thoracic breathing with the addition of an inspiratory hold or sniff as required in repetitions of 3-5. This utilised collateral ventilation to allow air to travel behind the secretions in order to clear in the direction of the mouth. The final component, forced expiratory technique, utilises a huff at different volumes to allow dynamic compression to expectorate secretions. It is possible that the physiological underpinnings differ among different disease populations and stage of the disease. Research has shown a significant difference in sputum wet weight with use of ACBT compared with controls within the Cystic Fibrosis population[122]. However this was not demonstrated in a bronchiectasis cohort when collecting sputum wet weight for a period of 24 hours, though it is unsurprising that the benefits of ACBT would extend for 24 hours and it is recommended to be performed regularly to optimise benefits[123]. There is little evidence in the use of ACBT for a COPD population as often patients have less secretions comparatively to other respiratory conditions. Typically, research targets the COPD population, rather than identifying phenotypes that may directly benefit. Nevertheless, this technique is recommended in the American College of Chest Physicians (ACCP) guidelines of best practice, though there is no speculation as to whom may benefit[124].

An alternative to ACBT is Autogenic Draining (AD) which uses exhalation at different lung volumes to mobilise secretions from the periphery to the central airways. It has been

demonstrated to be equally as effective as ACBT in a cohort of COPD patients demonstrated by an improvement in pulmonary function tests, arterial blood gases, physical performance and the sensation of dyspnoea. ACBT is more simple to perform than AD however this should be assessed on an individual basis[125]. Often breathing exercises can be applied alongside manual techniques and positive expiratory pressure devices.

Manual therapies are considered an important constituent of respiratory physiotherapy. They are particularly valuable in populations with copious amounts of difficult secretions and can play a vital role when breathing exercises alone are not sufficient. Manual therapies include vibrations, percussions and applied overpressures and are performed by a respiratory physiotherapist in isolation or as an adjunct to other techniques. Commonly, these techniques are utilised during an acute exacerbation of COPD and involves physical forces to enhance removal of sputum. A randomised controlled equivalence trial in 526 people hospitalised with an acute exacerbation of COPD found no difference in HRQoL at 6 months between those who received manual therapies, compared to a control group receiving advice on positioning and ACBT[126]. Although this trial did not target sputum producers solely, it demonstrates that the use of manual therapies does not have a place in the routine treatment of an acute exacerbation of COPD[127]. Immediate effects of manual therapy have been demonstrated to aid clearance[3]. The effectiveness of manual therapies is demonstrated in Cystic Fibrosis and bronchiectasis trials but its effectiveness in COPD is somewhat limited by the variation of the condition and therefore evidence is scarce[121]. Whilst attempts to find a phenotype to benefit have been unsuccessful, this does not exclude the utilisations of these techniques in selective patients where excessive sputum production or retention are clinically important problems.

Devices for sputum clearance are often appealing for patients and therapists due to ease of administering and the independence they promote. Devices for airway clearance can provide two distinguished mechanisms, Positive Expiratory Pressure (PEP) and oscillations. These can be utilised independently or combined and varies throughout devices. Positive

Expiratory Pressure (PEP) works by providing a pressure on exhalation in order to maintain the patency of the airways and utilise collateral ventilation to allow air behind secretions and aids the movement in the direction of the mouth. Whereas oscillation devices aim to breakdown secretion proteins by oscillating airflow and as a result vibrating the chest wall. Typically, these aspects are considered together rather than individually, most oscillatory therapies provide some degree of PEP, however PEP devices are available in the absence of oscillations. Devices include, but are not limited to, Flutter©, Acapella©, Aerobika©, Cornet© and PEP mask©. For the purpose of this research they will be explored together. Generally positive pressure devices tend to produce more positive outcomes than other methods of airway clearance[120]. The use of which has been demonstrated to reduce the need and or duration of ventilatory assistance, potentially due to better airway recruitment. It can also reduce length of stay for those hospitalised with an acute exacerbation of COPD. Evidence in patients with stable COPD shows significant reductions in respiratory related hospitalisations, however there were no other reported long-term difference, which is a limitation of this research[120]. PEP devices have not demonstrated any improvement in lung function measured by $FEV_1$ however this is commonly and insensitive marker. There has been some suggestion that PEP devices can have an impact on gas exchange during exertion[128] however, majority of the data do not detect a significant difference in SpO2 or PaCO2. PEP devices have been demonstrated to improve dyspnoea and HRQoL in several studies. The forced expiratory technique yields statistically significant greater improvements in sputum volume cleared immediately after airway clearance when compared to PEP[123]. Conversely, therapeutic PEP has greater improvements in sputum volume expectoration comparatively to a sham device [129]. Radio aerosol imaging revealed greater improvements in mucociliary clearance with non-PEP based airway clearance (breathing exercises and manual techniques) when compared with PEP[123]. Further exploration of airway clearance devices can be found in chapter 2.

Research surrounding airway clearance techniques encounter some inevitable limitations. The measurement of sputum via wet or dry weight is grossly unreliable, particularly as majority of patients tend to swallow most secretions. Comparisons between techniques are

also difficult as a technique is usually determined holistically with the patient's preference and ability at the heart of the decision-making process. Techniques are rarely standalone treatments and a combination of breathing exercises, PEP or oscillating devices and manual techniques are often combined for the maximal effect. The literature for secretion clearance in COPD is variable, particularly as a large proportion of patients with COPD will not produce sputum. Attempts to isolate a subgroup of patients who may benefit have been unsuccessful and therefore results are often underestimated due to the inclusion of non-sputum producers. However Gastaldi et al (2015) demonstrated an improvement in secretion clearance in those who have small volumes of sputum[130]. Further research is necessary in sputum clearance techniques for the management of patients with COPD, and the characteristics that may benefit from such treatments. Comparatively, evidence for physiotherapeutic interventions for respiratory conditions characterised by sputum, such as Cystic Fibrosis and bronchiectasis, are overwhelmingly positive, and sputum clearance is considered a cornerstone of treatment for those patient groups, therefore it is feasible that patients with COPD who regularly produce large volumes of sputum will likely benefit.

Despite the importance of both dyspnoea and secretion clearance in patients with COPD, treatment typically favours one aspect at a time and often clinicians have difficulty identifying treatable traits. Treatable traits have become an area of interest for targeting therapeutic management of patients with COPD, particularly in acute exacerbations, and includes the physiotherapy interventions such as airway clearance techniques and therefore it is important to develop effective strategies to address these clinical problems[131]. The duel treatment of these clinical problems may increase improvements in quality of life and self-management whilst reducing the burden of treatment. The Aerosure Medic© utilises both techniques of respiratory muscle training and oscillatory positive expiratory pressure for dyspnoea and secretion management. The mechanisms of this device are discussed in chapter 3. The use of this duel functioning device has the potential to harness benefits of respiratory muscle training and airway clearance and may demonstrate improvements in dyspnoea, quality of life, exercise capacity and sputum clearance, however this device has

not previously been researched in patients with respiratory disease and therefore it is important to explore its feasibility and clinical effectiveness.

## 1.8 Summary of aims and objectives of thesis

Hypothesis: The use of a novel device which provides both respiratory muscle training and oscillating therapy, improves symptoms for patients with COPD (including dyspnoea and secretion clearance) when compared to a sham. The aims and objectives of this thesis are outlined below:

### 1.8.1 Aims

1. Do current airway clearance devices improve outcomes for patients with COPD? (chapter 2)

   1a. Does the use of airway clearance devices improve common outcomes in COPD including exacerbation frequency, health related quality of life and sputum volume?

2. Is the investigation of the effectiveness of a HFAO device feasible in patients with COPD? (chapter 4)

   2a. Are patients with COPD willing to adhere to a specific training protocol using a HFAO at home, unsupervised?

3. Does the use of a HFAO improve dyspnoea, health related quality of life, exercise capacity and activity in patients with COPD when compared to a sham-placebo control? (chapter 5)
4. Is the use of the Lung Clearance Index feasible and repeatable in patients with COPD within visit and between visit? (chapter 6)

5. Does the use of the LCI give insight into potential therapeutic benefits of devices to aid secretion clearance and airflow improvements? (chapter 6)

### 1.8.2 Objectives

1. To understand the current literature of device use for secretion clearance within patients with COPD by performing an in-depth systematic review and meta-analysis.
    a. To assess the use in acute and stable patients.
    b. To explore the impact of devices on exacerbations, health-related quality of life, sputum clearance, symptoms, and hospitalisation frequency.
2. To assess the feasibility of a research trial investigating the use of a HFAO device within patients with COPD.
    a. To assess recruitment rates, attrition and compliance to device use among patients with COPD.
    b. To determine the acceptability of established outcome measures, investigating respiratory muscle strength, health related quality of life and exercise capacity.
3. To determine the effectiveness of a HFAO device on dyspnoea, health related quality of life, exercise capacity and activity when compared to a sham-placebo control.
    a. To compare effects on dyspnoea, health related quality of life and exercise capacity when compared to a sham control.
    b. To explore if there is a subgroup of patients which receive the most benefit of this therapy.
4. To demonstrate the feasibility and repeatability, both within day and at eight weeks, of the Lung Clearance Index measured via Multiple Breath Washout in patients with COPD.
    a. To assess patient's ability to perform the Multiple Breath Washout (MBW) in line with ERS/ATS standards and a variability of 10% FRC.
    b. To explore the repeatability of the MBW within visit and between visit.

5. To measure the lung clearance index and how it may give insight into the physiotherapeutic benefit of devices to aid secretion clearance and improve airflow.
    a. To understand the sensitivity of the Lung Clearance Index to changes in sputum clearance.
    b. To explore comparisons between CAT Sputum and the Lung Clearance Index in patients with stable COPD.

# 2. Systematic Review

## 2.1 Airway Clearance Devices in Chronic Obstructive Pulmonary Disease.

## 2.2 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is defined by an expiratory flow limitation that is not fully reversible. It affects 1.2million people in the UK and is the second most common respiratory condition which is a major source of mortality and burden to healthcare. Mucus hypersecretion and retention can affect between 2.7-22% of patients with a diagnosis and is often the key feature of an infective exacerbation[2]. Typically, those who report excess secretions have poorer outcomes, such as reduced $FEV_{1,}$ increased exacerbation frequency and reduced quality of life. It is also cited as an independent predictor of premature mortality and can lead to an increase in hospitalisations[120].

In those with Cystic Fibrosis and bronchiectasis, breathing exercises, manual therapies and devices can all aid secretion clearance and are regularly used. Evidence has demonstrated improvements in respiratory function, hospitalisations, health related quality of life (HRQoL) and sputum clearance in these populations, but their use in COPD is less frequent. Previous evidence from a small number of trials demonstrated a reduction in ventilator assistance and hospital length of stay during an acute exacerbation of COPD (AECOPD) and individual studies have suggested short-term improvements in HRQoL or reduced respiratory related hospitalisations in stable disease[120]. However, the evidence supporting airway clearance techniques across clinical outcomes in acute and stable COPD was considered to be weak and of poor quality, and therefore further research is likely to change the magnitude and precision of the effects. The provision of airway clearance devices is often limited by funding and resources. As an alternative, physiotherapists often provide breathing exercises however, these techniques are usually more difficult to master and require more

supervision and less independence for the patients. Due to the complexity of breathing exercises and the need to deliver during an acute admission, when patients tend to have reduced cognition, these become ineffective treatment techniques and therefore the use of devices may be preferable.

National clinical guidelines for COPD recommend considering the use of positive pressure devices for patients with excessive sputum or AECOPD however there are no formal recommendations made due to the inherent methodological flaws in the literature, diversity of patient groups and small sample sizes[3]. A previous systematic review has predominantly explored breathing exercises as an airway clearance technique, but not the effects of airways clearance devices alone[120]. Since then there has been a large amount of emerging evidence exploring the use of various airway clearance devices and consequently the evidence has not yet been synthesised. The 2018 National COPD guidelines make recommendations on airway clearance from searches performed in 2004 and based on six included studies and therefore there is a need to systematically review and collate the evidence on the use of devices in patients with COPD[3].

This review aims to synthesis the evidence using airway clearance devices as a strategy to manage secretions in patients with stable and/or an exacerbation of COPD. This will be achieved by:

- Systematically reviewing the evidence of the effects of airway clearance devices on secretion clearance in patients with COPD.
- Estimate the effects on secretion clearance (primary outcome), health related quality of life and hospitalisations/ exacerbation frequency (secondary outcomes).
- Investigate the variation effects among subgroups, stratified by duration of follow up and comparison group.

- Determine the robustness of the results and perform a sensitivity analysis that will exclude studies with a high risk of bias.
- Compare the evidence on stable COPD and acute exacerbations.

## 2.3 Methods

### 2.3.1 Eligibility

This review included randomised controlled trials (including cluster randomised controlled trials) and randomised crossover design trials, up until the point of crossover, to evaluate the effectiveness of airway clearance devices on secretion clearance, hospitalisations, exacerbation frequency and quality of life when compared to a control group. No restrictions on language or publication status were imposed. This review was registered on prospero, reference: CRD42018114101.

### 2.3.2 Population

Participants must have a diagnosis of COPD, emphysema or chronic bronchitis as defined by the investigator. This includes any reported severity of COPD as evidenced by their airflow obstruction. Participants are adults aged 18 or over. An acute exacerbation of COPD was included if they describe an exacerbation of their symptoms (dyspnoea, secretions or cough) which requires medical intervention despite their hospitalisation status. Participants were considered as stable if they have not required the use of acute medical management within the period of four weeks (excluding their usual medical management) prior to recruitment onto the study or as defined by the investigators. Stable and exacerbating participants were considered separately at analysis. Participants with a primary diagnosis of Asthma ($FEV_1$ >15% reversibility), bronchiectasis or Cystic Fibrosis were excluded. Those with co-existing respiratory disease were included, providing COPD was their primary diagnosis.

### 2.3.3 Intervention

Airway clearance devices were considered where the primary purpose is to clear sputum from the airways. This includes, but is not exclusive to flutter, acapella, cornet or other oscillating positive expiratory pressure devices (oPEP), positive expiratory pressure mask or valve (with the absence of oscillation), or other mechanical devices. Suctioning, breathing exercises and respiratory muscle training (inspiratory and expiratory) were excluded as they are not considered within the remit of this review.

### 2.3.4 Control

The control group should be comprised of either no intervention, sham intervention, breathing exercises or coughing alone. Studies that compare two separate devices of airway clearance, without a concurrent control arm were excluded.

### 2.3.5 Outcomes

In order to be included in the review, studies had to include at least one of the defined outcome measures. Number of exacerbations as defined by the investigator (risk and rate of). Sputum clearance was the primary outcome measured by either sputum wet or dry weight. Patient reported sputum clearance was also investigated and explored as a standardised mean difference. The use of sputum weight is the gold standard outcome measure for airway clearance trials and whilst there are more reliable methods (including lung imaging) sputum weight was used as it is representative of the current literature. Respiratory related hospital admissions, or number of hospitalisations or hospital bed days for participants with stable COPD. Health related quality of life and changes in symptoms were explored.

### 2.3.6 Search Strategy

Searches were performed on May 2018 and updated in February 2020. This was performed on key medical and therapeutic databases including: Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, CINAHL, AMED and PsychINFO. Handsearching of respiratory journals and meeting abstracts were explored. Searches use Medical Subject Headings (MeSH) where appropriate and include the following search strategy:

"COPD" OR "Chronic Obstructive Pulmonary Disease" OR "Chronic Airway Disease" OR "Obstructive Disease"

AND

"Bronchopulmonary hygiene" OR "Tracheobronchial clearance" OR "airway* Clearance" OR "chest clearance" OR "lung clearance" OR "sputum clearance" OR "mucus clearance" OR "positive expiratory pressure" OR "oscillat*" OR "PEP" OR "oPEP" OR "vibrat*" OR "incentive spiro*" OR "vest" OR "HFCWO" OR "chest wall oscillat*" OR "thoracic oscillat"

Search results were downloaded into a bibliographic database. Initially titles and abstracts were reviewed by two independent reviewers against the defined inclusion criteria. For the remaining included studies, full texts were sought and reassessed alongside the criteria by two independent reviewers. Discrepancies were resolved by discussion or through a third reviewer where an agreement cannot be met. Reasons for exclusions were documented.

### 2.3.7 Data extraction and appraisal

Data extraction was performed using a modified version of the Cochrane data extraction template for randomised controlled trials. This tool was piloted and refined for its use in this

systematic review. Data were extracted by one reviewer and 10% were assessed by a second reviewer and cross checked for accuracy. The following information were extracted: study methods (date/title, aims design, allocation, duration of intervention and study, outcomes and funding source), participants (age, gender, disease severity inclusion and exclusions criteria, recruitment, sample size, baseline differences), intervention (group name, control, group sample size, delivery and content of intervention, timing, frequency, duration) and outcomes (definition, type, units, person reporting, missing data).

The risk of bias was assessed using the Cochrane Risk of Bias Tool using the following criteria: random sequence generation, allocation concealment, blinding (outcome assessors/ patients), incomplete outcome data, reporting bias, and other bias. Each domain was classified as adequate, unclear or inadequate. Overall risk of bias for each study was classified as low risk of bias, moderate risk of bias or high risk of bias. In order to be classified as low all domains were required to be adequate. Moderate risk of bias required one criterion deemed inadequate or two as unclear and for high risk of bias more than one criterion listed as inadequate or more than two listed as unclear.

### 2.3.8 Data analysis

The primary measure for secretion clearance was sputum wet or dry weight. Patient reported outcomes of sputum clearance were also analysed. Data from wet and dry weight changes were treated as continuous data and were pooled together to determine a mean change. Studies evaluating sputum weight immediately after treatment and those evaluating it over a sustained period were considered separately due to the implication of the results. An increase in sputum clearance immediately after treatment is desirable whereas over a longer period this volume is expected to reduce as patient's sputum production diminishes. Health related quality of life include a number of questionnaires, most commonly the Saint Georges Respiratory Questionnaire (SGRQ), COPD Assessment Test (CAT) and the Breathlessness, Cough and Sputum Score (BCSS), these questionnaires

were categorised as health related quality of life (SGRQ) or symptom burden (CAT and BCSS) and were explored as continuous data[132, 133, 134]. For studies that reported more than one time point, the longest duration follow-up was inputted into the meta-analysis, unless otherwise stated. Exacerbation frequency, hospitalisations and bed day's data were treated as dichotomous data and were required in count format and were obtained from authors where not reported. Pooled studies were assessed for their heterogeneity using a generic inverse variance random effects method and explore any sources of heterogeneity identified by the $I^2$ test statistic (<30%). Analyses with a high $I^2$ (>30%) deemed the studies heterogeneous and differences in methodology were explored and studies were reanalysed. Analyses with a high $I^2$ reduce the generalisability of the results.

Data was explored according to the following subgroup analysis: acute and stable patients, short- and long-term interventions and usual care/sham versus breathing exercises (which are considered a tool for secretion clearance). Sensitivity analysis was performed where possible to assess the robustness of findings by removing studies with moderate to high risk of bias studies from the analysis. In accordance with Cochrane guidance, studies with multiple intervention groups (i.e. two airway clearance devices); were combined to create a single pair-wise comparison to the control group[135].

## 2.4 Results

### 2.4.1 Study screening

The initial searches yielded 2052 results and an additional 4 from hand searching. After duplicates were removed there were 1485 records eligible for screening. The title and abstract screening excluded 1440 records and for the remaining 45 citations, full texts were obtained. 19 (42%) full texts were eligible for this review (see figure 2.1). The most common reason for exclusion was republished data of the same study already included in the review or not containing the desired outcomes. One study included in the review recruited both

patients with COPD and Asthma and it was not possible to obtain COPD only data and therefore was removed from the analysis[136].

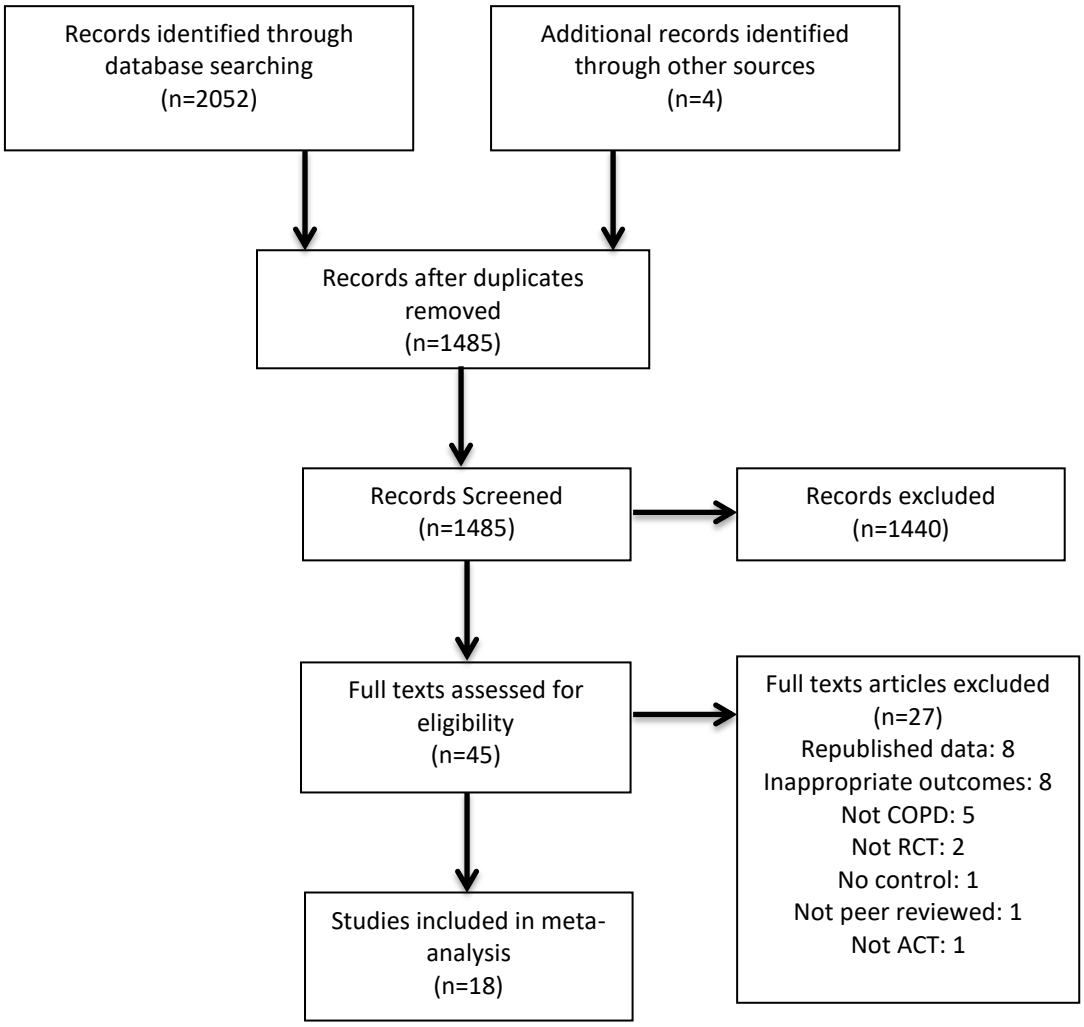



*Figure 2.1 Consort diagram of included studies*

### 2.4.2 Characteristics of studies

The studies included in this review range from 2002-2018 and were conducted in both stable and during acute exacerbation. This research was conducted in a variety of countries including Australia, Brazil, Canada, China, Italy, Philippines, Russia, and Turkey, United Kingdom and the United States. The sample sizes of the included studies varied from 11 to 120 participants in total. Studies used a variety of devices including lung flute, oscillating positive expiratory pressure (oPEP), positive expiratory pressure (PEP) mask, temporary positive expiratory pressure (TPEP), high frequency chest wall oscillations (HFCWO) and incentive spirometry. The duration of the interventions varied from one day to 26 weeks. Studies predominantly compared the intervention to usual care/medical management however three studies compare the device with breathing exercises[126, 137, 138]. Two studies compared more than one device to a control and were included in the review, these interventions were combined to make a single pair-wise comparison to the control group[139, 140]. The reported time points for the included studies ranged from immediately after the intervention session and up to six months. One study was a randomised crossover design and the remaining studies were randomised parallel group design[80] .

### 2.4.3 Risk of Bias

The overall risk of bias across the included studies was predominantly moderate (n=11). One study was considered low risk of bias and six studies had a high risk of bias (see table 2.1 and figure 2.2).

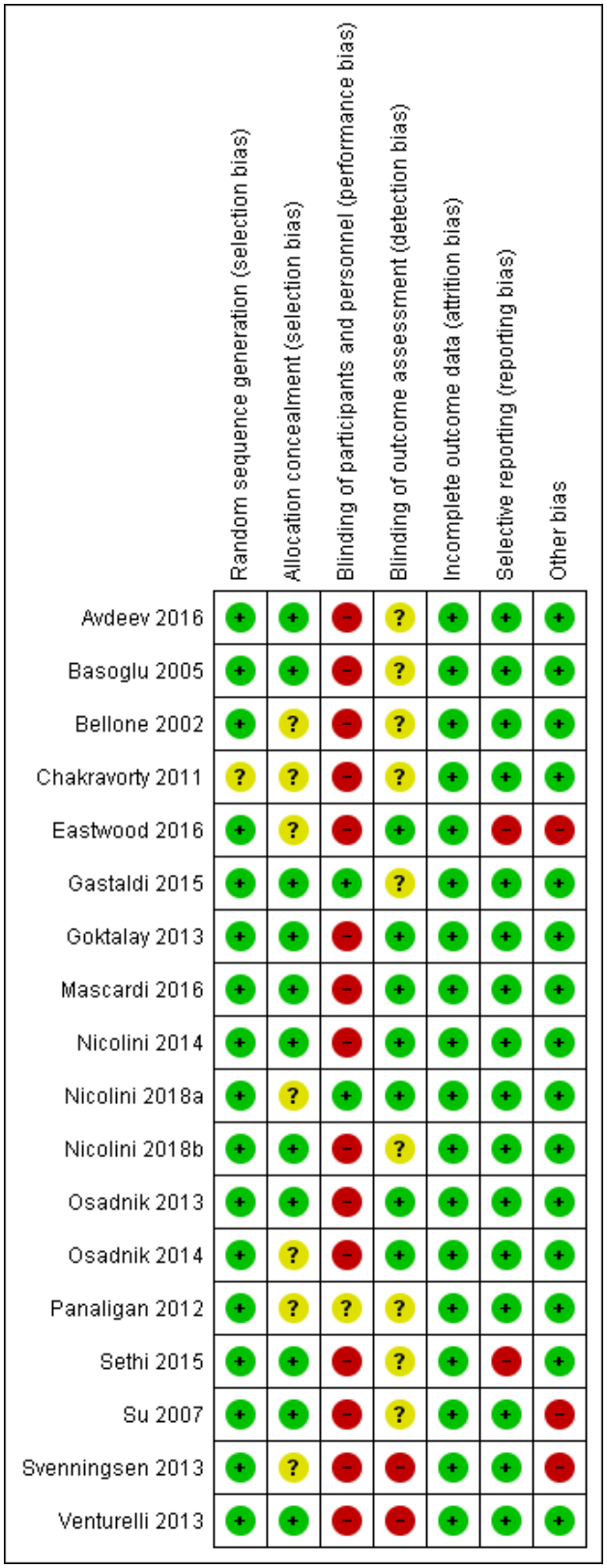



*Figure 2.2 Risk of bias assessment*

*Table 2.1 Included studies characteristics*

| Study | Participants | Intervention | Comparison | Outcome | Time points | Risk of Bias |
|---|---|---|---|---|---|---|
| **Stable COPD studies** | | | | | | |
| Chakravorty 2011[141] | N=30<br>Stable COPD (≥1 exacerbation in the previous 12 months).<br>Produces at least 25ml of sputum in a stable state. | HFCWO 2 treatment sessions per day at 20 minutes each for 4 weeks. 13-15Hz based on tolerance | Control | SGRQ<br>Non-standardised symptom score<br>Sputum wet volume | 4 & 10 weeks | High |
| Gastaldi 2015[142] | N=15<br>Stable COPD (no exacerbation in previous 4 weeks) | Flutter 30 mins with a break every 4 minutes. 1 day. | Sham | Sputum volume | Post intervention | Moderate |
| Mascardi 2016[143] | N=120<br>Stable COPD (GOLD stage 3-4) | TPEP 30 minutes per session twice daily. Duration of 15 days. | Control | Exacerbation frequency<br>CAT<br>BCSS | 15 days | Moderate |
| Nicolini 2013[144] | N=45<br>Severe-very severe stable COPD | TPEP 30-minute treatments twice daily for 15 days in total. | Control | CAT<br>BCSS | 15 days | Moderate |

| | | | | | | |
|---|---|---|---|---|---|---|
| Nicolini 2018a[139] | N=120<br>Stable COPD<br>(GOLD stage 3-4) | TPEP<br>oPEP<br>12 days 30 minutes twice a day | Control | Exacerbation frequency<br>CAT<br>BCSS | Exacerbation 1, 3, and 6 months<br>CAT, BCSS 26 weeks | Low |
| Nicolini 2018b[140] | N=63<br>Stable COPD<br>(GOLD stage 3-4) with bronchial hypersecretion (>20ml sputum for 2 consecutive days) | HFCWO<br>IPV<br>Twice per day 13-15hz 2-5cm$H_2O$. 20-minute treatments. Two-week interventions | Medical management | Sputum cell count<br>CAT<br>BCSS | 2 weeks | Moderate |
| Osadnik 2014[145] | N=13<br>Stable COPD<br>(≥GOLD stage 2) | PEP 10 tidal volume breaths to achieve a pressure of 10-20 cm$H_2O$ followed by 2 huffs and repeated 5 times over a 15 min period. | Huffs only | Sputum wet weight<br>VAS ease of expectorating | Post intervention (15 mins) | Moderate |
| Panaligan 2012[126] | N=25<br>Stable COPD<br>(moderate to severe) | Lung flute 20 sets of 2 deep breaths for 3 days | ACBT | Sputum Volume | Day 1,2 and 3 | Moderate |
| Sethi 2015[146] | N=69<br>Stable COPD<br>(GOLD stage 2-4) with cough productive of sputum. | Lung Flute Two breaths through the lung flute followed by 5 normal breaths and repeated 10 times followed by 2 huffs to complete 1 cycle. Two cycles twice a day for 26 weeks. | Usual care | CCQ<br>SGRQ<br>Exacerbation frequency | 2, 14 and 26 weeks | High |

| | | | | | | |
|---|---|---|---|---|---|---|
| Su 2007[147] | N=32<br>Stable COPD (produced 25cc of sputum in 24 hours) | PEP + Forced Expiratory Technique 10 cycles of 1-minute PEP + FET + relaxed breathing. Twice per day for 4 weeks. | Forced Expiratory Technique only | Sputum difficulty self-reported | 4 weeks | High |
| Svenningsen 2013[80] | N=27<br>Stable COPD self-reported sputum production. | oPEP 10-20 breaths 4 times per day for 28 days. | Control | SGRQ<br>PEQ | 28 days | High |
| Venturelli 2013[138] | N=39<br>Chronic mucus secretion patients (includes COPD) >25ml sputum per day. | TPEP Twice daily 20 minutes of breathing with 15 minutes of TPEP for 10 days. | Breathing exercises | Patient reported sputum<br>Sputum volume | Days 1 through to 10 | High |
| **Acute exacerbation studies** | | | | | | |
| Avdeev 2016[148] | N=50<br>Exacerbation of COPD and >25ml sputum production per day for 3 consecutive days. | HFCWO 15-20 minutes twice per day for 7 days | Control | BCSS<br>CAT | Day 1,3,7 | Moderate |
| Basoglu 2005[149] | N= 27<br>Hospitalised for exacerbation of COPD | Incentive Spirometry 5-10 breaths every hour for 2 months | Medical management | SGRQ | 2 months | Moderate |

| | | | | | | |
|---|---|---|---|---|---|---|
| Bellone 2002[150] | N=27<br>Hyper secretive COPD patients admitted to RICU | PEP Mask 10-15cm$H_2O$ 2 mins PEP breathing 2 mins assisted coughing and 2 mins undisturbed breathing (repeated for 30-40 mins) for 3 days | Cough assist | Sputum<br>Length of weaning<br>Treatment failure | Immediately after and one hour | Moderate |
| Eastwood 2016[137] | N=11<br>Exacerbation of COPD with self-reported sputum. | TheraPEP<br>3 sessions (2 unsupervised) in one day. 10 breaths 2 huffs, cough- repeat twice with a 5-minute break in between, 1-day intervention. | ACBT | BCSS<br>CAT<br>VAS | After treatment and one day post | High |
| Goktalay 2011[151] | N=50<br>COPD (GOLD stage 3-4) hospitalised with an exacerbation | HFCWO 20hz and 10hz. 20-minute treatment 3 times per day for five days. | Usual Care | SGRQ<br>Length of stay | 5 days | Moderate |
| Osadnik 2013[152] | N=92<br>Exacerbation of COPD with evidence of sputum or history of chronic sputum production. | PEP Mask 8-10 breaths at 10-20cm$H_2O$ followed by a huff and cough, repeated 5 times, 3 times per day for the duration of their admission | Usual Care | BCSS<br>SGRQ<br>Exacerbation frequency<br>Length of stay | At discharge, 8 weeks, 6 months | Moderate |

*Table 2.1 List of included studies. BCSS Breathlessness Cough and Sputum Score, CAT COPD Assessment Test, FET Forced Expiratory Technique, HFCWO High Frequency Chest Wall Oscillations, IPV Intermittent Pressure Ventilation, oPEP Oscillating Positive Expiratory Pressure, PEW Patient Experience Questionnaire, TPEP Temporary Positive Expiratory Pressure, SGRQ St Georges Respiratory Questionnaire, VAS Visual Analogue Scale*

### 2.4.4 Sputum clearance

Six studies assessed sputum volume objectively[126, 130, 138, 141, 145, 150]. The majority of these studies assessed sputum short term in where an increase in sputum clearance was considered favourable (n=5). Synthesis of five trials[126, 130, 138, 145, 150] yielded no significant effect on sputum volume, mean difference [95% CI] 0.43mls [-0.11, 0.97]. However, there was substantial heterogeneity ($I^2$ 59%) with a significant subgroup differences (p<0.01). There were no significant effects when compared to breathing exercises (0.02mls [-0.42, 0.46], p=0.93). When compared to a control or sham, there was a significant improvement on sputum volume with airway clearance devices (1.07mls [0.37,1.77], p<0.01). (Figure 2.3)

Three studies assess sputum clearance over a longer period, where the desired outcome is an overall decrease in sputum volume with treatment. There were no significant improvements for the intervention over a longer period (-0.22mls [-0.60, 0.16], p=0.71). One study used a control as a comparator and showed a reduction in sputum over time, which increased for those in the control group[141]. When compared to breathing exercises sputum volume reduces however this crosses the line of no effect (figure 2.4). All studies included were considered moderate to high risk of bias and therefore unable to perform sensitivity analysis.

Four studies[80, 138, 145, 147] assessed patient reported sputum; one study compared a device to breathing exercises and one with huffs only. There were no significant differences between groups (-0.39[-1.74,0.95], p=0.57), however there was substantial heterogeneity ($I^2$ 91%). Venturelli 2013 demonstrated a greater reduction in VAS using the TPEP compared to breathing exercises with a mean [SD] change of -15[23], -10.7[25.4] respectively, using a 100 point VAS scale of sputum clearance difficulty[138]. Those using the PEP in Osadnik 2014 had a higher VAS post intervention compared with the control group using huffs only, however this measure was not conducted at baseline and therefore were unable to determine the direction of change[145]. Due to differences in outcome measures and lack of

baseline measures, the analysis was performed with Venturelli 2013 and Osadnik 2014 removed[138, 145]. This resulted in significant improvements in patient reported sputum (-1.60[-2.19, -1.00], p<0.01), with heterogeneity $I^2$ of 0% (figure 2.5). One study was considered as low risk of bias and the results favoured the control group, however this data was collected post treatment and therefore baseline differences were not accounted for[145].

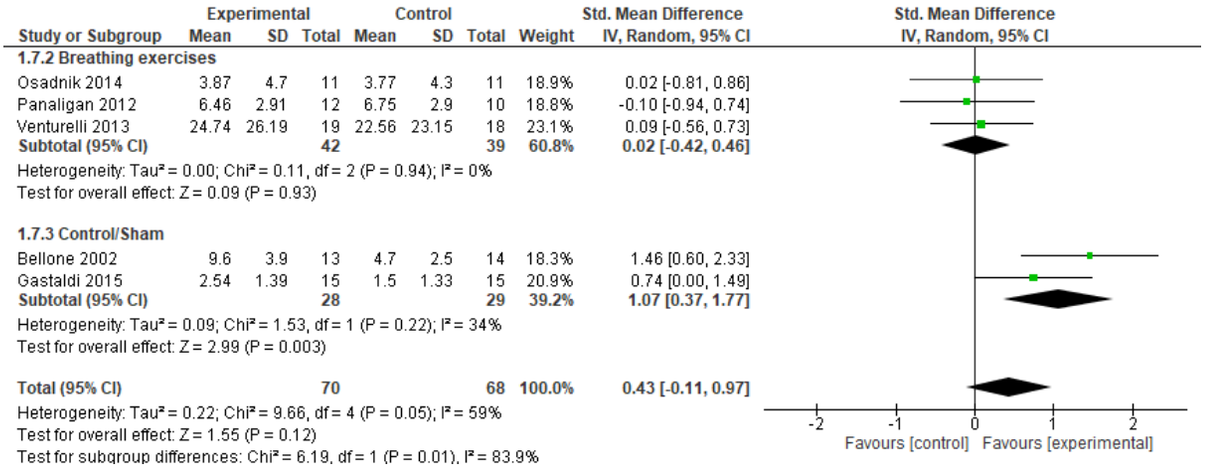



*Figure 2.3 Sputum volume short-term follow up*

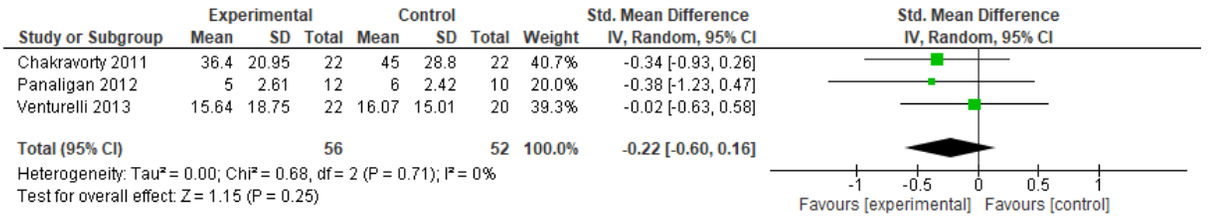



*Figure 2.4 Sputum volume long-term follow up*

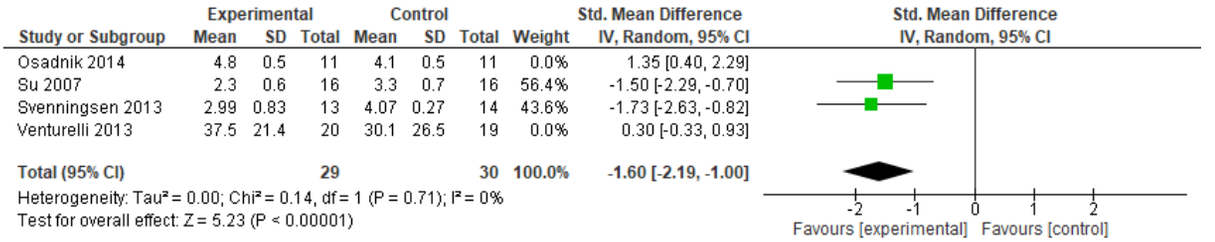



*Figure 2.5 Patient reported sputum clearance*

### 2.4.5 Exacerbation frequency

Four studies assessed the impact of devices on exacerbation frequency. Synthesis of these studies included a total of 330 participants. Two studies assessed 30 day exacerbation frequency with a rate ratio [CI] of 0.30[0.12, 0.72][139, 143] (figure 2.6). At six months, the rate ratio [CI] of 0.81 [0.58,1.12]. This did not reach statistical significance, however the $I^2$ was 58% and therefore these studies were considered heterogeneous. Osadnik 2013 compared PEP mask to a control group in patients hospitalised with an exacerbation of COPD and there was a considerably larger amount of exacerbations in this group (total 84 exacerbations across 86 participants) favouring the control group. The remaining three studies[139, 143, 146] explored exacerbation frequency in a stable cohort and there is a rate ratio [CI] of 0.50 [0.30,0.83] favouring the intervention, demonstrating statistical significance (p<0.01)(Figure 2.7). All the included studies compared airway clearance devices to usual care. All studies had a moderate to high risk of bias and therefore no sensitivity analysis was performed.

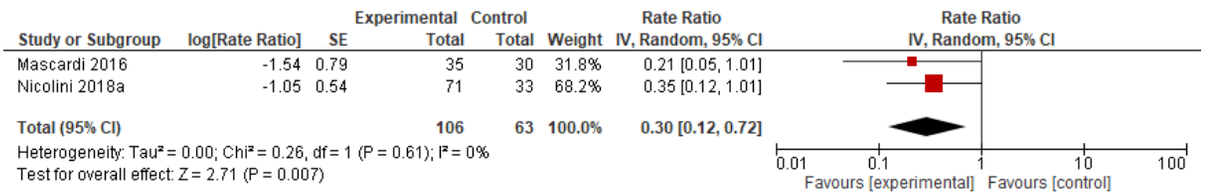



*Figure 2.6 30-day exacerbation*

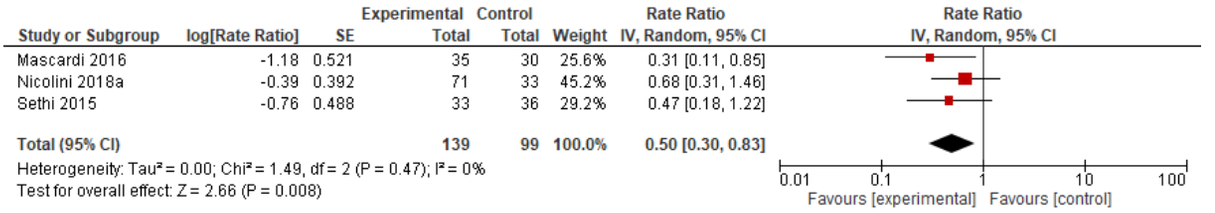



*Figure 2.7 6-months exacerbation*

### 2.4.6 Hospitalisations

One study reported hospitalisation frequency on patients recruited during an exacerbation when using PEP mask compared to usual care[152]. The incidence of hospitalisations was higher in the treatment group however this was not a significant difference. There were no other studies included in this review that explored hospitalisation frequency and therefore a meta-analysis was not performed. Two studies explored length of stay[151, 152] and compared HFCWO or PEP to a control or huffs only (figure 2.8). The mean [CI] length of stay was greater in those receiving the intervention however this was not significant (0.25[-0.03, 0.53], p=0.08). The included studies were considered moderate evidence and therefore no sensitivity analysis was performed.

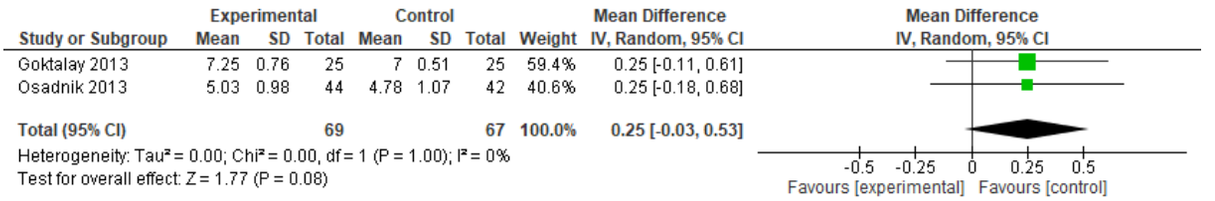



*Figure 2.8 Length of stay*

### 2.4.7 Health related quality of life

Health related quality of life was measured via the SGRQ and was reported in six studies with a total of 278 patients[80, 141, 146, 149, 151, 152]. Synthesis of the six studies demonstrated no significant improvements in SGRQ (-4.25[-9.35, 0.84], p=0.10) however these studies demonstrated high heterogeneity ($I^2$ 69%). Three of these studies recruited patients during an exacerbation and compared to usual care[149, 151, 153]. At eight weeks there were no significant differences between groups (-7.15[-20.46, 6.17], p=0.29), however these studies are heterogeneous ($I^2$ 86%)[149, 152]. Basoglu et al 2005 continued the intervention for 2 months whereas Osadnik et al 2013 and Goktalay et al 2013 intervention lasted the duration of the admission (approximately 5 days)[149, 151, 152]. Comparing these studies, there is a greater improvement in HRQoL when the intervention is continued post discharge with a between group difference of -22.5 [-32.88, -12.12] point improvement favouring the intervention for a longer period compared to a shorter duration. Three studies explored the SGRQ in a stable cohort of patients with COPD[80, 141, 146]. The mean difference is an improvement of -1.56 [-3.41, 0.30] points favouring the intervention however this is not statistically significant (p=0.10) (figure 2.9).

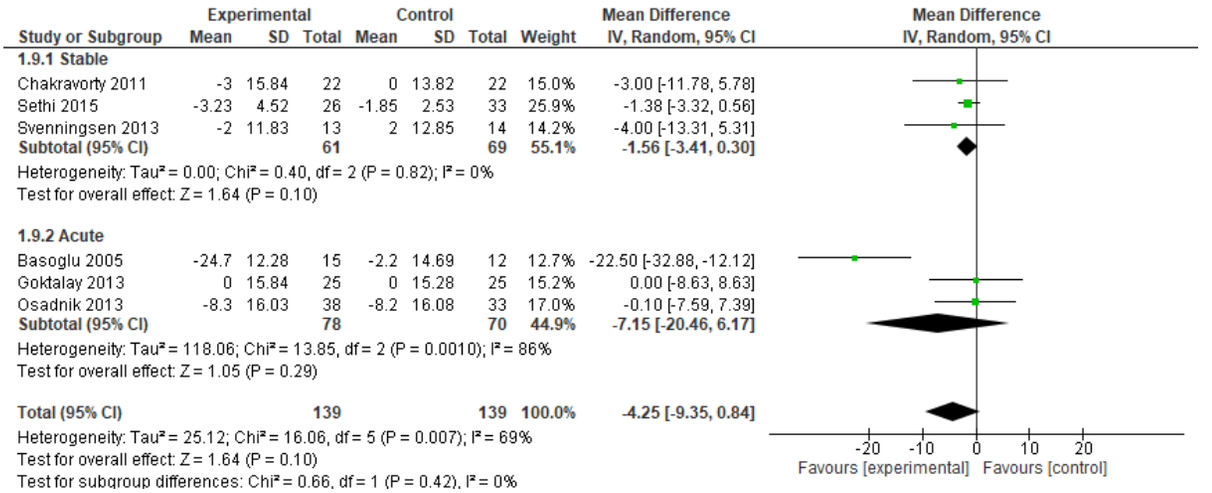



*Figure 2.9 Health Related Quality of Life*

### 2.4.8 Symptom burden

Symptom burden is measured using various tools including the CAT, BCSS and the Chronic COPD Questionnaire (CCQ). One study used the CCQ[25] and demonstrated an improvement in the intervention group when compared to usual care. Six studies used the CAT as a measure of symptom burden with a pooled sample of 289[137, 139, 140, 143, 144, 148] . There is a statistically significant improvement in the CAT -5.73 [-7.30, -4.15], p<0.01 in favour of the device group. There is a high heterogeneity among these studies ($I^2$ 53%). One study compared the intervention to breathing exercises and saw a favourable improvement in those receiving the intervention[137]. The intervention duration varied from one day to two weeks. Two studies recruited patients with an exacerbation of COPD and demonstrated greater improvements in the intervention arm[137, 148]. Two studies used HFCWO as an intervention to variable improvement[140, 148]. There was a large variation among studies included in the meta-analysis, which is unexplained by study design differences. One study was considered as low risk of bias, and there was a mean change [CI] -5.30 [-6.86, -3.74] in favour of the intervention. See figure 2.10.

The BCSS was used in six studies with a pooled sample of 376 patients[137, 139, 140, 144, 148, 152, 154]. There were statistically significant improvements favouring the intervention (-1.72 [-2.85, -0.59], p<0.01), however there was high heterogeneity among these studies $I^2$ 83%. Three studies recruited patients during an exacerbation of COPD with an intervention duration of one, five and seven days[137, 148, 152] -1.71 [-3.50, 0.08] (p=0.06, $I^2$ 84%) The stable cohort had intervention phases between 12 and 15 days. Overall, the results favour the intervention with a mean difference of -1.74 [-3.46, -0.02] (p=0.01, $I^2$ 38%); however, there is a large variation. One study was considered low risk of bias and included in the sensitivity analysis. The mean change [CI] was 0.50 [-0.58, 1.58] in favour of the control group (figure 2.11)[139].

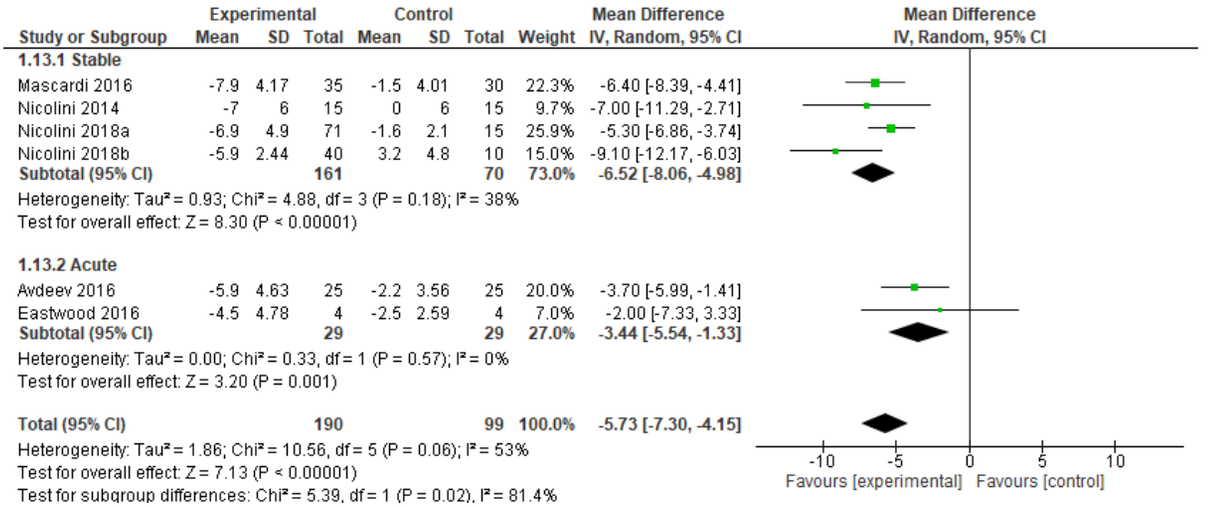



*Figure 2.10 COPD Assessment Test*

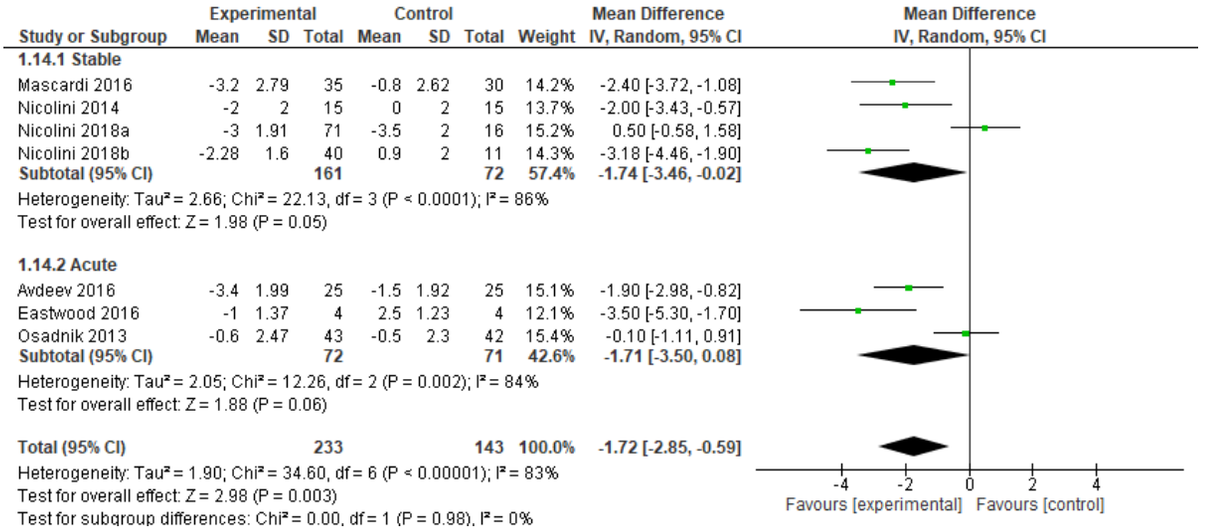



*Figure 2.11 Breathlessness Cough and Sputum Scale*

## 2.5 Discussion

### 2.5.1 Main findings

Of the 18 included studies, these were predominantly moderate risk of bias (61%). 6% of studies had a low risk of bias and 33% considered high risk of bias. These studies used a variety of different devices for airway clearance in both stable and exacerbating cohorts. Three studies compared devices to breathing exercises, one to a sham and the remaining 15 to medical management or usual care. The results of this systematic review and meta-analysis demonstrates significant improvements in sputum clearance (short term), patient reported sputum clearance, exacerbation frequency at 30 days and 6 months and symptom burden for participants using a device to aid secretion clearance. There were statistically significant improvements in health-related quality of life in a cohort of AECOPD.

Sputum clearance measured by weight has been considered as short-term and long-term follow up as it is believed the intentions of these outcomes are different. Airway clearance techniques intend to clear more sputum in the short term but an overall reduction in sputum retention in the long term, leading to a reduction in long term sputum weight. Sputum clearance was significantly better for the intervention when compared to a control however this is not seen when compared to breathing exercises as both interventions are equally as effective at clearing sputum. When compared to breathing exercises or control, long term sputum clearance using devices has no additional effect. Patient reported sputum outcomes favour the intervention when compared to a control and have a longer intervention, however these results are variable. Participants recruited into the included studies were not necessarily recruited based on sputum retention as a symptom and therefore this may include participants that do not self-report issues with sputum retention which may underestimate its effect. Additionally, the use of sputum weight as a measurement lacks clinical application and meaning for patients as it is unexplained whether a reduction in sputum weight is caused by more effective clearance techniques or

a reduction in sputum production. Patient reported sputum clearance measures have demonstrated variability and therefore are difficult to interpret.

The use of devices demonstrates a significant reduction in exacerbation frequency in a stable cohort which may have potential in reducing healthcare costs. Participants receiving the intervention at the time of an exacerbation have a longer length of stay; however, this may be skewed by the need to deliver the active treatment resulting in a delay in discharge. Health related quality of life as measured by the SGRQ, improves with device use in stable cohorts though this is not statistically significant. There were improvements in the SGRQ for exacerbating cohorts which were significant if patients receive a longer intervention (2 months). This questionnaire is not specific to the symptoms of excess sputum and includes other domains of activity and impact. The breakdown of these domains is not reported, and it is likely the interventions mostly impact on the symptom domain and may explain the results being non-significant though, mean changes do meet the minimal clinical important difference (4 points)[155]. Symptoms measured by the CAT and BCSS are hugely variable and are not explained by differences in the methodology. This may be reflective of the outcome measures implemented in the study. The CAT has good internal consistency and high repeatability, however, has a variety of domains that may be unaffected by sputum clearance such as activity and confidence. The BCSS has acceptable validity and repeatability however was intended to be used as part of a daily diary. The variability may be explained by properties not reported in the studies such as how the questionnaire was administered, and the level of recall required.

### 2.5.2 Comparison to previous reviews

These results demonstrate significant improvements in sputum clearance with a short term follow up which is comparable to other reviews that include breathing exercises as an airway clearance technique[120] . This review has shown statistically significant reductions in exacerbation frequency for stable patients that have not been noted in previous reviews

and that exceed the known minimal clinical important difference. Results did not demonstrate statistically significant improvements in HRQoL; however, this did meet the minimal clinical important difference which has been reported in previous reviews. These results add further exploration of symptoms that have not previously been reported[2, 120] .

### 2.5.3 Strengths and limitations

This research systematically reviewed and synthesised the available evidence on use of airway clearance devices in the management of patients with COPD by following a pre-set, publicly available protocol. This review includes 18 studies with a pooled sample of 855 participants. The wide inclusion criteria and sensitivity analysis strengthens the results of the study. Of the 18 included studies, these were predominantly moderate risk of bias (61%).

Participants that were included in these studies were not recruited on their sputum retention status and therefore these results are generalizable to the entire COPD population, however the results may underestimate the effect on patients with larger volumes of sputum. Additionally, the use of sputum weight as a measurement lacks clinical application and meaning for patients as it is unclear whether a reduction in sputum weight is caused by improved clearance or a reduction in sputum production. Patient reported sputum clearance measures have demonstrated variability and therefore are difficult to interpret. The reduction in exacerbation frequency exceeds the reported MCID of 20%[155]. The substantial heterogeneity demonstrated in the estimate of effect of airway clearance devices on symptom burden outcomes, particularly BCSS, was not addressed through pre-specified subgroup or sensitivity analysis and therefore the results should be interpreted with caution. HRQoL improves with device use in stable cohorts and in exacerbating cohorts which receive a longer intervention (2 months). The SGRQ is not specific to the symptoms of excess sputum and includes other domains of activity and impact. The breakdown of these

domains is not reported, and it is likely the interventions mostly impact on the symptom domain.

### 2.5.4 Implications for research

There has been an increase in airway clearance research which has strengthened the evidence base for this intervention. The research exploring devices during an exacerbation or hospitalisation is limited and more research into this area is recommended. Patient reported sputum clearance and symptom burden measurements seem to demonstrate a large variability and therefore further research into suitable outcome measures for airway clearance would be recommended. Further research to determine which patients have the greatest response to treatment may be useful for areas where services are limited.

### 2.5.5 Implications for practice

This review supports the use of airway clearance devices for patients with COPD. The use of devices is effective at improving sputum clearance, reducing exacerbations and improving symptom burden. The risk ratio of exacerbations at 6 months is 0.50[0.30, 0.83] based on moderate to high quality evidence. The results based on the CAT and BCSS meet the minimal clinical important difference. Based on this review the provision of devices to manage secretions is appropriate, particularly in a stable cohort of patients which is based on moderate to strong evidence. This research makes no clinical recommendations for the types of devices that should be offered, or whether they are superior to breathing exercises. Current guidelines recommend the use of airway clearance devices for patients with excess secretions however based on these results devices are beneficial for all patients with COPD population. The recommendation states devices may be useful in managing an exacerbation however, the evidence is limited for the provision of devices in AECOPD[3].

## 2.6 Conclusion

The use of devices is effective at sputum clearance however these improvements are not superior when compared to breathing exercises. The results of this study demonstrate improvements in exacerbation frequency, health related quality of life and symptom burden when using devices for airway clearance, which exceed the known minimal clinically important difference. The improvements in health-related quality of life during an exacerbation are significant when the intervention is continued for a longer duration than the hospital admission. The use of patient reported sputum clearance as a tool, demonstrates variability particularly when used as a short term follow up. These results support the use of devices for airway clearance however there is a need for further evidence in exacerbating cohorts and a demand for specific and reliable outcome measures. The interpretation of these results should be based on the quality and quantity of the evidence.

# 3 Methods

## 3.1 Ethical Approval

Ethical approval was obtained through local research ethics committees, the health research authority and research and innovations department and University Hospitals of Leicester. Ethical approval for the feasibility trial was obtained by the London Central Research Ethics Committee (reference 16/LO/0924) and from the Leicester South Research Ethics Committee for the randomised controlled trial (reference 167/EM/0156) (appendix 3). Trials were registered through the ISRCTN registry. ISRCTN81979106 and ISRCTN45695543.

## 3.2 Sample Population

Participants were recruited in two respective cohorts for the feasibility and randomised controlled trial, however many of the methods overlap. Participants were sampled from a variety of avenues including consultant respiratory and pulmonary rehabilitation clinics, research databases, pulmonary rehabilitation databases and self-referral from posters displayed in Glenfield Hospital. Once identified, potential participants were given a copy of the participant information sheet and a reply slip to express their interest. On receipt of the reply slip participants were screened via the telephone and eligibility was confirmed at the beginning of visit one and through the review of the medical notes and spirometry. The full eligibility criteria are listed below:

- Inclusion:
    - Participants willing and able to give written informed consent for participation into the study.
    - Aged 40 years or above.

- Confirmed diagnosis of COPD ($FEV_1$/FVC ratio <0.70)
- MRC score of 3 or more (however this was changed to 2 or more for the randomised controlled trial to increase recruitment and to compare to other breathlessness interventions such as pulmonary rehabilitation where inclusion is MRC 2 or more).
- Able to read and write in English.

- Exclusion:
  - Significant disease other than COPD that could cause dyspnoea or exercise limitation.
  - Contraindications to exercise (e.g. unstable cardiovascular disease, hypertension).
  - Contraindications to using HFAO device (severe right heart failure with hypertension, current severe haemoptysis, ineffective cough, rib fractures, pregnancy, current or previous pneumothorax, epilepsy, current pulmonary embolism, oesophageal varices, recent thoracic, gastro-intestinal tract or facial surgery or trauma, haemodynamic instability, acute sinusitis or active nosebleed, raised intracranial pressure, recent dental, head, neck, ear, nose or throat surgery or trauma).
  - Currently using the Aerosure device or any other secretion clearance devices as part of their normal COPD management.
  - Previously engaged in exercise-based research or pulmonary rehabilitation in the last six months.
  - Inability to secure informed consent.
  - Those unable to communicate in full English were excluded as the user manual is only available in English.

## 3.3 Pulmonary function

### 3.3.1 Spirometry

#### *3.5.1a Equipment*

Spirometry was performed with a Vitalograph ALPHA touch spirometer with Spirotac software. The user inputs the participants gender, date of birth, ethnicity, height, weight and smoking status. Predicted values were calculated based on the age, height, gender and ethnicity based on the European Respiratory Society (ERS) 1993 reference values; however, it is recognised that these values may lead to under-diagnosis in the elderly, black and Asian populations[156, 157, 158]. Spirometers were calibrated daily by departmental staff. Spirometry was used as a screening tool and for comparison with the lung clearance index and it is not expected to change following the intervention phase.

#### *3.5.1b Testing procedure*

Spirometry was performed in line with the best practice guidelines provided by the ERS/ATS[158]. The patient was positioned in upright sitting with a nose clip in situ. After full inspiration, patients were instructed to forcefully exhale until they reached end expiratory volume. This was performed a minimum of three times and until FVC is within 10%. The test was repeated up to seven times in order to replicate 3 acceptable tests. The best score was taken from the three tests. The results displayed the following: Forced Expiratory Volume in 1 Second ($FEV_1$), Forced Vital Capacity (FVC), and the $FEV_1$/FVC ratio, all of which were presented as absolute values and as a percentage of predicted values based on the ERS 1993 reference values. In this instance, spirometry was performed to confirm a diagnosis of COPD and was not used for initial diagnostic purposes. In order to confirm a diagnosis of COPD the $FEV_1$/FVC ratio must be below 0.70.

### 3.3.2 Maximal respiratory pressure testing

Maximal voluntary inspiratory and expiratory mouth pressures ($PI_{max}$/$PE_{max}$) are the most frequently reported non-invasive estimates of respiratory muscle force. The generated pressure is recorded at the mouth during a quasi-static short maximal inspiration (Muller manoeuvre) or expiration (Valsalva manoeuvre). No airflow occurs during these manoeuvres. The assessment is performed using a handheld device (Micro RPM), in which participants were instructed to forcefully exhale from total lung capacity (TLC), and inhale forcefully from residual volume (RV) for two seconds as per the American Thoracic Society and European Respiratory Society (ATS/ERS) statement[159]. The device has a built-in leak in order to allow for the glottis to open and pressure obtained to reflect the pressure of the respiratory muscles. In the absence of this, the recorded pressures obtained may be a result of the cheeks, mouth and buccal muscles. Participants were positioned in upright siting and performed the test through a rubber flanged mouthpiece with a nose clip in situ. It is possible that pressures may be higher if using a non-flanged mouthpiece due to a reduction in leak, however this is not significant. On expiration, participants are instructed to support their cheeks to prevent a loss in pressure due to inflation of the cheeks. The test is performed a minimum of four times and continued for up to seven attempts in order to gain the participants best effort. Variability would be within 5-10%. Familiarisation tests are not necessary as no learning effect has been demonstrated[160]. The test was performed by an experienced technician to achieve maximal effort and was be explained clearly to participants as this test is unfamiliar.

There is a considerable variability in reported normal values in both $PI_{max}$ and $PE_{max}$. In this population group it is unlikely to have an expiratory pressure less than the inspiratory pressure. There is a decline in respiratory function in the aging population, and the reported variance if respiratory muscle pressures is low. Expiratory muscle weakness was assessed via the individual lower limit of normal based on age and gender as per Evans formula: 117-(0.83xage) for males and 95-(0.57x age) for females[161]. Inspiratory muscle weakness was

defined as below 60cm$H_2O$ as per the ATS/ERS guidelines, however a diagnosis of inspiratory muscle weakness should be interpreted with caution, though a 'normal' $PI_{max}$ value is likely to exclude clinically relevant inspiratory muscle pathology. With the variability in reference values for respiratory muscle weakness it is difficult to definitively diagnose, however as an outcome measure, it is possible to detect a change in response to an intervention. The minimal clinically important difference for the $PI_{max}/PE_{max}$ is unknown at present however the cited mean change in the meta-analysis was 13cm$H_2O$[162] .

### 3.3.3 Lung clearance index

#### *3.5.3.a Equipment.*

The Lung Clearance Index (LCI) is calculated via a Multiple Breath Washout (MBW) and was measured using an open circuit, modified Innocor photo-acoustic gas analyser (Innovision A/S, Denmark). The photo-acoustic gas analyser measures the absorption of Carbon Dioxide ($CO_2$), Sulphur Hexafluoride ($SF_6$) and Nitrogen ($N_2O$) at high accuracy and is sensitive to low levels of $SF_6$ ranging between 0-0.5% (Innocor manual). $SF_6$ is commonly used as a measure of MBW and is an inert gas not found in room air and therefore requires a period of wash in. The photo-acoustic gas analyser exposes the gas sample to infra-red light at three frequencies which is absorbed by the gases and converted into heat. The separate frequencies enable cyclical heating and cooling of the gases which produces pressure waves at specific frequencies for each compound. These waves are then detected by a microphone and used to determine the concentration of each compound. Accuracy of the MBW relies on calibrations which were performed at three different flow rates using a 1L syringe prior to use. Figure 3.1 shows the Innocor.

The Innocor is modified to reduce pre-capillary dead-space and is connected to the pneumotachometer, bacterial filter, and rubber mouthpiece which are the patient interface. Dead space is accounted for during the analysis phase. The gas sample needle is

attached distally to the pneumotachometer mesh. The patient interface is connected to a Douglas bag which contains $SF_6$. The MBW system set up is seen in Figure 3.2.

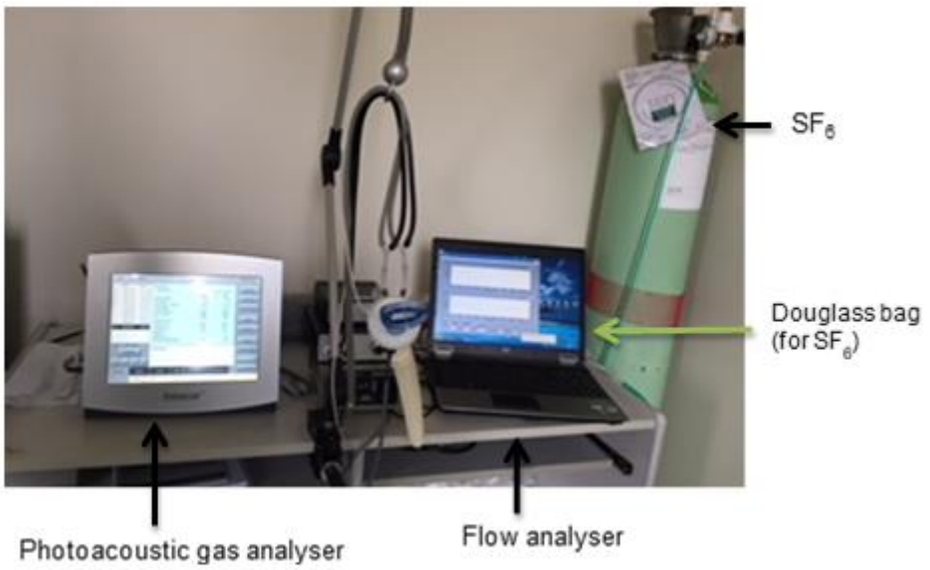



*Figure 3.1 Innocor set up*

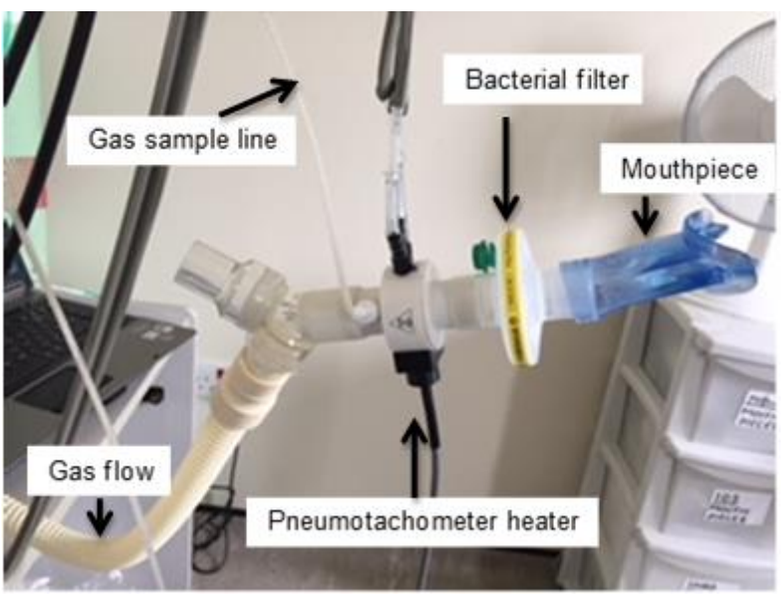



*Figure 3.2 Patient interface of Innocor*

### *3.5.3.b Testing Procedure.*

Participants were seated in comfortable upright sitting, wearing a nose clip and breathing exclusively through the rubber mouthpiece. A good seal around the mouthpiece is required for the duration of the test. Participants were instructed to perform tidal breathing calculated by 7-12mls per kg of their actual body weight. Some testing protocols advise standardised tidal breathing of 1L however this was not performed due to the likelihood of higher tidal volumes in COPD particularly among those who are hyperinflated. The initial phase of the test requires a wash in phase of $SF_6$ gas, during which participants breathe a mixture of air containing 0.2% $SF_6$ which is stored in the Douglas bag. Participants inhaled via this open circuit system (figure 3.1) and exhaled through a valve into the atmosphere. Once participants had achieved 0.2% $SF_6$ concentration the Douglas bag was disconnected, and the washout phase began. Participants remained breathing via the rubber mouthpiece at tidal volumes until the $SF_6$ tracer gas reached $1/40^{th}$ of the initial concentration for a minimum of three consecutive breaths[163]. At this point the test was then terminated. The MBW requires testing in triplicate for each participant and for a valid dataset, the participant must achieve a minimum of two consistent tests differing no more than 10% in the FRC. If there were not two consistent tests' then the participant data was excluded.

### *3.5.3.c Analysis of LCI data.*

Data from the Innocor was transferred to a computer and analysed using custom MatLab algorithm software provided by the team at the Respiratory BRC in collaboration with the University of Nottingham. Flow-gas delay time was calculated for each washout which is used to synchronise flow and $SF_6$ concentration signals. FRC was calculated by dividing the total volume of $SF_6$ expired by the difference between end tidal volume concentration ($C_{et}$) at the beginning and end of the washout period. The $C_{et}$ was calculated as the first breath that fell below $1/40^{th}$. The total volume of expired $SF_6$ was calculated by integrating the flow of $SF_6$ concentration and subtracting re-inspired $SF_6$. LCI was defined as the cumulative

expired volume at the point in which the $C_{et}$ fell below 1/40$^{th}$ of the initial value and divided by the FRC. This is then corrected for equipment dead-space. Phase III slope parameters were calculated by a custom MATLAB algorithm and pooled slopes were analysed as a mean of the three tests (two, where one was eliminated).

## 3.4 Exercise capacity

### 3.4.1 Incremental Shuttle Walking Test (ISWT)

The Incremental Shuttle Walking Test (ISWT) is recommended clinically as an outcome measure for exercise tolerance and is widely used, particularly in pulmonary rehabilitation[164]. Participants were required to complete a familiarisation walk, as differences can be attributed to a learning effect of approximately 30m. During the incremental shuttle walking test, participants were required to walk at a speed dictated by a pre-recorded tape. The test was performed on a 10-metre track and paced externally by a bleep recording. Participants were asked to keep in time with the bleeps and were initially paced by the investigator. Every minute they were instructed to increase their walking speed to keep up with the increasing speed of the tape. Participants were instructed to stop the test when they become too breathless to carry on. The test was stopped by the researcher if safety was compromised, commonly exercise induced desaturation or raised heart rate approaching participants maximum. Participants had a 30-minute break between each exercise test to ensure adequate rest. This was a progressive and maximal exercise test in order to understand the participants true exercise tolerance. Upon completing the test, the assessor explores the patients perceived dyspnoea and exertion based on a ten-point scale- the Borg breathlessness score and the rate of perceived exertion. Participants oxygen saturations and heart rate were measured throughout the duration of the test and the blood pressure was recorded pre and post in order to monitor the participants response to exercise and to maintain safety[164]. The ISWT scores were presented in metres and an improvement of 35m is considered clinically meaningful[165].

### 3.4.2 Endurance Shuttle Walking Test (ESWT)

The Endurance Shuttle Walking Test is an externally paced test. The maximal score achieved on the ISWT was used to calculate the endurance speed. The $VO_2$ peak is estimated based on 4.19+(0.025xISWT distance) and the closest speed CD is used for the test[166]. This was performed at 80-85% of their maximal speed achieved on the ISWT. Participants were required to walk a 10-metre track, turning around the cones and in time with a series of recorded bleeps. The test began with a warm-up period of two minutes, after which the test speed increased, and patients were instructed to increase their walking speed. This speed continued for the duration of the test. This test was timed and the participant were instructed to continue for the maximum duration until dyspnoea prevails[164]. The time was recorded in seconds from after the warm-up until participant completion and the Borg scale of perceived breathlessness and rate of perceived exertion was recorded. The MCID for the ESWT is an improvement of 174-279 seconds[167].

## 3.5 Health Related Quality of Life

All health-related quality of life questionnaires was administered by the participant with minimal guidance from the researcher during the assessment. The Chronic Respiratory Questionnaire and COPD Assessment Test was also completed at three months via a postal follow up in the Training to Improve Dyspnoea Study (Chapter 5).

### 3.5.1 Chronic Respiratory Questionnaire

The Chronic Respiratory questionnaire (CRQ)-self reported measures both physical and emotional aspects of chronic respiratory disease. This is a 20-item questionnaire in which patients respond on a 7-point scale per question. This explores four categories: dyspnoea, emotion, fatigue and mastery. The dyspnoea domain was used as a primary outcome measure for the results of the randomised controlled trial in chapter 5. This tool enabled

patients to identify activities that were most important to them and score on a seven-point scale with responses tailored to each question. The lower the score the higher degree of disability. Scores were used per domain and as a total change[67]. The minimally clinically important difference (MCID) is 0.5 per domain and total change of 2[168]. The scores are presented as a mean and sum of the domains.

### 3.5.2 COPD Assessment Test

The COPD assessment test (CAT) is a patient administered questionnaire assessing globally the impact of COPD on health status. Domains explore cough, sputum, dyspnoea, chest tightness, stairs, activities of daily living, confidence, sleep and energy. Each domain was scored on a six-point Likert scale from zero to five and added together for a total score out of a maximum of 40. The higher the score dictates a higher symptom severity and burden on quality of life. The CAT was developed by Jones et al based on a number of focus groups and interviews with patients with COPD and physicians[133]. These explored aspects of COPD which were most important in defining patients. A decrease in total score would demonstrates improvements in symptoms and a change of two points was considered clinically significant[169].

### 3.5.3 Hospital Anxiety and Depression Scale

The Hospital Anxiety and Depression Scale is a 14-item questionnaire with 4 choice of responses which are score 0-3. Half of the questions relate to anxiety and the other half relate to depression. There is a maximum score of 21 per domain. A score of 8-11 would indicate mild symptoms of anxiety or depression, 12-15 indicates moderate symptoms of anxiety or depression and 16 and over would be categorised as severe. For the purpose of this research, patients' raw scores were compared to assess changes in anxiety and depression symptoms. A change of -1.5 in either domain was considered clinically meaningful[170].

### 3.5.4 Leicester Cough Questionnaire

The Leicester Cough Questionnaire was developed as a health-related quality of life questionnaire to assess the impact of idiopathic chronic cough. It was designed in brief and simple to administer and score and is appropriate to monitor patients in relation to their cough frequency and how this has impacted them. This measure can was self-completed and was designed to be sensitive to detect change in symptoms and subsequently health-related quality of life. The questionnaire was designed on a population of adults with chronic cough, defined as an unexplained cough lasting more than three weeks. This questionnaire contains 19 items that make up three domains: physical, psychological and social[171].

Each question was scored on a seven-point Likert response scale tailored to each question. This was self-administered and took 5 minutes to complete. Data was analysed in 3 domains: physical, psychological and social or as a total score. The lower the score, the more a cough is impacting a patient's wellbeing. Scores were presented as a mean for each domain and the sum of the domains. The total score was 21 with a higher score indicated less affected by symptoms of cough. In order to be considered clinically significant there must be a total change of between 1.3-2.8, however this has only been validated in chronic cough and not within COPD[172].

### 3.5.5 London Activity of Daily Living Questionnaire

The London Chest Activity of Daily Living (LCADL) questionnaire is composed of a list of 15 activities with a response of: 'wouldn't do anyway', 'do not get breathless', 'I get moderately breathless', 'I get very breathless', 'I can't do this anymore' and 'I need someone else to do this'. Each question was scored from 0-5 respectively and categorised into domains self-care, domestic, physical and leisure. This questionnaire allows for valuable insight into activities patients can no longer do as a result of dyspnoea comparatively to

questionnaires that only capture activities that provoke dyspnoea[69]. This questionnaire was self-administered with a brief instruction. A higher score indicates a higher limitation in activities of daily living with a maximum score of 75. A 4 point change in the total score would be considered clinically meaningful[173].

### 3.5.6 Medical Research Council Dyspnoea Scale

The Medical Research Council (MRC) dyspnoea scale is clinically used, and often in conjunction with spirometry measures to assist with diagnosis and severity[174]. This scale grades breathlessness according to the level of exertion required to experience it[3]. This scale measures the perceived respiratory disability and categorised patients in a five-point scale seen in table 3.1[175]. The MRC dyspnoea scale is simple to administer and has been demonstrated to compliment $FEV_1$ in the classification of disease severity[176]. The MRC dyspnoea scale is widely used both clinically and in research. However, it is not sensitive to the effects of an intervention. The differences between scores are non-linear and therefore a change from a two to a one is not comparable to a change from a three to a two etc. In this study, the MRC dyspnoea scale was predominantly used as a screening tool, in order to ensure participants are suitably breathless to benefit from a device aimed at improving dyspnoea. The minimal clinically important difference for the MRC dyspnoea scale was a one-point change[155].

*Table 3.1 Medical Research Council Dyspnoea score*

| MRC Grade | Description |
|---|---|
| 1 | Not troubled by breathlessness except on strenuous exercise |
| 2 | Troubled by shortness of breath when hurrying or walking up a slight hill |
| 3 | Walks slower than contemporaries on a level surface due to breathlessness or has to stop for breath when walking on a level surface at your own pace |
| 4 | Stops for breath after walking 100 yards or after a few minutes on a level surface |
| 5 | Too breathless to leave the house or breathless when dressing or undressing |

*Table 3.1 MRC Medical Research Council.*

### 3.5.7 Multidimensional Dyspnoea Profile

The Multidimensional Dyspnoea Profile (MDP) is a questionnaire developed at Harvard University to further explore the impact of dyspnoea in relation to distinct sensations. With the expanding knowledge that dyspnoea is multi-factorial and may follow pain pathways, there is a need to capture the complexity of dyspnoea[51]. Dyspnoea outcome measures are often limited to the quantity of dyspnoea, however the MDP aims to explore the type of sensation, its level of unpleasantness and any emotions associated with this. This questionnaire was administered by the researcher and explored sensory and affective aspects of dyspnoea. The time point was chosen by the researcher, in this instance it was the previous two weeks in order for comparison across other, similar questionnaires (such as the CRQ). This questionnaire explored different sensations of dyspnoea and any emotions or feelings associated with it. This was scored in three components: affective scale, in which patients score the unpleasantness of their breathing on a 0-10 Likert scale; Sensory choice, where patients chose the sensation that best describes their dyspnoea; Sensory scale which scores the five sensations 0-10 based on intensity and lastly; affective scale, where patients score five emotions on a 0-10 scale based on intensity. The sensations explored were chest tightness, air hunger, muscle work/effort, mental effort/concentration

and breathing a lot. The emotional aspects explored were depression, anxiety, frustration, anger and fear. There was space to add other sensations or feelings if appropriate to do so. This questionnaire was analysed in individual domains and total score with a higher score indicating more severe breathlessness[39].

## 3.6 Physical activity

Physical activity was measured using an accelerometer Actigraph device developed by ActiLife. The use of Actigraph for activity monitoring has been validated in patients with COPD and has been demonstrated to be more reliable if worn around the waist[177]. Participants were instructed to wear the accelerometer around their waist, on the anterior superior iliac spine of the dominant leg. Devices were worn for one week, day and night and removed for water-based activities. The devices were worn prior to the intervention phase and on the last week of the intervention phase. Step counts and time spent in sedentary, light, moderate and vigorous activity were analysed. Data was downloaded and analysed using Actilife software and inputted into SPSS. In order to be eligible for analysis there had to be at least one day of wear. One day must have at least eight hours of data in order to be included. The mean for the total eligible days was used in the analysis.

## 3.7 Device

The HFAO device used in this thesis was the 'Aerosure Medic© by Revitive' which is characterised as a High Frequency Airway Oscillating device (HFAO). This is a handheld, battery operated device which delivers oscillations at two different frequencies. There are two established settings with varying frequencies of oscillations at 15 and 25Hz. The device is used in self-ventilating patients and they are instructed to turn the device on, place the mouthpiece in their mouth and initiate maximal breathing, attempting to reach full vital capacity on inhalation, and forced exhalation to reach residual volume. This is continued for a minimum of five minutes to patients' tolerance. This device is not designed to be used

with those with severe right sided heart failure, history of pneumothorax, current significant haemoptysis or cardiovascular instability. It is hypothesised that this device is a flow resistive device, whereby a higher flow through the device would deliver a higher resistance to the user. Therefore, it is reasonable to assume that this device would provide some degree of respiratory muscle training, however the exact pressures a user is receiving is unknown.

Benchmark testing carried out independently by Actegy LTD and Kings College London attempts to explain these pressures. The protocol for this testing compared the Aerosure Medic© (setting one), Acapella Blue© low flow, Acapella Green© high flow and the Flutter©. The Acapella© has a valve mechanism that provides oscillations on exhalation, the resistance can be changed minimally, and the blue version was developed for patients that are unable to achieve the desired flow to initiate the oscillations. The flutter has a steel ball inside that creates oscillations to the breath. This can be used in upright sitting or at 45-degree head tilt to target the central and peripheral airways, respectively. These devices are all known oscillatory positive expiratory pressure devices used primarily to target secretion clearance. Three versions of each device were tested for continuity and placed in a test rig with the following measures taken: Maximum-minimum range ($cmH_2O$), mean pressure ($cmH_2O$) and peak pressure ($cmH_2O$). These measurements were taken over five repetitions per device. The expiratory flow rates of 10, 20, 30 and 50l/min were delivered through the devices. The Acapella Blue was intended as a low flow device and therefore was tested at volumes of 10 and 20l/min. Test data was analysed for outputs of: average cyclic frequency (Hz), minimum-maximum pressure range ($cmH_2O$), mean pressure ($cmH_2O$), maximum pressure ($cmH_2O$), and minimum pressure ($cmH_2O$). The protocol also compared identified inspiratory muscle training devices: Aerosure Medic (setting 2), Aerosure Sport (setting 1- low, setting 1- high) and Respifit. These devices were tested at inspiratory flow rates of 20, 40, 60, 80 and 100 l/min.

The frequency of oscillations remains the same throughout different flow rates for the Aerosure Medic© device as described by the manufacturer. Setting one is described to deliver oscillations at a frequency of 15Hz and setting two at 25Hz. Testing revealed that oscillations were delivered at a mean of 16 and 27Hz respectively, this difference is considered negligible. Other devices show a variance in frequencies as the oscillations are developed by the user's flow, whereas the Aerosure Medic© delivers oscillations provided by the battery-operated spinning valve. The mean pressure of the Aerosure medic© ranges from 5-42cm$H_2O$ throughout flow rates 10-50l/min, confirming the hypothesis that this device is flow resistive. Figure 3.3 compares the mean pressures of each device at each flow rate. The Acapella green and blue were tested at low, medium and high settings, as these devices have an adjustable dial to increase resistance. The flutter was tested at 0- and 30-degrees tilt as per user guide, as this is believed to increase the treatment effect. The respiratory muscle training devices, with the exclusion of the Aerosure Medic© and Aerosure Sport©, are designed for inspiratory flow only and therefore this is the mechanism by which they were tested to allow for useful comparison across devices with the same intended purpose of increasing respiratory muscle strength. Again, the Aerosure Medic© setting two demonstrated a flow resistive pattern of increasing pressure as a result of increased flow rate. This device was tested at larger flow rates however as this was performed with a negative flow, it is difficult for cross comparison between setting one and two of the device and is difficult to understand whether a high frequency of oscillations would increase the pressures a patient would receive. Figure 3.4 displays the results of the respiratory muscle training devices as mean pressures. These devices are: Aerosure Medic (setting 2), Aerosure Sport (setting 1- low, setting 1- high) and Respifit. These devices were tested at inspiratory flow rates of 20, 40, 60, 80 and 100 l/min and is shown in Figure 3.4. Further information regarding benchmark testing can be found in appendix 1.

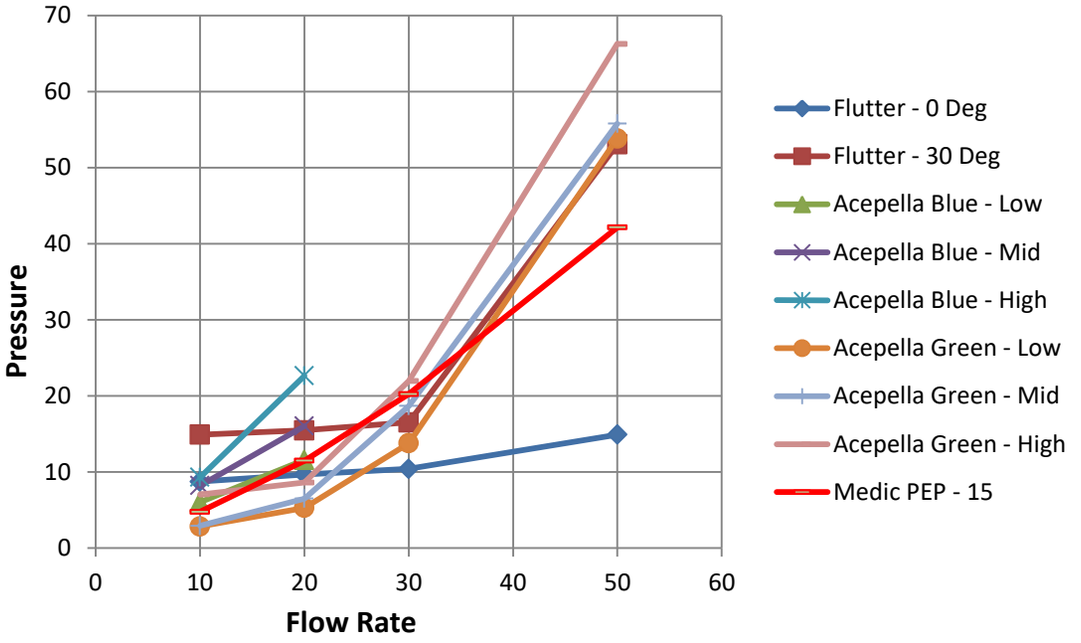



*Figure 3.3: Mean pressure of oscillating positive expiratory pressure devices (the Aerosure is presented as the 'Medic PEP – 15')*

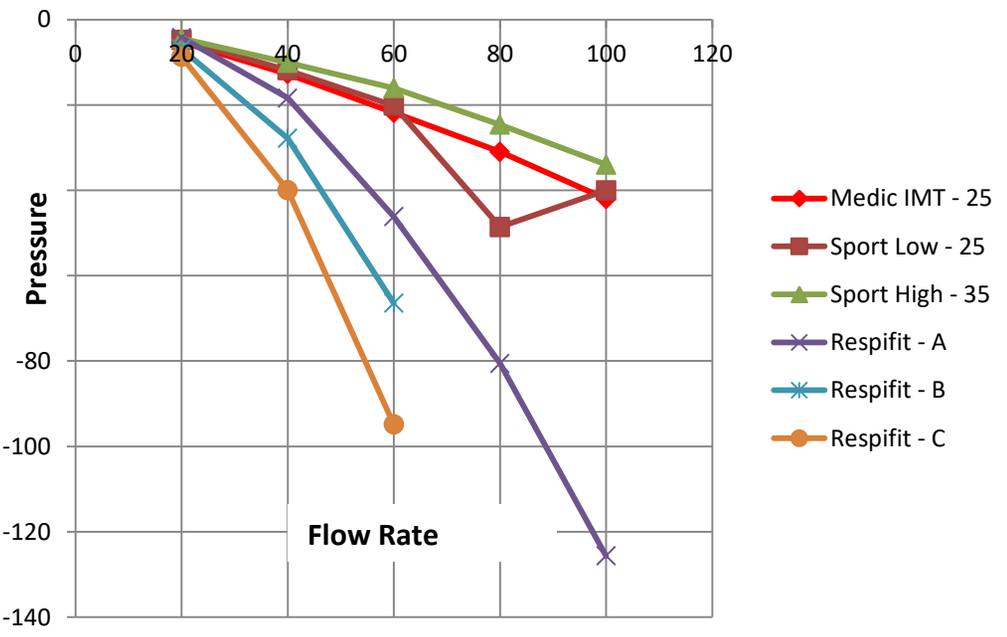



*Figure 3.4: Mean pressures of respiratory muscle training devices (the Aerosure is presented as the 'Medic IMT – 25')*

This benchmark testing confirms the hypothesis that the Aerosure Medic provides a flow resistive pressure however this is not measurable per user. Comparison between setting one and two is not possible due to the differences in flow delivered between these modes. It would be useful to understand the inspiratory and expiratory flow of each setting as this is how the product is intended to be used and therefore further testing may be necessary. Based on these results however it is sensible to advise maximal breathing, aiming to reach levels of full vital capacity and residual volume in order for the greatest training benefits.

Currently the device is branded to reduce shortness of breath and relieve breathlessness with regular use, increase respiratory fitness with regular use and to improve mucus clearance in COPD, Cystic Fibrosis and Asthma however there is no evidence to support these claims. It is hypothesised that the use of this device may improve dyspnoea by respiratory muscle training and mucus clearance which may also impact on cough frequency, exercise capacity and health related quality of life[178].

# 4 Feasibility Study

## 4.1 High Frequency Airway Oscillating Device for Respiratory Muscle Training in Subjects with COPD.

### 4.1.1 Introduction

Chronic Obstructive Pulmonary Disease (COPD) is characterised by expiratory flow limitation resulting in dyspnoea and reduced exercise capacity. Dyspnoea is a multidimensional symptom and may, in part, be a result of the muscles of respiration unable to meet the mechanical load and capacity causing respiratory muscle dysfunction and the sensation of dyspnoea. Increasing dyspnoea and associated disease progression reduces quality of life and exercise capacity in patients with COPD. Effective management of dyspnoea can improve quality of life and increase exercise capacity, therefore dyspnoea management is pertinent for patients with COPD[179]. A method of management of dyspnoea is inspiratory muscle training that is often employed in patients with COPD.

The benefits of inspiratory muscle training have been discussed in chapter one. In summary, the key benefits of inspiratory muscle training have been demonstrated in a systematic review by Gosselink et al[116]. The benefits include increased inspiratory muscle strength and endurance, functional exercise capacity and Health Related Quality of Life (HRQoL) when compared to a control[116]. These improvements appear meaningful in relation to quality of life, dyspnoea and muscle strength. This meta-analysis explored randomised controlled trials using inspiratory muscle training programmes of 30-50% of their maximum. Research has suggested that long term inspiratory muscle training can decrease the use of health services and reduce hospital length of stay[180]. However, recent literature has shown conflicting evidence with Charususin et al demonstrating that improvements in inspiratory

muscle function did not translate to additional benefits of exercise capacity and health related quality of life when used as an adjunct to pulmonary rehabilitation[181].

Combined respiratory muscle training (inspiratory and expiratory) is an additional technique for the management of dyspnoea although this technique is less frequently implemented despite the additional benefit of expiratory muscle training. While there is limited evidence for combined training it has been shown to improve respiratory muscle strength and endurance with an increase in the six minute walk distance compared with inspiratory muscle training alone[118]. Reference values for maximal expiratory muscle pressures have been discussed but there is no defined categorisation of weakness and therefore it is difficult to identify patients with defined expiratory weakness.

The mechanisms and effectiveness of respiratory muscle training have been a topic for debate and are not fully accepted as a method to manage COPD. The joint American College of Chest Physicians/American Association of Cardiovascular and Pulmonary Rehabilitation Committee declared that a stimulus or load applied to the respiratory muscles during training is sufficient to augment respiratory muscle strength and is associated with increased exercise capacity and decreased dyspnoea[182]. However, the National Institute for Clinical Excellence does not yet recommend respiratory muscle training in COPD management due to a disparity in the research[3].

The High Frequency Airway Oscillating device (HFAO) 'Aerosure by Revitive' (Aerosure, Bracknell, United Kingdom) is a flow-resistive designed to offer resistance on inspiration and expiration with the aim to reduce dyspnoea by improving breathing efficiency. The device also offers oscillations for mucociliary clearance, which may assist with reducing dyspnoea by addressing air-flow obstruction. The combination of respiratory muscle training and mucociliary clearance may contribute further to the management of dyspnoea. This study assessed numerous outcomes including dyspnoea, cough frequency, and sputum clearance to provide quantitative data on the use of a HFAO device which will inform and refine the

potential for a clinical effectiveness trial. The HFAO device has not been researched in patients with COPD and therefore it is necessary to explore the feasibility of using this device in the desired population. The aims of this study are:

- To assess recruitment rate of participants and eligibility in relation to the inclusion and exclusion criteria.
- To assess the attrition rate of using this device in a COPD population.
- To explore compliance of the device and the training programme.
- To monitor adverse events and determine the safety of using a HFAO device.
- To assess quantity and completeness of outcomes and understand their feasibility in the use of a large clinical effectiveness trial.
- To explore and establish a primary outcome measure for the design of a clinical effectiveness trial and give insight into the sample size necessary.

### 4.1.2 Methods

Ethical approval was obtained by the National Health Service Health Research Authority and the Local Research Ethics Committee (appendix 3). This trial was registered with the ISRCTN, trial number: ISRCTN81979106. In order to understand feasibility, twenty-four symptomatic patients with COPD were recruited from the pulmonary rehabilitation database at the University Hospitals of Leicester. Subjects were included if they had stable COPD, and a Medical Research Council (MRC) dyspnoea score of three or more. COPD participants were excluded if they had completed pulmonary rehabilitation within the last six months as the benefits of pulmonary rehabilitation are expected to be maintained for six months. Participants were also excluded if they were unable to give informed consent or are not fluent in English as the manual is only available in English. COPD diagnosis was confirmed by spirometry testing as outlined by the GOLD standards ($FEV_1$/FVC ratio <0.70)[21]. Participants that did not meet these criteria were excluded.

Feasibility was assessed by, recruitment rate, attrition and compliance to the intervention. Compliance was determined by analysing self-reported diaries with a compliance threshold of ≥75% to the proposed number of training sessions. The clinical outcomes assessed Health Related Quality of Life (HRQoL), exercise capacity and respiratory muscle function. Respiratory muscle function was measured by maximal inspiratory and expiratory mouth pressures ($PI_{max}$/$PE_{max}$), performed in line with the American Thoracic Society (ATS) and European Respiratory Society (ERS) statement[183]. The Incremental Shuttle Walk Test (ISWT) and Endurance Shuttle Walk Test (ESWT) were used to determine exercise capacity and were performed with line with the ERS/ATS guidelines, which included a familiarisation ISWT to account for a learning affect. HRQoL was assessed using the Medical Research Council dyspnoea scale (MRC), COPD Assessment Test (CAT), Chronic Respiratory Questionnaire (CRQ), Leicester Cough Questionnaire (LCQ), London Chest Activity of Daily Living (LCADL) questionnaire and the Hospital Anxiety and Depression Scale (HADS)[67, 69, 171, 184]. Questionnaires were completed by the individual with supervision of the researcher and were performed pre-and post-intervention. The administration of each outcome measure is further described in chapter three.

The intervention used a High Frequency Airway Oscillating (HFAO) device, the 'Aerosure by Revitive'© [Actegy Ltd]. This device provides a resistance to flow for respiratory muscle training with the addition of oscillations for sputum clearance. Participants were instructed to use the device for five minutes at a time, three times per day, and to perform deep maximal breathing. Further description of the device can be found in chapter one and three. The intervention was used for a period of eight weeks with a self-reported daily diary (see appendix 6). Participants received weekly telephone calls for monitoring and management of any device related issues. All participants received the HFAO device to use for the period of the intervention phase. The study design can be seen in figure 4.1.

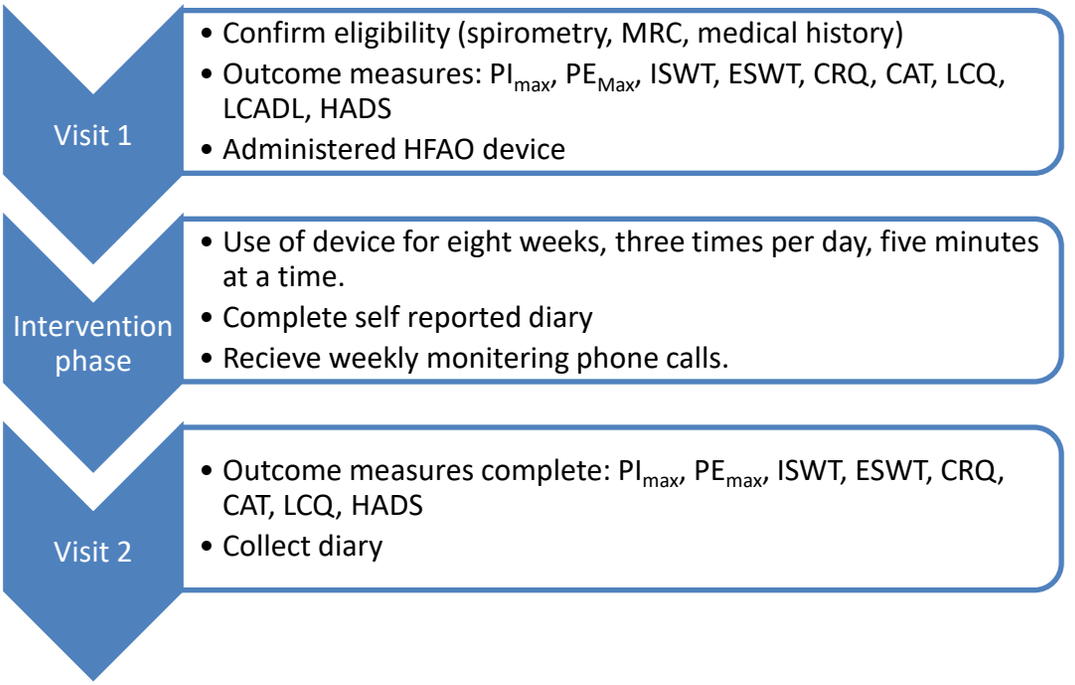



*Figure 4.1: Feasibility study flow diagram*

Data were analyzed using SPSS version 24 (IBM, North Castle, New York). Feasibility was determined by a recruitment rate of over 50% and an attrition rate of less than 20%. Subjects were considered adherent if they completed 75% of the training protocol, as recorded in the self-reported diary. The paired t-test and Wilcoxon signed-rank test was used for parametric and non-parametric variables, respectively. $PI_{max}$ was considered weak if ≤60 $cmH_2O$ as reported in the literature. As there are no reference values are available for $PE_{max}$, this was calculated based on the Evans formula to calculate the lower limit of normal: $PE_{max}$ for males = 117-(0.83 x age); $PE_{max}$ for females = 95-(0.57 x age)[161]. A pre-defined sub-group analysis was performed on subjects with poor inspiratory muscle strength (≤60 cm $H_2O$) compared to those with normal inspiratory muscle strength (≥60 $cmH_2O$)

### 4.1.3 Results

#### *Patient Recruitment*

Of the 39 subjects screened for eligibility 24 (61.5%) were initially recruited. One participant was withdrawn following normal spirometry at the first visit. 59% of the initial identified participants were eligible for recruitment, therefore the inclusion and exclusion criteria were deemed appropriate (figure 4.2). 20 out the 23 eligible patients completed the study and there was a dropout rate of 13%. There was a self-reported compliance rate of 90% of participants meeting the minimum training requirement of 75%. Compliance reduced marginally from week six to eight 75% of participants completing the minimum training requirements (figure 4.3).

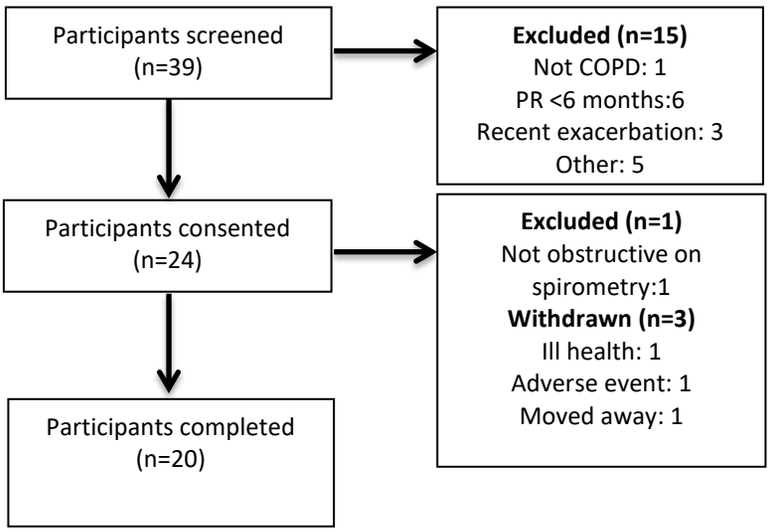



*Figure 4.2 Consort diagram of feasibility study*

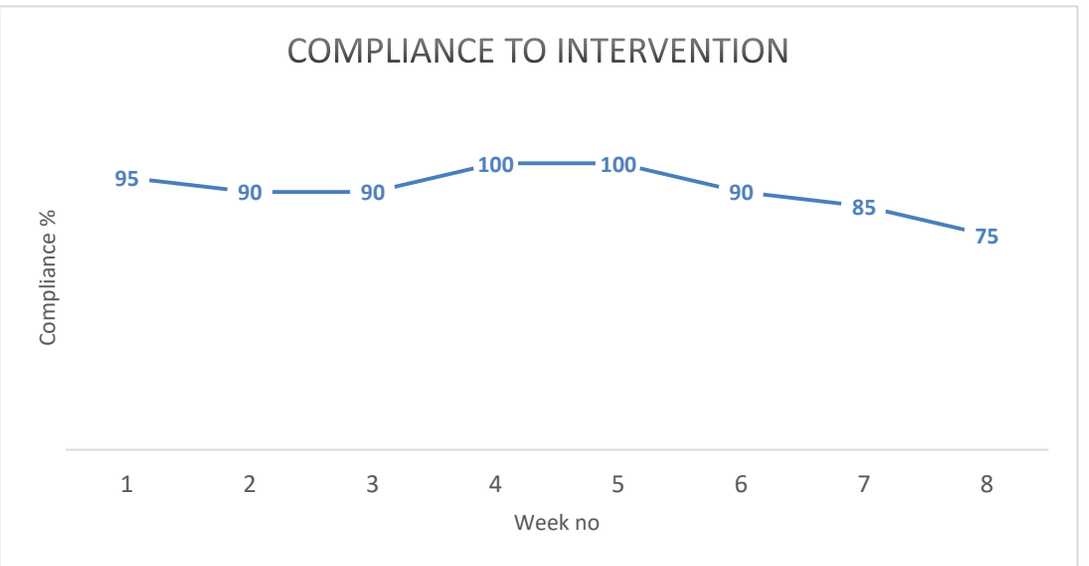



*Figure 4.3 Self-reported compliance (percentage of patients demonstrating compliance to ≥75% of training sessions)*

During the trial period, there was one serious adverse event resulting in hospitalisation to an acute respiratory ward following a non-infective exacerbation of COPD. This is an

expected adverse event for patients with COPD not deemed related to the intervention. There was one reported adverse event causing vocal irritation, and affecting the participants voice that was not resolved by rehydration

### *Baseline Characteristics*

Baseline characteristics are shown in table 4.1. The cohort was predominantly categorised as moderate, GOLD staging II, with a median MRC score of 4 [3.00-4.75]. Mean [SD] $PI_{max}$ were 57.48cm$H_2O$ [±26], which is considered as inspiratory muscle weakness[183]. Based on Evans calculations seven patients demonstrated expiratory muscle weakness ranging from 41.33% to 88.64% of predicted values[161].

Of the 23 eligible participants recruited, one was withdrawn due to ill health, one was withdrawn for social reasons and one participant stopped using the device due to an adverse event of which the device caused vocal irritation. Therefore 20 participants were available for analysis.

*Table 4.1 Baseline Characteristics (feasibility)*

| | N=23 |
|---|---|
| Age (years) | 65 [5] |
| Gender (% male) | 65 |
| MRC (Median [IQR]) | 4 [3.00-4.75] |
| GOLD staging | I 4 (17%)<br>II 8 (35%)<br>III 5 (22%)<br>IV 6 (26%) |
| $FEV_1$ (% predicted) | 43 [16] |
| $PI_{max}$ ($cmH_2O$) | 57 [26] |
| $PE_{max}$ ($cmH_2O$) | 94 [33] |
| ISWT (m) | 217 [118] |
| ESWT (seconds) | 206 [113] |

*Table 4.1: Baseline mean [SD]. GOLD (Global Initiative for Chronic Obstructive Lung Disease) staging presented as numerical format and percentage per stage. MRC Medical Research Council Score, $FEV_1$ Forced Expiratory Volume in 1 second, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CAT COPD Assessment Test.*

Of the 20 participants that completed the intervention, 19 completed exercise tests and respiratory muscle strength tests. All participants completed health related quality of life outcomes (seen in table 4.2).

Overall participants improved their MRC score from 4 to 3 (p=.003) (95% CI 2.68-3.32). Participants median [IQR] $PI_{max}$ improved from 59$cmH_2O$ [34-74] to 63$cmH_2O$ [42-85]. $PE_{max}$ improved from a median [IQR] of 102$cmH_2O$ [62-125] to 110$cmH_2O$ [97-137]. There was a trend in improving exercise performance (ISWT or ESWT). There were some small improvements in HRQoL seen in table 4.2.

Subgroup analysis demonstrated a greater improvement in $PI_{max}$ and ISWT in those with identified inspiratory muscle weakness (<60$cmH_2O$) (see table 4.3). There was complete

data on all the questionnaires, however one patient did not return to hospital to complete the study and completed questionnaires at home, therefore there was missing data on the MRC, respiratory muscle strength testing and exercise capacity (5% missing data).

*Table 4.2 Outcomes of feasibility study*

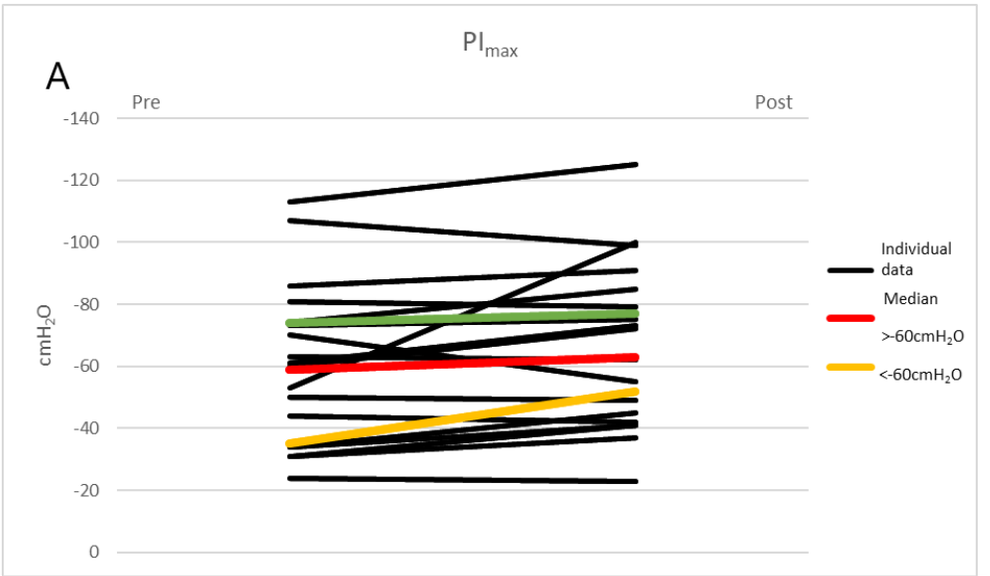
| N=20 | Pre | Post | % of missing data |
|---|---|---|---|
| MRC | 4.0 [3.0-5.0] | 3.0 [3.0-3.0] | 5% |
| $PI_{max}$ ($cmH_2O$) | 59.0 [34.0-74.0] | 63.0 [42.0-85.0] | 5% |
| $PE_{max}$ ($cmH_2O$) | 102.0 [62.0-125.0] | 110.0 [97.0-137.0] | 5% |
| ISWT (m) | 200.0 [140.0-260.0] | 240.0 [170.0-270.0] | 5% |
| ESWT (secs) | 170.5 [130.5-246.8] | 203.0 [142.3-274.3] | 5% |
| CRQ dyspnoea | 2.6 [2.0-2.8] | 2.5 [2.05-3.70] | 0% |
| CRQ total | 17.0 [12.9-18.1] | 16.7 [14.8-19.6] | 0% |
| LCQ total | 15.7 [12.7-19.4] | 21.5 [16.3-25.5] | 0% |
| HADS Anxiety | 6.0 [3.0-10.0] | 6.0 [3.3-11.3] | 0% |
| HADS Depression | 6.0 [4.0-10.0] | 5.0 [4.0-7.5] | 0% |
| LCADL total | 32.0 [28.0-45.0] | 29.0 [23.25-39] | 0% |
| CAT Total | 24.0 [18.0-29.0] | 21.5 [16.25-25.5] | 0% |
| CAT Sputum | 3.0 [2.0-4.0] | 3.0 [2.0-3.75] | 0% |

*Table 4.2: median [IQR] and % missing data. MRC Medical Research Council Score, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire, LCQ Leicester Cough Questionnaire, HADS Hospital Anxiety and Depression Score, LCADL London Activity of Daily Living, CAT COPD Assessment Test.*

*Table 4.3 Sub-group analysis (Inspiratory muscle strength <60cm$H_2O$ and >60cm$H_2O$)*

| | Reduced inspiratory muscle strength (<60cm$H_2O$). n=9 | | Normal inspiratory muscle strength (>60cm$H_2O$) n=10 | |
|---|---|---|---|---|
| | Pre | Post | Pre | Post |
| MRC | 4 [3-5] | 3 [3-3] | 4 [3-4] | 3 [2-3] |
| $PI_{max}$ ($cmH_2O$) | 35 [31-49] | 42 [39-56] | 74 [63-86] | 77 [70-93] |
| $PE_{max}$ ($cmH_2O$) | 77 [57-102] | 105 [83-111] | 118 [108-134] | 125 [109-159] |
| ISWT (m) | 150 [100-245] | 200 [160-260] | 250 [180-290] | 265 [185-283] |
| ESWT (secs) | 200 [120-278] | 285 [104-376] | 156 [134-190] | 179 [144-224] |

*Table 4.3: Median [IQR]. MRC Medical Research Council Score, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test.*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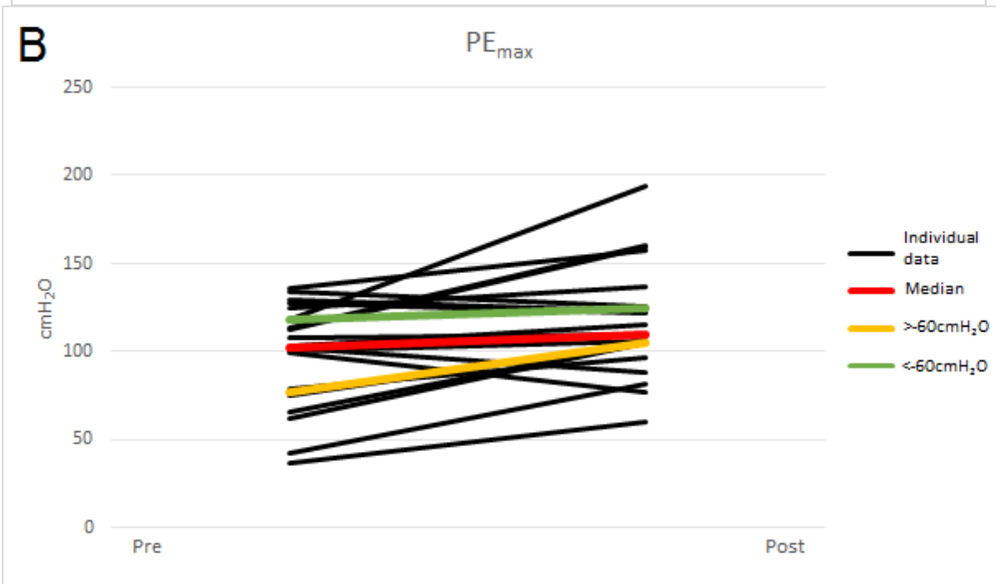
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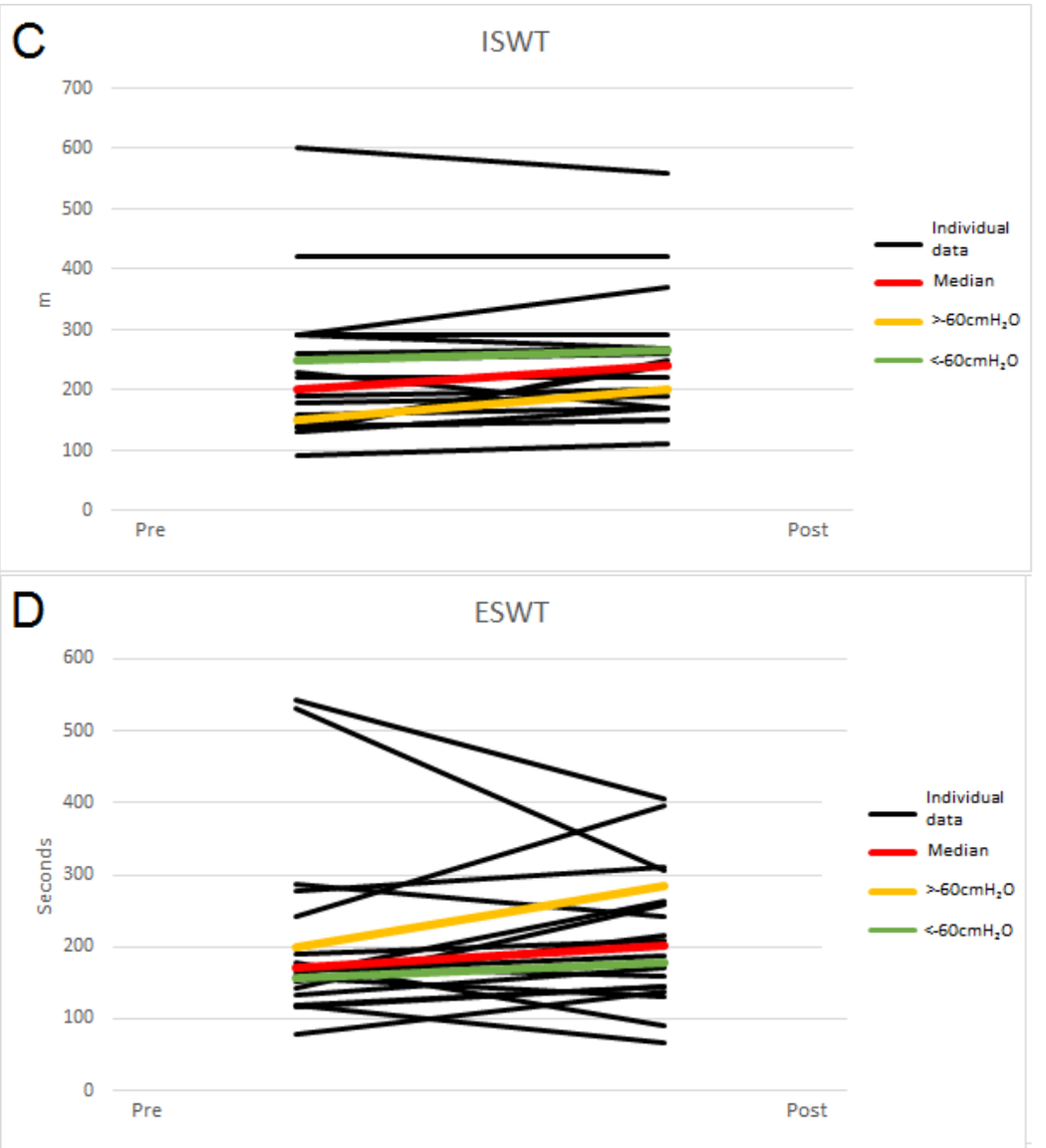



*Figure 4.4 Changes from baseline. A $PI_{max}$ Inspiratory muscle pressures. B $PE_{max}$ expiratory muscle pressure. C Incremental Shuttle Walking Test. D Endurance Shuttle Walking Test measured at pre-and post-intervention phase. Individual data plotted, median data (red), ≤60cm$H_2O$ $PI_{max}$ (yellow) and >60cm$H_2O$ $PI_{max}$ (green).*

Mean changes were explored to gain insight into trends of outcome measures and to determine an appropriate measure for the power calculation, however due to the non-normally distributed data, these results are not considered in the interpretation of effectiveness and therefore significance was not explored (table 4.4).

*Table 4.4 Changes from baseline*

| N=20 | Mean difference |
|---|---|
| $PI_{max}$ ($cmH_2O$) | 5.7 [12.4] |
| $PE_{max}$ ($cmH_2O$) | 19.0 [25.4] |
| ISWT (m) | 17.4 [43.3] |
| ESWT (secs) | 3.8 [91.8] |
| CRQ Dyspnoea | 0.3 [0.8] |
| CRQ Total | 0.6 [4.6] |
| CAT Sputum | -0.1 [0.8] |
| CAT Total | -0.1 [4.6] |
| HADS Anxiety | 0.7 [3.1] |
| HADS Depression | -0.7 [1.9] |
| LCADL | -2.6 [10.3] |
| MRC | -0.7 [0.8] |

*Table 4.4 Mean [SD] PI/$PE_{max}$ Maximal inspiratory/expiratory muscle pressures; ISWT Incremental Shuttle Walking Test; ESWT Endurance Shuttle Walking Test; CRQ Chronic Respiratory Questionnaire; CAT COPD Assessment Test; HADS Hospital Anxiety and Depression Scale; LCADL London Chest Activity of Daily Living questionnaire; MRC Medical Research Council Score.*

The CRQ dyspnoea domain will be used as the primary outcome for the randomised controlled trial (RCT) as there was a slight improvement and is a measure of dyspnoea. The sample size was calculated using the following formula:

$$n = \frac{f(\frac{a}{2},b) \quad *(p1)*(1-p1)+p2*(100-p2)}{(p2-p1)2}$$

The sample size was based on a 0.5 change in the CRQ dyspnoea domain (p1), which is the reported minimal clinical important difference[168]. The standard deviation used was from the feasibility study which is reported as 0.85. The study will be 80% powered with a significance level of 5%. Therefore, in order to detect a difference of 0.5, the RCT will require 92-94 participants to complete the protocol. This number is inflated by 13% to account for attrition and therefore 104 patients are required.

### 4.1.4 Discussion

The results of this study demonstrate appropriate eligibility and a recruitment rate of 61.5% which is considered acceptable by the researchers. It is likely that this is an underestimate of eligible patients as those who were currently experiencing an exacerbation were excluded and would likely be included once they were deemed stable (no exacerbation in the last four weeks) if the study were to continue for a longer period and those who did not fulfil the six month post pulmonary rehabilitation criteria would also become eligible during the trial period. This accounts for 21% of excluded participants and therefore could increase recruitment rate to 82.5% when recruiting over a longer period. The attrition rate was low at 13% which is less than a commonly reported attrition in clinical trials of 20%. The self-reported compliance was high with 90% of patients reporting completing at least 75% of the training sessions at the desired intensity. Self-reporting compliance encounters limitations and it was noted that compliance began to reduce after six weeks and therefore it is not feasible to increase the intervention phase past the current eight-week mark. The study design is appropriate, and a larger randomised controlled trial is deemed feasible.

The use of the device for eight weeks has shown trends towards improvements in respiratory muscle strength measured by inspiratory and expiratory mouth pressures. There were some improvements in dyspnoea as measured by the MRC and CRQ dyspnoea domain. We observed an increase in exercise capacity as measured by the ISWT. There was a notable difference between GOLD staging severity and MRC dyspnoea score at baseline, however due to the subjectivity of dyspnoea and the inability of the MRC score to capture its complexity, this is unsurprising. Participants that demonstrate inspiratory muscle weakness have a greater improvement in $PI_{max}$, $PE_{max}$, ISWT and ESWT compare with participants who do not demonstrate weakness, however the sample size for this analysis is small.

Public and patient involvement was utilised throughout the project and gave important insights into the feasibility of the trial, particularly the training intensity/use of the device and questionnaire burden. It was discussed between staff and public and patients whether the intervention should be shortened to six weeks given the results on compliance tapered towards the end of the intervention period, however it was agreed that the intervention needs to be long enough to augment adaptations and to allow for a two week recall from the questionnaires such as CRQ and LCQ. Public and patient involvement was useful to assist with the design of a clinical effectiveness trial and identified areas that need addressing for example, diary cards, training intensity and follow up calls. Diary cards were redesigned with the help of public and patient involvement and the training intensity was agreed with members and previous feasibility participants that it was an appropriate intensity. Follow up calls were not deemed appropriate for the large clinical effectiveness trial as it would risk unblinding and may be considered an intervention. A power calculation was performed based on a 0.5-point change in CRQ Dyspnoea domain score and 92-94 patients are required to complete the study at the endpoint of week eight following the intervention phase for the randomised controlled trial. This was inflated by 13% to account for the attrition rate seen in this study. All outcome measures were deemed appropriate by the participants to assess the effects of the device. It may be necessary to add in further measures of dyspnoea in order to capture its complexity. There was a discussion around

reducing questionnaire burden however it was agreed between researchers and public and patient involvement members that as they are completed during the required rest time between walking tests that this would not be too burdensome for the patient.

Dyspnoea is the most common complaint for patients with COPD. It is a held opinion that respiratory muscle weakness is uncommon in patients with COPD, however this population demonstrated weakness in both inspiratory and expiratory muscles, which is comparable to the current literature[185]. This study was not selective of participants in relation to respiratory muscle weakness, however, subgroup analysis indicates that those classified as 'weak' had greater improvements in inspiratory muscle strength and ISWT. Conversely, both groups improved dyspnoea scores and therefore both groups should be included in the RCT as this is the intent of the device. Furthermore, the threshold for weakness is arbitrary and does not account for an increased ventilatory demand as associated with patients with COPD. Additionally, inspiratory muscle weakness has been associated with hyperinflation induced diaphragm shortening and fibre shift toward oxidative type 1 fibres in the diaphragm of patients with COPD. Less is understood regarding expiratory muscle weakness; however, it has been suggested that 50% of moderate to severe COPD patients exhibit expiratory muscle weakness in parallel with inspiratory muscles. Reference values for $PE_{max}$ have been discussed, with no definitive conclusion of values that categorise expiratory muscle weakness. This study utilised Evans formula to calculate expiratory weakness[161]. The implementation of respiratory muscle training is inconsistently applied to the COPD population and there is a need for rigorous trials investigating this treatment. There is a large body of evidence for the evaluation of inspiratory muscle training. However, differences in training protocols make it difficult to reach consensus and therefore limiting clinical application. Expiratory muscle training has been shown to improve respiratory function when trained in combination for patients with mild to severe COPD. In the present study, we proposed an eight-week training programme, three times per day of combined inspiratory and expiratory muscle training using a device, which provides flow resistance and additional oscillations.

### 4.1.5 Strengths and Limitations

This single armed study was devised to explore the feasibility of using the HFAO in patients with stable COPD. This study has a small sample size design and therefore not generalisable to the COPD population. This was a single armed, non-blinded study and therefore is subject to bias. In the absence of a control group it is not possible to make any comment on clinical effectiveness as it is not possible to disprove the potential of a placebo effect. Subgroup analysis may allow for some indication of population groups that may benefit from this device; however, this should be interpreted with caution due to the small sample size. Self-reported compliance is a limitation of this study. Other options of compliance measures were explored such as electronic monitoring or location sensors however it was not possible to use these methods reliably or without affecting the delivery of the intervention, and therefore there were deemed no appropriate alternatives. The device does not have the function to increase or reduce resistance and therefore may not be suitable for all patients with COPD, however the device is accepted by participants and does not allow for adjustments to be made by the participant outside of the protocol.

### 4.1.6 Implications

The results of this study indicate that a fully powered randomised controlled trial is feasible. Sample size calculations revealed that a total of 92-94 participants (46-47 per group) is adequate for an 80% powered study based on a 0.5-point change in CRQ dyspnoea score. The study will aim to recruit 104 patients accounting for an expected attrition rate of 13%. The intervention was deemed appropriate and not burdensome for participants. The outcome measures will be included in the large clinical effectiveness trial with the addition of further dyspnoea measures to explore the complexity and quality of dyspnoea. It is not possible to derive conclusions of clinical effectiveness from this study due to the small sample size and potential for bias; however, this will be addressed within the randomised controlled trial.

# 5 Training to Improve Dyspnoea (TIDe)

## 5.1 A Randomised Controlled Trial to Investigate the Use of High Frequency Airway Oscillations as Training to Improve Dyspnoea.

## 5.2 Introduction

COPD is characterised by expiratory flow limitation resulting in excessive dyspnoea, reduced exercise tolerance and reduced HRQoL. Dyspnoea is a multi-dimensional symptom with many influencing factors. The inability of the respiratory muscles to meet the demands of the mechanical load and capacity which leads to respiratory muscle dysfunction and excessive dyspnoea. Persistent and recurrent dyspnoea can impact activity and quality of life. Respiratory muscle training can be utilised to impact this mechanism of dyspnoea with a theoretical underpinning that stronger respiratory muscles will require less effort and oxygen demand to perform at tidal volumes. This can also reduce the muscle effort during periods of activity. Research primarily explores the use of inspiratory muscle training in COPD and has demonstrated meaningful improvements in inspiratory muscle strength and endurance, dyspnoea and exercise capacity[116]. Recently there has been a body of literature demonstrating non-significant improvements in these outcomes, and the focus of these results is to determine specific outcome measures for this intervention[181]. It is recommended to select thorough symptom-based outcome measures for dyspnoea (such as the MDP and Borg score) particularly in response to exercise. It is suggested that more detailed measures of dyspnoea may be beneficial to the assessment of the impact of these results.

Combined inspiratory and expiratory training may be a useful addition into the management of dyspnoea however this technique is employed less frequently due to a smaller evidence base. It has been reported that 50% of patients with moderate to severe COPD will exhibit both inspiratory and expiratory weakness in parallel and therefore may be a useful addition in the treatment of dyspnoea. The Joint American College of Chest Physicians and American Association for Cardiovascular and Pulmonary Rehabilitation committee stated that stimulus or load applied to the muscles during respiratory muscle training is sufficient to augment increases in strength and is associated with increased exercise capacity and decreased dyspnoea, however the National Institute for Clinical Excellence (NICE) acknowledge the disparity in the research and therefore make no clinical recommendations for its use in patients with COPD[3, 182].

Moreover, sputum retention is a commonly reported symptom that may contribute to dyspnoea[2]. Excessive sputum can be a troubling symptom for patients and often results in poorer health outcomes such as increased exacerbations and hospitalisations and faster lung function decline measured by $FEV_1$. Therapies are available for the treatment of sputum retention and can include manual therapies, device use and breathing techniques. Management of this symptom has demonstrated a reduction in hospital admissions, reduce the need for ventilatory assistance and improved quality of life through various methods of sputum clearance[120]. This thesis has reported that the use of devices can improve symptoms and exacerbations (see chapter two). The quality of the evidence base for sputum clearance devices offers moderate risk of bias and therefore there is a need for high quality evidence to support the provision of airway clearance devices.

The Aerosure Medic by Revitive (Actegy LTD) is a duel functioning device for the management of sputum and dyspnoea. This HFAO device provides flow resistance on both inspiration and expiration with the aim of providing respiratory muscle training alongside oscillations at either 15 hertz or 25 hertz with the aim to aid sputum clearance. Further explanation of the mechanism of this device can be found in chapter one and three. The

results from the feasibility study encouraged a fully powered randomised control trial, demonstrating feasibility in achieving recruitment targets, low attrition and high compliance to the device use (chapter 4). Results demonstrated an improvement in dyspnoea as measured by the CRQ dyspnoea domain (mean improvement 0.27[0.80]) and the MRC dyspnoea score (-0.74[0.80]). There were also improvements in respiratory muscle strength and health related quality of life[178]. Trends were noted in improving walking capacity based on the incremental shuttle walking test. In order to determine clinical effectiveness, a fully powered randomised control trial is necessary. This will compare the HFAO device with a sham. The aims of this study are listed below.

1. To determine the effectiveness of the HFAO device on dyspnoea, lung function, HRQoL, exercise capacity and activity when compared to a sham. These will be measured using:
    a. Dyspnoea
        i. Chronic Respiratory Questionnaire Dyspnoea domain
        ii. Multidimensional Dyspnoea Profile
    b. Lung function
        i. Maximal Inspiratory muscle strength
        ii. Maximal expiratory muscle strength
        iii. Lung Clearance Index (discussed in chapter 6)
    c. Health Related Quality of Life
        i. Chronic Respiratory Questionnaire Fatigue, Mastery, Emotion domains and total score
        ii. Leicester Cough Questionnaire
        iii. London Chest Activity of Daily Living Questionnaire
        iv. Hospital Anxiety and Depression Scale
        v. COPD Assessment Test
    d. Exercise capacity
        i. Incremental Shuttle Walking Test
        ii. Endurance Shuttle Walking Test

2. To explore if there is a subgroup of patients which receive the most benefit of this therapy. Predefined subgroups are:
    a. Inspiratory muscle weakness as defined by ≤60cm$H_2O$ maximal inspiratory pressures.
    b. Complaint as determined by self-report diary completing ≥75% of the treatment sessions
    c. Sputum retention, as defined by a score of 3-5 points on the COPD Assessment Test sputum domain
    d. Frequent exacerbators determined by ≥2 exacerbations in the previous 12 months
3. To explore the impact of the HFAO device on physical activity pre and post the intervention when compared to a sham.
4. To understand the device use three months after the trial and how this has impacted participants HRQoL.

## 5.3 Methods

Ethical Approval was gained from the Leicester South Research Ethics Committee and the Health Research Authority (17/EM/0156) (appendix 3). Patient and public representatives were utilised throughout the trial period including assisting with protocol development, developing patient facing documents, forming members of the steering committee and assisting with dissemination of results. The published protocol can be seen in appendix 2 and patient documents (patient information sheet and informed consent form) in appendix 4 and 5, respectively. From the feasibility study it was discussed to remove the weekly telephone reminder calls and replace with a text message where appropriate to do so (see appendix 7). Additional measures of dyspnoea were included and the addition of a sham device from the feasibility trial. Physical activity monitoring was performed to assess improvements in activity that may not be captured by the walking tests. This trial was registered on the ISRCTN trial registry (ref: ISRCTN4595543.)

Participants were included if they had a confirmed diagnosis of COPD, MRC dyspnoea score of 2 or more, and can communicate in full English (as the device manual is only available in English). Participants were recruited from consensual research databases and respiratory clinics within the University Hospitals of Leicester. Spirometry was used to confirm a diagnosis of COPD on their initial visit as defined by international guidelines of $FEV_1$/FVC Ratio of >0.70[186]. Participants were excluded if they had engaged with a pulmonary rehabilitation programme in the six months prior to commencing the research trial. Participants with severe right sided heart failure, current or recent pneumothorax, untreated pulmonary embolism, recent gastric, thoracic or facial surgery or trauma were excluded from the trial as per device contraindications. Participants are excluded if they are already using a HFAO device or any other device for chest clearance or respiratory muscle training as it would be unethical to prevent the use of devices that is perceived to add value to their routine management.

The primary outcome for this study was the difference in change in the CRQ Dyspnoea domain between the HFAO intervention group and the sham group post intervention phase. Secondary outcomes were: COPD Assessment Test (CAT), Leicester Cough Questionnaire (LCQ), London Chest Activity of Daily Living (LCADL) questionnaire, Hospital Anxiety and Depression Scale (HADS), Multidimensional Dyspnoea Profile (MDP), maximal inspiratory and expiratory pressures ($PI/PE_{max}$), incremental and endurance shuttle walking tests (ISWT/ESWT).

Exploratory outcomes were physical activity as measured by actigraph accelerometers and the Lung Clearance Index (LCI) measured via a Multiple Breath Washout. The LCI outcome will be discussed in Chapter 6. All outcomes were collected at baseline and post intervention (eight weeks). The CAT and CRQ were assessed again at three months post intervention, at which point all participants were receiving the HFAO device. A survey of device usage was also sent at three months post intervention (appendix 8). This survey was developed by the researchers and PPI groups to assess whether participants continued to

use the device after the intervention phase and how frequently, this also allowed participants to comment on the device with free text responses. The study visits are summarised in figure 5.1.

Participants were recruited from research databases and respiratory clinics at the Glenfield Hospital in Leicester. Participants completed spirometry and the MRC dyspnoea score as part of the screening process. Maximal inspiratory and expiratory pressures, walking tests and health related quality of life were all completed at visit one. Participants were issued an activity monitor to wear for one week and returned for visit two at the same time of day (where possible). Participants completed the Multiple Breath Washout testing and were issued a device and diary by an unblinded member of the team and instructed to use the device three times per day for five minutes at a time. One week prior to their follow up participants received the activity monitor to wear for one week. Participants returned for their follow up, at a similar time of day, to complete all the remaining outcomes. On completion of the visit, participants were unblinded and offered a HFAO device to retain and instructed to use it how they wished, but it was recommended to use three times per day for five minutes at a time. Three months later, participants received a survey of usage and the CRQ and CAT questionnaire to complete (figure 5.1).

Data were analysed using STATA statistical package and SPSS. Baseline differences were assessed using an independent t-test. Between group differences were assessed using a repeated mixed measures approach and adjusting for any baseline differences. A paired t-test was used to determine within group differences for continuous data. Categorical data was analysed using a Chi squared for a single time point and McNemars for changes over time. Actigraph physical activity data was downloaded and analysed using Actilife software and were included where participants had at least one day (8 hours) of wear time. Statistical significance was set at $p \leq 0.05$.

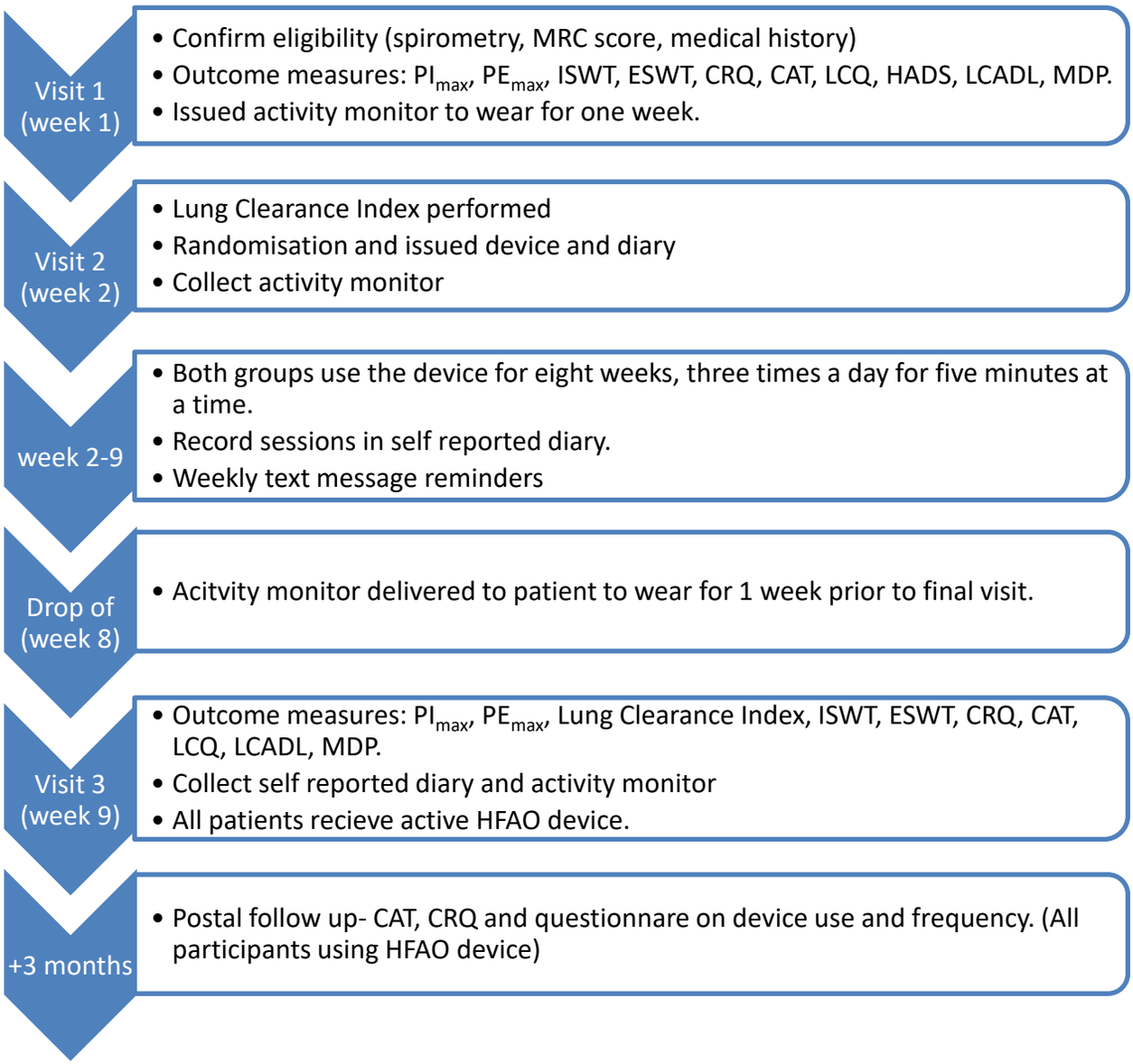



*Figure 5.1 TIDe study flow diagram. MRC Medical Research Council, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, HADS Hospital Anxiety and Depression Scale, LCADL London Chest Activity of Daily Living Questionnaire, MDP Multidimensional Dyspnoea Profile.*

### 5.3.1 Intervention

Participants were randomised on a ratio of 1:1 to either the HFAO device or a sham control. The sham was developed by Actegy with the resistance and oscillating mechanisms removed. The device switches on and mimics the noise of the original device. On the surface both devices look identical (see figure 5.2 and 5.3) however without the presence of the oscillating valve. Participants were presented with the device intact and taught how to use the device by the unblinded assessor. The intervention phase was eight weeks in duration with participants performing deep breathing in and out of the device for five minutes at a time three times per day. This was recorded in the self-reported diary alongside the intensity of the session (0-10-point scale). Participants were considered compliant if they completed 75% of the sessions or more.

Participants only saw the device they were randomised to until the end of the trial. The outcome assessor and participants remained blinded throughout the study. Upon completion of the outcome measures the participants were unblinded and offered the active HFAO device to retain. From visit three onwards all participants were using the active HFAO device if they wish to continue with it. Therefore, three-month follow up data was collected on all participants using the HFAO device.

*Figure 5.2 High Frequency Airway Oscillating Device Left Active Aerosure Medic device, middle active Aerosure Medic Aerosol Head, right active Aerosure Medic Aerosol Head worms eye view.*

*Figure 5.3 Sham device Left Sham Aerosure Medic Device, middle Sham Aerosure Medic Aerosol Head, right sham Aerosure medic head worm eye view. Note: mechanism removed.*

### 5.3.2 Data analysis

Data was analysed using SPSS v24 and STATA statistical package. Baseline differences were assessed using independent sample t-test for continuous data and chi squared for categorical data. Response to the intervention was analysed using a paired samples t-test and comparisons between groups were made using a mixed model approach. Baseline differences were accounted for in the analysis where it was appropriate to do so. Data is reported as mean and standard deviation [SD]. Changes were considered statistically significant at a level of 0.05. Predefined subgroup analysis includes participants with inspiratory muscle weakness ($PI_{max}$ ≤60cm$H_2O$); ≥75% compliance to the intervention as recorded in self-reported diaries; excessive sputum measured by a CAT sputum score of 3-5, and those with frequent exacerbations (≥2 exacerbations in the preceding 12 months). The sample size was calculated to detect a 0.5-point change in the CRQ Dyspnoea domain with a standard deviation of 0.85 as demonstrated in the feasibility trial[178]. 94 participants were required to complete the trial (47 per group). This was inflated by 13% to account for attrition and therefore 104 patients were recruited to this study[178].

## 5.4 Results

121 participants consented to this study. 12 (9.9%) were excluded as they were unable to demonstrate an obstructive pattern on spirometry testing. 2 were excluded for withdrawing interest, 2 were MRC 1 and 1 was already using the Aerosure device (see figure 5.4). Therefore 104 participants were randomised to this trial, 53 in the HFAO group and 51 in the sham group. Participants were 68% male with a mean [SD] age of 69.75[7.41], $FEV_1$ 48.22[18.76]. The baseline characteristics can be seen in table 5.1. Statistically significant baseline differences were noted between groups in $FEV_1$ percent predicted, inspiratory muscle strength and expiratory muscle strength and BMI.

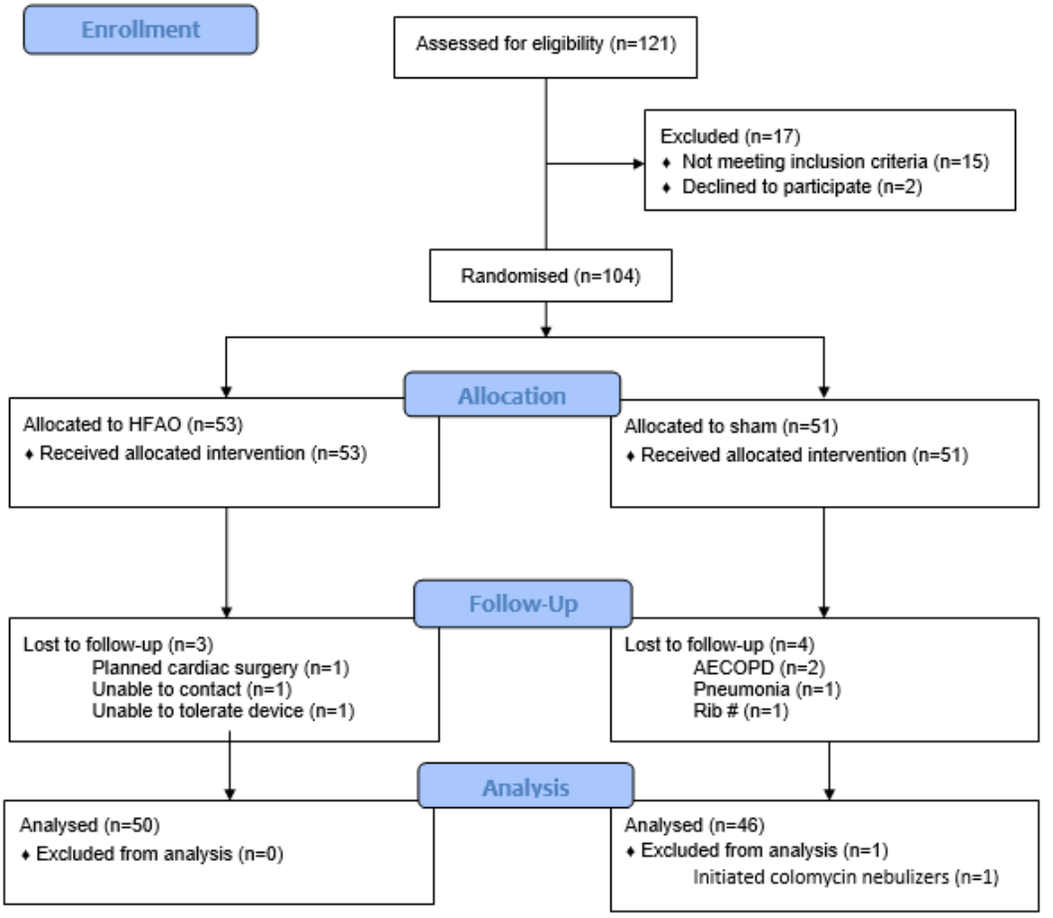



*Figure 5.4 Consort diagram of TIDe study*

*Table 5.1 Baseline Characteristics (TIDe)*

| | HFAO (n=53) | Sham (n=51) | Total (n=104) | Between group differences (p=) |
|---|---|---|---|---|
| Age (years) | 69.40 [7.58] | 70.10 [ 7.36] | 69.75 [7.41] | 0.50 |
| Gender m/f | 36/16 | 35/17 | 71/33 | 0.73 |
| Ethnicity (%Caucasian) | 100% | 96% | 98% | 0.15 |
| Smoking history | 43.26 [40.70] | 41.95 [30.31] | 42.62 [35.77] | 0.69 |
| GOLD 1/2/3/4 | 1/20/20/11 | 4/23/15/10 | 5/43/35/21 | 0.44 |
| $FEV_1$ % predicted | 45.31[17.39] | 51.14 [19.76] | 48.22 [18.76] | **0.05** |
| MRC 2/3/4/5 | 20/21/7/4 | 19/19/7/7 | 39/40/14/11 | 0.98 |
| BMI | 27.20 [5.21] | 29.70 [7.41] | 28.43 [6.5] | **0.05** |
| $PI_{max}$ ($cmH_2O$) | 60.69 [23.73] | 72.35 [24.86] | 66.47 [24.88] | **<0.01** |
| $PE_{max}$ ($cmH_2O$) | 109.33 [40.21] | 129.63 [47.95] | 119.38 [45.16] | **<0.01** |

*Table 5.1 Mean [SD] HFAO High Frequency Airway Oscillations, GOLD Global institute for Obstructive Lung Disease, $FEV_1$ Forced Expiratory Volume in 1 second, MRC Medical Research Council, BMI Body Mass Index, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure.*

96 participants completed the trial at the primary endpoint (post intervention, visit 3). From the self-reported diary 81% were considered to meet the compliance threshold of ≥75% of the treatment.

### 5.4.1 Primary outcome

Participants in the HFAO group had a mean [SD] improvement of 0.45 [0.78] in the CRQ dyspnoea domain, and by 0.78 [1.09] in the sham group. Both groups demonstrated statistically significant improvements over time however there were no statistical significances between groups (figure 5.5). The improvement in the sham group meets the minimal clinically important difference of 0.50.

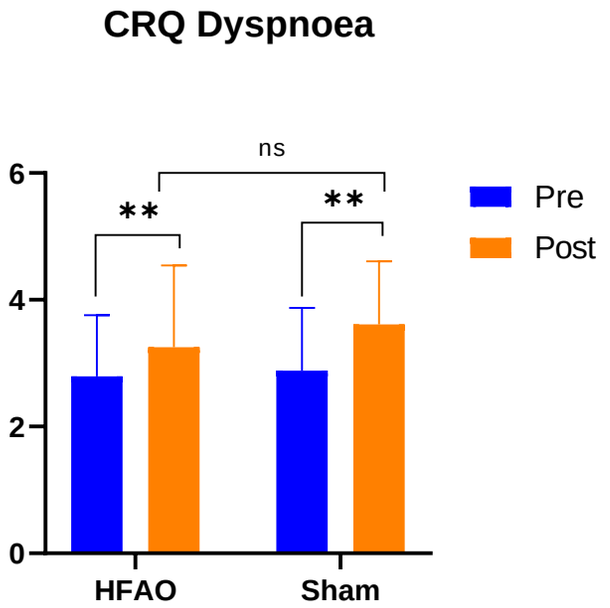



*Figure 5.5 Chronic Respiratory Questionnaire mean change [SD] (**p<0.01 over time) no differences between groups.*

### 5.4.2 Respiratory muscle function and exercise capacity

There were statistically significant improvements in maximal expiratory pressures ($PI_{max}$) in those receiving the HFAO with a mean [SD] improvement of 5.63[11.35] $cmH_2O$. No significant differences were seen in the sham group (mean [SD] change 0.20[11.86] $cmH_2O$). There was a statistically significant difference between groups favouring the HFAO intervention.

There were statistically significant improvements in maximal expiratory pressure ($PE_{max}$) for those receiving the HFAO device (mean [SD] 9.63[19.01]). No improvement was seen in the sham group (mean [SD] change of 4.70 [27.99] $cmH_2O$). However, the difference between groups was not statistically significant (table 5.2).

Exercise capacity assessed by the ISWT demonstrated a change of 5.36m [41.89] over the intervention phase in the HFAO group and a change of -7.95m [59.70] in the sham group. This was not statistically significant over time or between groups (table 5.2). The ESWT had an increase of 33.02 [150.38] seconds in the HFAO and 29.95 [193.67] in the sham however this was not statistically significant.

*Table 5.2 Respiratory muscle function and exercise capacity for HFAO and sham group*

| | HFAO (n=50) | | | Sham (n=46) | | | Between group difference |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 61.46[23.50] | 67.09[22.50] | 5.63[11.35]** | 78.45[22.91] | 78.65[21.19] | 0.20[11.86] | 0.05 |
| $PE_{max}$ ($cmH_2O$) | 107.22[36.19] | 116.85[40.63] | 9.63[19.01]** | 132.60[50.63] | 137.30[47.50] | 4.70[27.99] | ns |
| ISWT (m) | 282.00[142.00] | 287.00[132.00] | 5.63[41.89] | 357.00[153.00] | 349.00[157.00] | 7.95[59.70] | ns |
| ESWT (secs) | 246.77[181.42] | 279.79[232.38] | 33.02[150.38] | 352.18[326.15] | 322.24[234.10] | 29.95[193.67] | ns |

*Table 5.2 Mean [SD]. $PI_{max}$ maximal inspiratory pressures, $PE_{max}$ maximal expiratory pressures, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test. *p<0.05 **p<0.01 within group. Analysis corrected for baseline differences in $FEV_1$ and $PI_{max}$. *p<0.05, **p<0.01, ns not significant*

Additionally, participants dyspnoea in response to exercise was explored after the ISWT and ESWT. The Borg score for perceived breathlessness and rate of perceived exertion was taken immediately after exercise testing and the reason for stopping assessed. There were no improvements in Borg or RPE scores following the ISWT. There was a statistically significant improvement of 0.54[1.48] points on the Borg score following the intervention phase however this was not significant between groups (HFAO change 0.03[1.51]) (table 5.3).

*Table 5.3 Changes in post exercise test for HFAO and sham group*

| | HFAO (n=50) | Sham (n=46) | Between group p= |
|---|---|---|---|
| ISWT Borg | -0.10[1.59] | -0.13[1.65] | 0.12 |
| ISWT RPE | 0.02[2.07] | 0.03[2.11] | 0.37 |
| ESWT Borg | 0.03[1.51] | -0.54[1.48] * | 0.09 |
| ESWT RPE | -0.13[1.99] | -0.28[2.21] | 0.74 |

*Table 5.3 Mean [SD] changes from baseline in Borg breathlessness score and RPE. HFAO High Frequency Airway Oscillating Device, RPE Rate of Perceived Exertion.*

The reasons for stopping for both the ISWT and ESWT at baseline was most commonly shortness of breath. There were less participants reporting this as the primary reason for stopping the ISWT at follow up in both HFAO and sham groups, however this was not statistically significant. There were less participants reporting shortness of breath as the primary reason for stopping after the ESWT in the sham which was statistically significant. More participants reported shortness of breath as the primary reason for stopping in the HFAO for the ESWT however this was not statistically significant. Table 5.4 explores the primary reason for stopping for the ISWT and ESWT at baseline and after the intervention. Those that had ISWT and ESWT data at both time points were included.

*Table 5.4 Reasons for exercise termination*

| | | HFAO (n=41) | | | Sham (n=40) | | |
|---|---|---|---|---|---|---|---|
| | Reason | Baseline | Follow up | p | Baseline | Follow up | p |
| ISWT | SOB | 33(80%) | 25 (61%) | 0.07 | 26(65%) | 20 (50%) | 0.15 |
| | Fatigue | 4(10%) | 9 (22%) | 0.13 | 8 (20%) | 8 (20%) | 1.00 |
| | Other | 4(10%) | 7 (17%) | 0.77 | 6 (15%) | 12 (30%) | 0.04 |
| ESWT | SOB | 26 (63%) | 30 (73%) | 0.38 | 28 (70%) | 20 (51%) | 0.04 |
| | Fatigue | 8 (20%) | 6 (15%) | 0.69 | 5 (12%) | 11 (28%) | 0.11 |
| | Other | 7 (17%) | 5 (12%) | 1.00 | 7 (18%) | 8 (21%) | 0.75 |

*Table 5.4 n (%) patients terminating exercise test- reasons given. ESWT Endurance Shuttle Walking Test, HFAO High Frequency Airway Oscillations, ISWT Incremental Shuttle Walking Test, SOB Shortness of Breath.*

It is reasonable to assume that participants may maintain their incremental walking test results but have a reduction in breathlessness, however the changes in the Borg score were small. Figure 5.6 shows the spread of participants changes in incremental walking distance and Borg score post exercise for each participant.

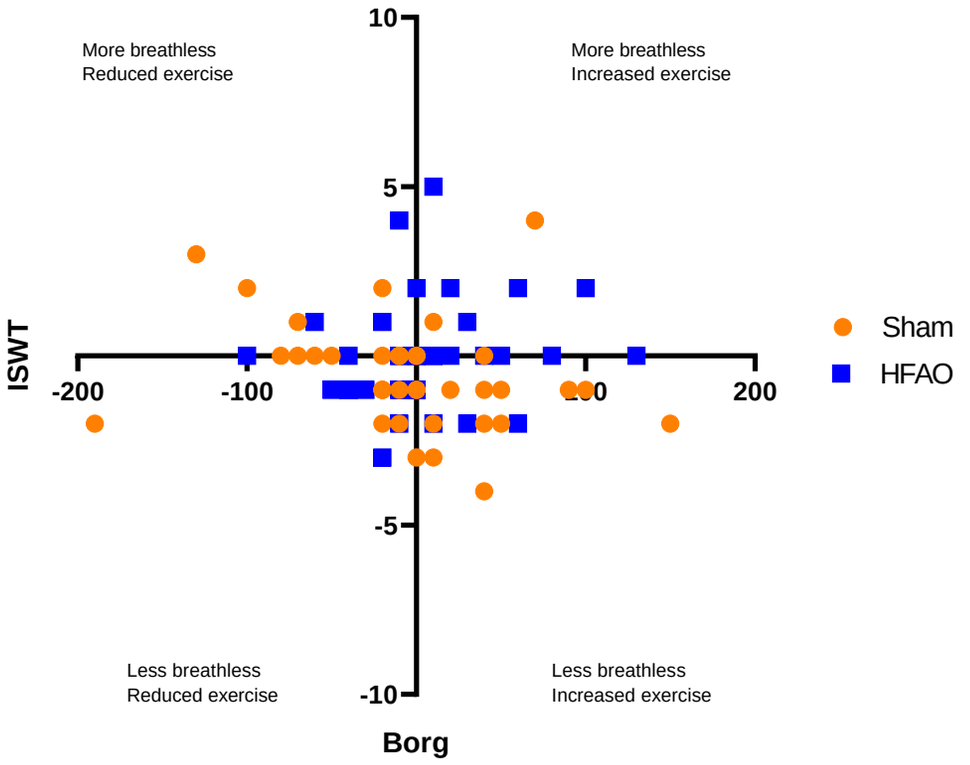



*Figure 5.6 Changes in Incremental Shuttle Walking Test and Borg scores*

### 5.4.3 Health related Quality of Life

The CRQ fatigue domain did not improve over the intervention phase in either the HFAO or sham group. There were statistically significant improvements in the CRQ emotion domain in the sham group (mean [SD] 0.30 [0.88]) compared to a change of 0.13 [0.67]) in the HFAO group however this was not statistically significant between group. There were statistically significant improvements in the CRQ mastery domain (mean [SD] 0.31 [0.86], 0.43 [0.97] HFAO and sham respectively) over time however this was not statistically significant between group. The total score improved by 1.08 [2.40] in the HFAO and 1.76 [2.93] in the sham group, but this was not significant between groups. This change does not meet the known minimal clinically important difference of 2 points[67, 168, 187].

The total COPD Assessment Test changed by 0.68 [4.29] in the HFAO group and 0.74 [4.27] in the sham group however this was not statistically significant. The CAT cough domain demonstrated a change of 0.26 [0.94] in the HFAO group compared to 0.00 [0.92] in the sham. However, when accounting for baseline differences ($PI_{max}$ and $FEV_1$) this was statistically significant between groups (p=0.04). There were statistically significant improvements in the CAT chest tightness domain of 0.38 [1.12] in the HFAO group and a change of -0.15 [1.06] in the sham group. This was statistically significant between groups (p=0.01). Changes for each symptom and total score is shown in figure 5.7.

The Leicester Cough Questionnaire (LCQ) total score changed by 0.51 [2.45] in the HFAO group and improved by 0.86 [2.69] in the sham. The improvement in the sham was significant over time but this was not significant between groups. The psychological domain significantly improved over time in the HFAO group (0.29 [0.95]) compared to the sham (0.29 [0.10]) however this was not statistically significant between groups. The social domain changed by 0.09 [0.92] in the HFAO group and improved by 0.34 [1.05] in the sham group however this was not statistically significant between groups. The London Chest Activity of Daily Living (LCADL) self-care domain was statistically significant over time for the sham group but not significant when compared to the HFAO group (0.26 [3.10] HFAO and 0.64 [2.12] sham). There were no statistically significant differences in other domains of the LCADL within or between groups (table 5.5). Changes in HRQoL can be seen in table 5.5.

*Table 5.5 Health Related Quality of Life*

| | HFAO (n=50) | | | Sham (n=46) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| CRQ-D | 2.79[0.97] | 3.25[1.29] | 0.45[0.78] ** | 2.88[0.99] | 3.61[1.45] | 0.73[1.10] ** | ns |
| CRQ-E | 4.48[1.16] | 4.60[1.26] | 0.13[0.67] | 4.63[1.33] | 4.93[1.29] | 0.30[0.88] * | ns |
| CRQ-F | 3.73[0.91] | 3.89[1.01] | 0.16[0.78] | 3.77[1.27] | 4.07[1.32] | 0.31[1.04] | ns |
| CRQ-M | 4.54[1.44] | 4.84[1.39] | 0.31[0.86] ** | 4.77[1.51] | 5.21[1.38] | 0.43[0.97] ** | ns |
| CRQ-Total | 15.45[3.81] | 16.63[4.14] | 1.08[2.40] ** | 16.05[4.38] | 17.82[4.60] | 1.76[2.93] ** | ns |
| CAT Total | 20.20[6.91] | 19.52[7.41] | -0.68[4.29] | 19.22[6.92] | 18.48[7.51] | -0.74[4.24] | ns |
| LCQ Total | 15.79[3.71] | 16.30[3.57] | 0.51[2.45] | 15.99[3.65] | 16.85[3.27] | 0.86[2.69] | ns |
| LCADL Total | 28.82[10.07] | 29.30[11.35] | 0.48[8.48] | 27.13[11.37] | 27.36[13.44] | 0.22[6.03] | ns |
| HADS A | 7.04[3.79] | 6.68[3.90] | -0.36[2.22] | 6.27[4.07] | 5.86[4.03] | -0.41[2.62] | ns |
| HADS D | 5.78[3.79] | 5.90[3.72] | 0.12[2.66] | 5.84[4.14] | 5.23[3.77] | -0.61[3.00] | ns |

*Table 5.5 Mean [SD]. CRQ Chronic Respiratory Questionnaire D Dyspnoea, E Emotion, F Fatigue, M Mastery domains, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living Questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety, D Depression domains. *p<0.05, **p<0.01 withing group, ns not significant*

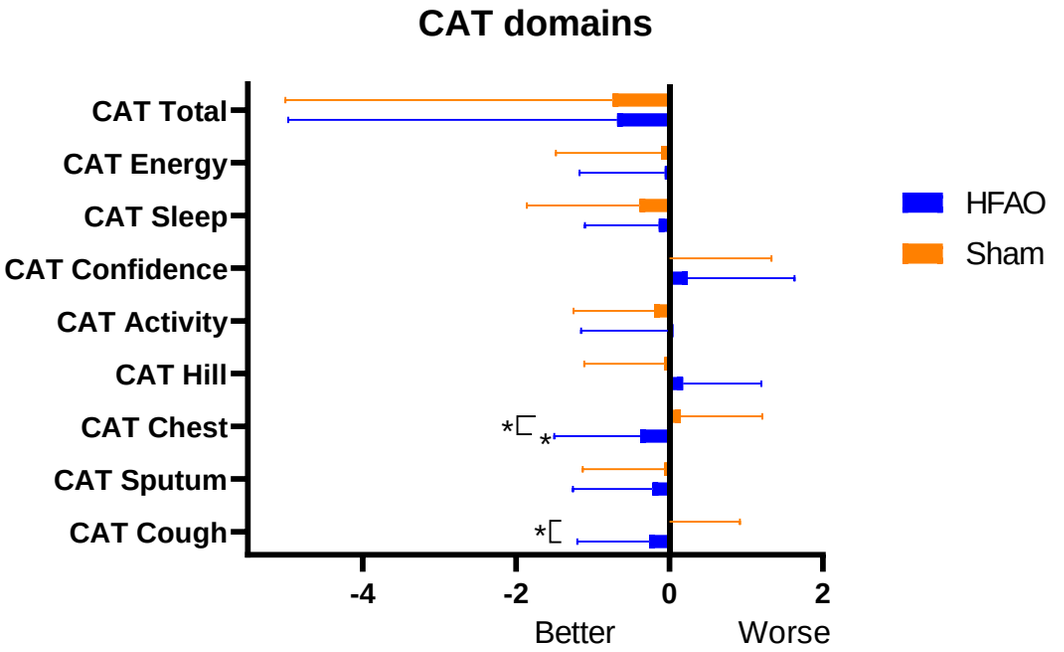



*Figure 5.7 COPD Assessment test mean [SD] changes from baseline. *p<0.05*

### 5.4.4 Dyspnoea

The Multidimensional Dyspnoea Profile (MDP) demonstrated statistically significant improvements in the sensory dyspnoea scale domain in the HFAO group (mean [SD] 3.28 [10.89]) but not in the sham group (1.65 [7.41]), however this was not statistically significant between groups. The most common reported sensation of dyspnoea was “air hunger” in both the sham and the HFAO group at baseline. The frequency of the forced choice question of the MDP can be seen in figure 5.8. After eight weeks the most reported dyspnoea sensation was “breathing a lot” for the sham group and “chest tightness” for the HFAO group which suggests a shift in dyspnoea sensations (figure 5.9). Each sensory domain was scored on a 10-point visual analogue scale, where zero is none and 10 is “as intense as I can imagine”. The mean scores for each sensation are listed in table 5.6 for the sham and HFAO group. Despite “air hunger” being the most commonly reported description of breathlessness, the intensity was higher in the “breathing a lot” sensation in the sham

group and “muscle work/effort” or “breathing a lot” sensations for the HFAO group (table 5.6 and figure 5.10). The greatest reduction in sensory intensity was in the “mental effort/concentration” domain in the HFAO group and in the “breathing a lot” domain in the sham group. As the sham group were required to breathe deeply through the device, it is reasonable to see improvements in breathing frequency, which did not appear to translate into the other sensations of dyspnoea. The overall improvement in the sensory component of the MDP was statistically significant over the intervention phase for the HFAO group but this was not significant between groups.

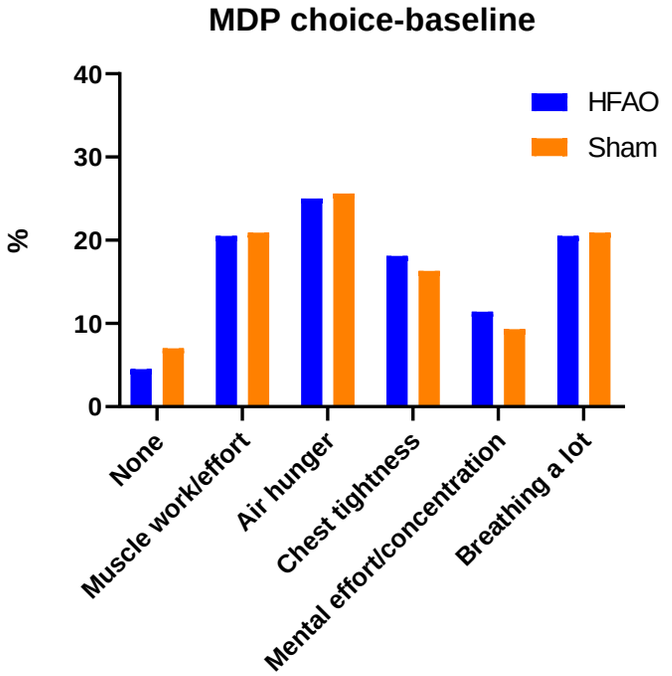



*Figure 5.8 Multidimensional Dyspnoea Profile sensory choice question (% of patients reporting sensation as primary breathlessness)*

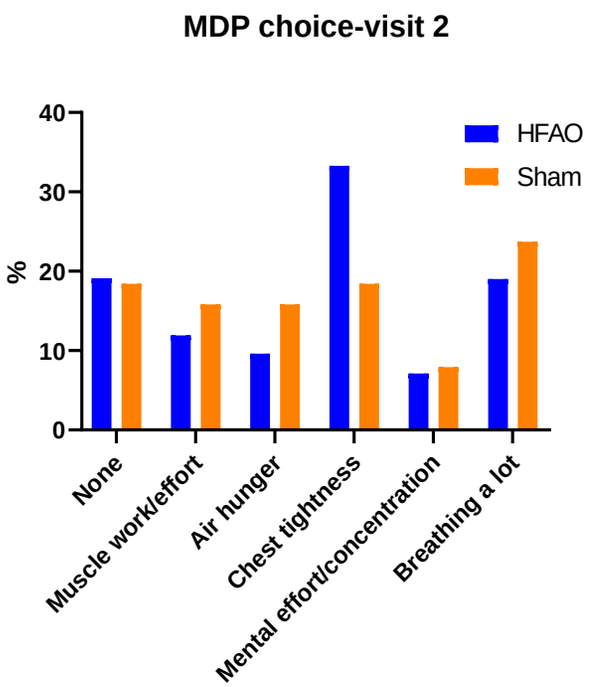



*Figure 5.9 Multidimensional Dyspnoea Profile sensory choice question visit two (% of patients reporting sensation as primary breathlessness)*

*Table 5.6 Multidimensional Dyspnoea Profile sensory scores*

| | HFAO (n=50) | | | Sham (n=46) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | P |
| Muscle work/effort | 3.61[2.73] | 2.88[2.27] | -0.72[2.58] | 2.76[2.47] | 2.37[2.66] | -0.39[1.93] | ns |
| Air hunger | 3.07[3.31] | 2.44[2.78] | -0.63[2.94] | 2.66[2.73] | 2.50[3.03] | -0.16[2.06] | ns |
| Chest tightness | 2.95[2.84] | 2.53[2.58] | -0.42[2.76] | 2.71[3.09] | 2.42[3.08] | -0.29[2.48] | ns |
| Mental effort/ concentration | 2.93[2.93] | 2.09[2.59] | -0.84[2.90] | 1.95[2.58] | 2.11[2.69] | 0.16[2.69] | ns |
| Breathing a lot | 3.60[2.85] | 2.84[2.89] | -0.77[2.83] | 3.34[3.20] | 2.74[3.14] | -0.61[1.92] | ns |
| Total | 16.30[12.87] | 13.02[11.41] | 3.28[10.89] * | 13.58[11.35] | 11.97[13.57] | 1.61[7.39] | ns |

*Table 5.6 Mean [SD]. HFAO High Frequency Airway Oscillations. * p<0.05, **p<0.01 within group, ns not significant*

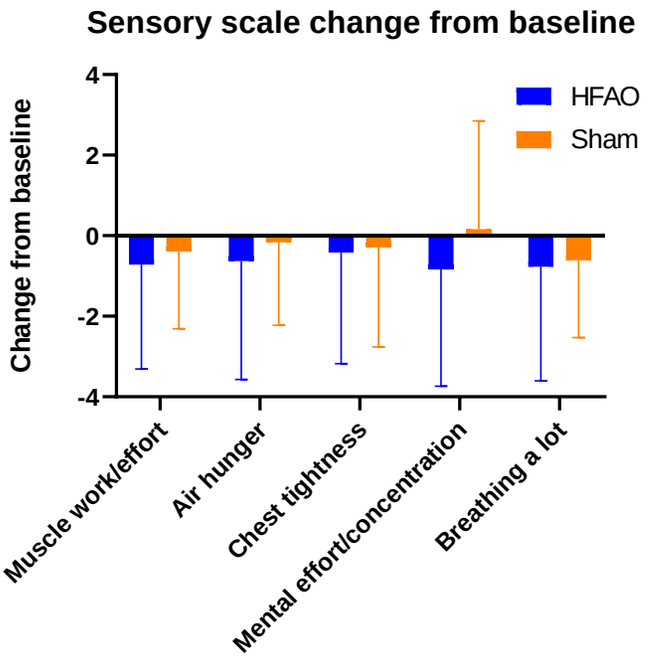



*Figure 5.10 Multidimensional Dyspnoea Profile sensory response- mean [SD] changes from baseline.*

The affective domain explored the impact of dyspnoea on five common emotions: depression, anxiety, frustration anger and fear. This was scored on a 10-point visual analogue scale where zero was none and 10 was “the most I can imagine”. The highest severity emotion was frustration for both the sham and HFAO groups. The largest improvement was in the anxiety domain in the sham and depression domain in the HFAO group. The affective domain demonstrated an improvement of 3.25 [10.80] in the HFAO group and 1.65 [10.03] in the sham however this was not statistically significant between groups. The overall unpleasantness of dyspnoea was measured on a zero to ten-point visual analogue scale the mean [SD] change for the HFAO group was -0.21 [1.78] and for the sham was -0.32 [1.88]. This was not statistically significant over time or between groups (table 5.7 and figure 5.11).

*Table 5.7 Multidimensional Dyspnoea Profile emotion scores*

| | HFAO (n=50) | | | Sham (n=46) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | P |
| Depressed | 3.26[3.13] | 2.42[2.51] | -0.84[2.42] * | 2.16[2.59] | 1.92[2.60] | -0.24[2.10] | ns |
| Anxious | 3.60[2.92] | 2.84[2.88] | -0.77[2.87] | 2.76[3.04] | 2.18[2.69] | -0.58[2.77] | ns |
| Frustrated | 4.30[3.17] | 3.84[2.88] | -0.47[2.54] | 3.68[3.51] | 3.52[3.16] | -0.26[2.47] | ns |
| Angry | 3.42[3.42] | 2.70[2.81] | -0.72[3.17] | 2.89[3.33] | 2.82[3.23] | -0.08[2.99] | ns |
| Afraid | 2.86[3.26] | 2.58[2.98] | -0.28[2.39] | 2.32[3.41] | 1.95[3.18] | -0.37[2.14] | ns |
| Total | 17.65[14.19] | 14.40[12.83] | -3.26[10.80] * | 13.82[14.08] | 12.29[13.42] | -1.53[9.92] | ns |

*Table 5.7 Mean [SD]. HFAO High Frequency Airway Oscillations. *p<0.05 **p<0.01 within group, ns not significant*

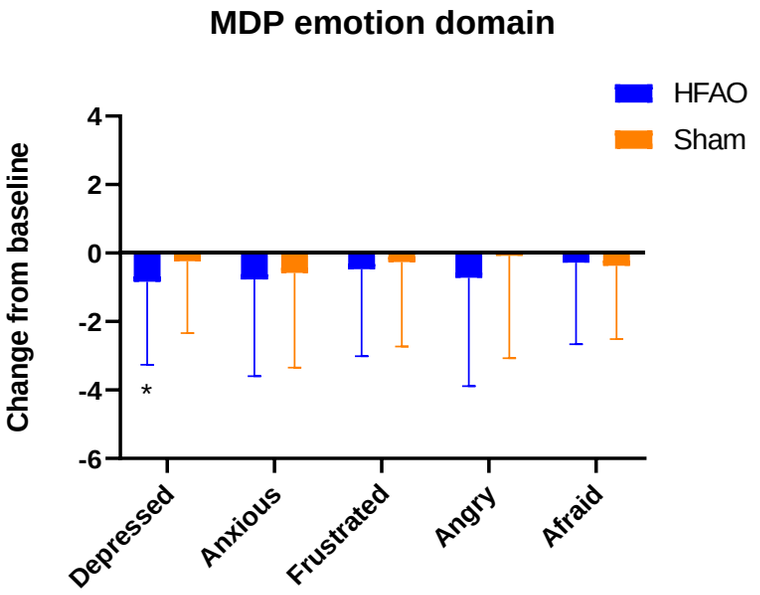



*Figure 5.11 Multidimensional Dyspnoea Profile emotional response- mean[SD] change from baseline*

The total score combines all previously reported domains and overall, improved by 6.86 [20.16] and 3.86 [16.10] for the HFAO and sham group, respectively. The improvement in the HFAO was statistically significant over time but this was not significant between groups.

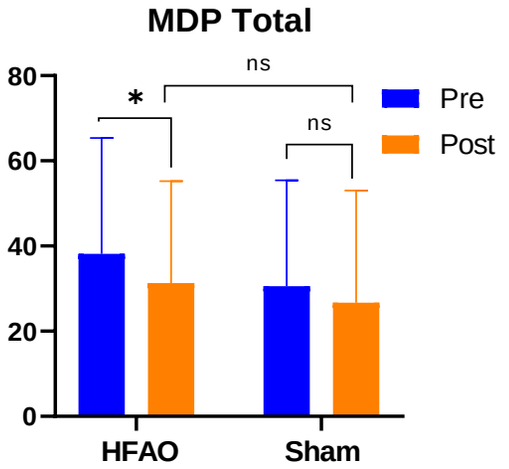



*Figure 5.12 Multidimensional Dyspnoea Profile total score- mean [SD] change from baseline. *p≤0.05, ns not significant*

The MDP was explored in relation to the GOLD staging. There was a change in reported MDP sensory score for all GOLD stages. This was not stratified by treatment group due to sample size challenges. A one-way ANOVA was used to explore the changed in MDP sensory and emotional scores stratified by the treatment group and GOLD staging. There were statistically significant differences for patients using the HFAO group sensory domain of the MDP with patients with GOLD stage four demonstrating the greatest benefit. There were no significant differences for the placebo group (table 5.8). Due to a small sample size GOLD stage one was not included in the analysis (<2 in a group). This demonstrates that patients with more severe airflow obstruction had a greater reduction in breathlessness.

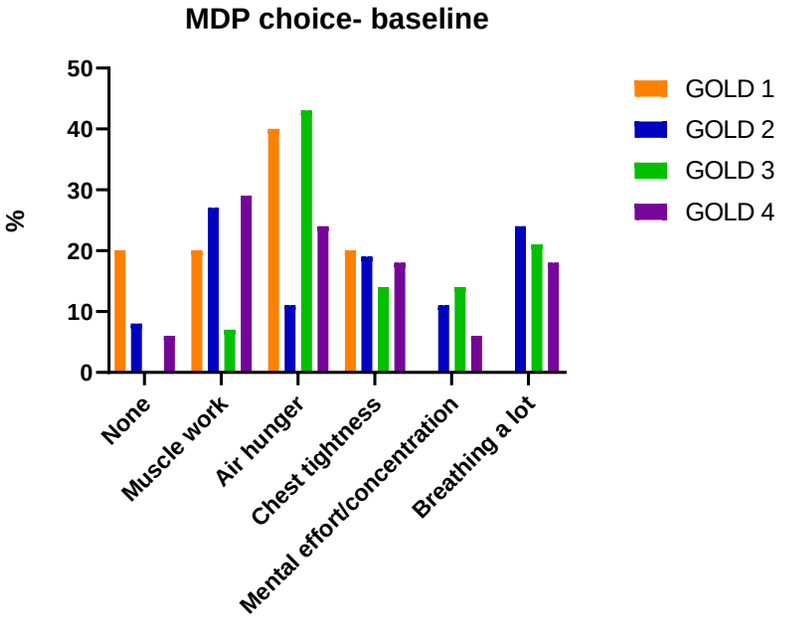



*Figure 5.13 Multidimensional Dyspnoea Profile sensory choice question and GOLD staging (% of patients reporting sensation as primary breathlessness)*

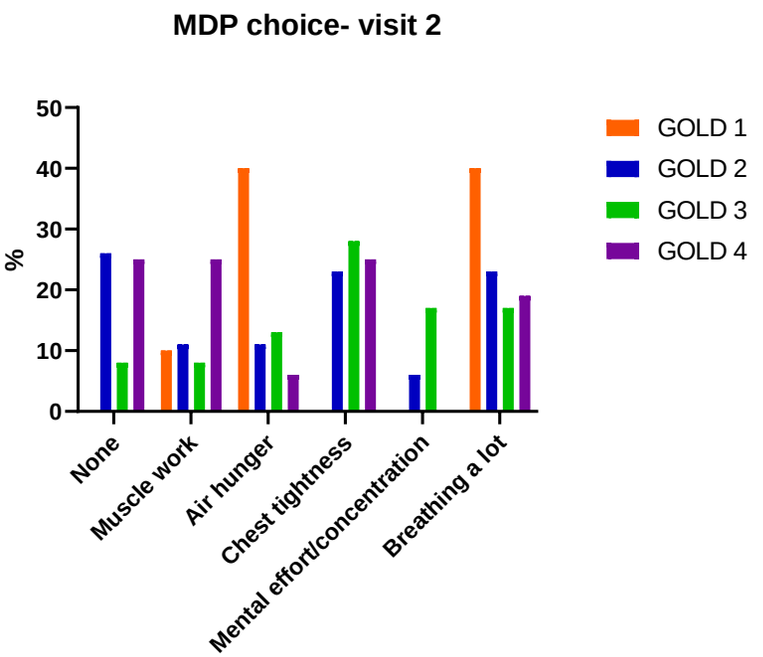



*Figure 5.14 Multidimensional Dyspnoea Profile sensory choice question and GOLD staging (% of patients reporting sensation as primary breathlessness)*

*Table 5.8 One way ANOVA of MDP and GOLD staging.*

| | | GOLD 2 | GOLD 3 | GOLD 4 | p= |
|---|---|---|---|---|---|
| HFAO | N= | 17 | 17 | 8 | |
| | MDP sensory domain | -0.78[5.67] | -2.18[12.25] | -12.63[12.94] | 0.02 |
| | MDP affective domain | -1.53[6.87] | -1.41[13.29] | -11.50[9.56] | 0.06 |
| Sham | N= | 18 | 8 | 8 | |
| | MDP sensory domain | -2.72[7.37] | -0.25[4.95] | 1.75[6.92] | 0.29 |
| | MDP affective domain | 0.22[9.86] | -4.13[6.49] | 0.35[11.04] | 0.53 |

*Table 5.8 One-Way ANOVA of MDP sensory and affective changes from baseline stratified by GOLD staging. Mean [SD]*

### 5.4.5 Predefined subgroup analysis- Inspiratory muscle strength

Subgroup analysis was performed on participants with weakened inspiratory muscles as commonly defined by ≤60cm$H_2O$ on their baseline inspiratory muscle strength test. There were 26 (49%) and 13 (25%) participants in the HFAO and sham group respectively who demonstrated inspiratory muscle weakness. There were statistically significant improvements in $PI_{max}$ for those receiving the HFAO device of 7.92cm$H_2O$ [11.10]. The improvement accounted for an 18% improvement. Those receiving the sham had an improvement of 9.11cm$H_2O$ [12.74] which is an improvement of 18% however this was not statistically significant. There were no statistically significant differences between groups following the intervention as seen in table 5.9. There were improvements in $PE_{max}$ of 7.71cm$H_2O$ [17.34] and 26.56cm$H_2O$ [25.40] in the HFAO and sham group, respectively. This was statistically significant over time and between groups favouring the sham. The ISWT was 76.75m higher at baseline in those using the sham device however this was not

statistically significant (p=0.90). There was a 1.00 [37.12] metre increase in those that received the HFAO device compared to an 8.75 [67.71] increase in those that received the sham. Similarly, there was a baseline difference of 154.29 seconds however this was not statistically significant (p=0.38). There was an increase of 22.42 [138.40] seconds in the HFAO group and 71.00 [302.77] in the sham however this was not statistically significant.

Both groups achieved statistically significant improvements in the CRQ total score (1.12 [2.57] HFAO, 1.59 [2.10] sham) however this was not statistically significant between groups. Those receiving the sham had statistically significant improvements in the CRQ emotion domain however this was not significant between groups (0.40 [0.60]). There were statistically significant differences between groups in the CAT chest domain (-0.43[1.21] HFAO, +0.46 [1.27] sham) (p=0.01) and CAT energy (-0.23 [1.28] HFAO, -0.46 [1.56] sham)(p=0.04) in favour of the HFAO group. There were statistically significant between group differences in the CAT activity domain (+0.19 [1.10] HFAO, -0.39 [1.33] sham) in favour of the sham group. The MDP affective domain improved by 3.42 [11.84] in the HFAO and worsened by 3.38 [13.41] in the sham group which was statistically significant between groups (p=0.05). There were statistically significant differences in favour of the HFAO group in the LCQ physical domain however this did not remain significant when adjusted for baseline differences ($FEV_1$ and $PI_{max}$).

*Table 5.9 TIDe subgroup analysis- inspiratory muscle weakness ≤60cm$H_2O$*

| | HFAO ≤60cm$H_2O$ (n=26) | | | Sham ≤60cm$H_2O$ (n=13) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ (cm$H_2O$) | 43.96[12.13] | 51.88[16.67] | 7.92[11.10]** | 51.89[6.25] | 61.00[14.42] | 9.11[12.74] | ns |
| $PE_{max}$ (cm$H_2O$) | 91.79[21.73] | 99.50[33.57] | 7.71[17.34] * | 83.78[23.46] | 110.33[25.95] | 26.56[25.40]** | 0.03 |
| ISWT (m) | 242.00[127.80] | 243.00[131.39] | 1.00[37.12] | 318.75[257.53] | 327.50[181.88] | 8.75[67.71] | ns |
| ESWT (secs) | 206.96[105.00] | 229.37[185.61] | 22.42[138.40] | 361.25[398.83] | 290.25[176.82] | 71.00[302.77] | ns |
| CRQ-D | 2.82[1.08] | 3.14[1.44] | 0.32[1.24] | 2.28[0.86] | 2.78[1.35] | 0.51[1.23] | ns |
| CRQ-Total | 14.91[4.17] | 16.03[4.63] | 1.12[2.57] * | 13.09[3.72] | 14.68[4.03] | 1.59[2.10] | ns |
| CAT | 20.31[6.36] | 20.04[7.73] | 0.27[4.91] | 21.15[8.94] | 21.15[9.24] | 0.00[5.16] | ns |
| LCQ | 16.00[3.80] | 16.61[3.87] | 0.61[2.48] | 15.23[3.93] | 15.61[3.93] | 0.39[2.69] | ns |
| LCADL | 30.62[11.27] | 31.69[11.84] | 1.08[10.43] | 35.50[14.17] | 33.58[18.47] | 1.81[11.41] | ns |
| HADS-A | 8.15[3.77] | 7.54[4.18] | 0.62[2.26] | 8.36[4.20] | 7.09[4.37] * | 1.27[1.49] | ns |
| HADS-D | 6.50[3.35] | 6.12[3.77] | 0.39[2.90] | 6.27[4.56] | 5.64[3.20] | 0.63[3.30] | ns |
| MDP Total | 38.74[30.66] | 33.68[27.06] | 5.05[23.62] | 40.50[32.80] | 47.38[33.87] | 6.88[18.61] | ns |

*Table 5.9 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05, **p<0.01 within group, ns not significant*

There were 24 participants in the HFAO group and 33 in the sham group that did not demonstrate inspiratory muscle weakness. Both groups demonstrated a significant improvement in the primary outcome measure, CRQ Dyspnoea domain (0.60[1.20] HFAO, 0.79[1.05] sham) however there was no statistically significant differences between groups (table 5.10). The CRQ mastery domain achieved statistical significance over time in the sham group (0.39[1.01]) however this was not significant between groups. The CRQ total had significant improvements over time for both groups (1.04[2.25] HFAO, 1.71[3.16] sham) though this did not demonstrate significance between groups. The CAT Cough domain remained significant between groups in favour of the HFAO group (-0.29[1.00] HFAO, -0.03[0.81] sham). There were significant improvements in the LCQ Physical domain in the sham group (0.36[0.95]) however this was not significant between groups. Both groups demonstrated a significant improvement in the MDP sensory scale (-4.71[9.31] HFAO, -2.97[7.29] sham) and the MDP total score (-8.29[17.34] HFAO, -6.45[14.55] sham) though this was not significant between groups. There was a statistically significant improvement in $PI_{max}$ of 11.72cm$H_2O$ [20.89] in the HFAO group however this was not significant between group (0.44 [27.78] sham, p=0.35). There were large differences seen at baseline for the ISWT and ESWT however these were not statistically significant (p=0.43, p-0.45 respectively). There were respective improvements in the ISWT and ESWT of 9.52 [46.57] meters and 43.10 [163.90] seconds in the HFAO group and a decrease of -12.58 [57.27] meters and -14.50 [162.11] seconds in the sham group however this was not statistically significant between groups. Results can be seen in table 5.10

*Table 5.10 TIDe subgroup analysis- without inspiratory muscle weakness >60cm$H_2O$*

| | HFAO >60cm$H_2O$ (n=24) | | | Sham >60cm$H_2O$ (n=33) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ (cm$H_2O$) | 80.55[17.05] | 83.68[17.21] | 3.14[11.34] | 84.88[20.95] | 82.78[20.65] | -2.09[10.39] | ns |
| $PE_{max}$ (cm$H_2O$) | 124.05[35.63] | 135.77[39.80] | 11.72[20.89] | 144.44[48.63] | 144.88[48.93] | 0.44[27.78] | ns |
| ISWT (m) | 319.52[148.34] | 329.05[121.49] | 9.52[46.57] | 352.58[156.92] | 340.00[149.58] | -12.58[57.27] | ns |
| ESWT (secs) | 284.60[228.68] | 327.70[265.33] | 43.10[163.90] | 336.57[313.89] | 322.07[246.23] | -14.50[162.11] | ns |
| CRQ-D | 2.77[0.84] | 3.37[1.12] | 0.60[1.20] * | 3.06[1.02] | 3.84[1.43] | 0.79[1.05] * | ns |
| CRQ-Total | 16.23[3.32] | 17.27[3.50] | 1.04[2.25] * | 16.89[4.44] | 18.58[4.63] | 1.71[3.16] ** | ns |
| CAT | 20.08[7.59] | 18.96[7.17] | -1.13[3.54] | 19.03[7.01] | 18.00[7.43] | -1.03[3.93] | ns |
| LCQ | 15.56[3.67] | 15.97[3.34] | 0.41[2.47] | 16.06[3.74] | 17.00[3.31] | 0.94[1.58] | ns |
| LCADL | 26.88[8.39] | 26.71[10.42] | -0.17[5.87] | 25.09[10.18] | 25.24[10.53] | 0.15[5.66] | ns |
| HADS-A | 5.83[3.48] | 5.75[3.42] | -0.08[2.19] | 5.82[4.12] | 5.64[4.14] | -0.18[2.84] | ns |
| HADS-D | 5.00[3.08] | 5.67[3.74] | 0.67[2.29] | 6.00[4.58] | 5.24[4.14] | -0.76[3.06] | ns |
| MDP Total | 37.67[24.81] | 29.38[21.56] | -8.29[17.34]* | 29.97[23.56] | 23.52[23.98] | -6.45[14.55] * | ns |

*Table 5.10 Mean [SD]. $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05, **p<0.01 within group, ns not significant*

### 5.4.6 Predefined subgroup analysis- Compliant

There were 43 (81%) participants in the HFAO group and 46 (90%) in the sham that self-reported compliance of over 75% of the training regime. Both groups had a significant improvement in the primary outcome, CRQ Dyspnoea domain (0.53[1.23] HFAO, 0.73[1.09] sham) which meets the minimal clinically important difference; however, this was not significant between groups. Similarly, the CRQ Mastery (0.30 [0.89] HFAO, 0.42 [0.97] sham) and total scores (1.18 [2.49] HFAO, 1.75 [2.90] sham) achieved significance over time but not between groups. The CRQ Fatigue domain improved by 0.30 [1.03] in the sham group but this was not significant between groups. The CAT cough and chest domains remain significant over time in the HFAO group and is significant between groups (CAT cough -0.30 [0.96] HFAO, -0.02 [0.92] sham, p=0.05; CAT chest -0.44 [1.10] HFAO, +0.28 [1.12] sham, p=0.01). The LCQ total score improved in both groups but this was not statistically significant between groups. Participants receiving the HFAO device had a statistically significant improvement in their $PI_{max}$ (5.24 [10.88]) and $PE_{max}$ (8.74 [18.97]) compared to the sham (0.37 [11.76] $PI_{max}$, 6.17 [29.11] $PE_{max}$]) however this was not statistically significant between groups. There were no significant improvements observed in exercise capacity for either groups (table 5.11).

*Table 5.11 TIDe subgroup analysis- compliant to the intervention phase*

| | HFAO ≥75% compliance (n=43) | | | Sham ≥75% compliance (n=36) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 61.83[24.45] | 67.07[23.12] | 5.24[10.88]** | 80.52[22.78] | 80.06[21.62] | -0.46[12.46] | 0.05 |
| $PE_{max}$ ($cmH_2O$) | 109.36[36.49] | 118.10[42.11] | 8.74[18.97]** | 137.52[53.52] | 139.09[47.74] | 1.58[27.33] | ns |
| ISWT (m) | 277.44[144.82] | 284.62[135.16] | 7.18[42.11] | 346.88[152.64] | 338.13[160.25] | -8.75[60.09] | ns |
| ESWT (secs) | 424.11[184.86] | 271.81[224.27] | 29.70[140.68] | 352.06[319.04] | 322.32[246.14] | -29.74[162.13] | ns |
| CRQ-D | 2.73[0.91] | 3.26[1.28] | 0.53[1.23] * | 2.95[1.07] | 3.61[1.47] | 0.66[1.03] ** | ns |
| CRQ-Total | 15.59[3.90] | 16.77[4.14] | 1.18[2.49] ** | 16.45[4.52] | 18.23[4.64] | 1.78[3.14] | ns |
| CAT | 20.14[6.64] | 19.19[7.53] | -0.95[4.38] | 19.39[7.12] | 18.22[7.09] | -1.17[3.88] | ns |
| LCQ | 15.55[3.78] | 16.33[3.48] | 0.78[0.37] * | 16.07[3.62] | 17.02[3.16] | 0.95[2.82] * | ns |
| LCADL | 28.81[9.61] | 27.72[9.42] | -1.09[5.23] | 26.42[11.14] | 26.22[12.35] | -0.19[5.73] | ns |
| HADS-A | 6.91[3.87] | 6.26[3.88] | -0.65[2.03] | 6.19[4.31] | 5.83[4.20] | -0.36[2.75] | ns |
| HADS-D | 5.65[3.47] | 5.51[3.52] | -0.14[2.49] | 5.53[3.88] | 5.06[3.57] | -0.47[2.98] | ns |
| MDP Total | 38.97[27.93] | 31.50[24.06] | -7.47[21.22] | 29.28[24.65] | 23.93[23.93] | -5.34[15.87] | ns |

*Table 5.11 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05, **p<0.01 within group, ns not significant*

### 5.4.7 Predefined subgroup analysis- Sputum status

Due to the oscillatory element believed to improve secretion clearance, participants were stratified based on their self-reported level of sputum retention using the CAT phlegm domain. There were 25 (47%) participants in the HFAO group and 20 (39%) in the sham that perceived minimal concerns with sputum retention (CAT phlegm score 0-2). Both groups had a statistically significant improvement in the CRQ Dyspnoea domain (0.53 [1.26] HFAO, 0.90 [1.15] sham) which meets the minimal clinically important difference; however, this was not statistically significant between groups. Similarly, the CRQ total score improved by 1.64 [2.13] in the HFAO and 2.04 [3.68] in the sham which exceeds the minimal clinically important difference of 2 points, however this was not significant between groups. The CRQ fatigue, emotion and mastery domains improved statistically significantly in the HFAO group but not in the sham however this difference was not significant. The MDP affective domain significantly improved in the HFAO group (4.55 [8.35]) but not in the sham (1.69 [9.17]) yet this was not significant between groups. There were no notable improvements in the inspiratory or expiratory muscle strength. There was a small, but statistically significant improvement in the ESWT for the HFAO group of 72[144.82] seconds comparatively to the sham (17.13[282.01]) however this was not significant between groups.

There were 25 (49%) participants in the HFAO group and 27 (53%) in the sham group that report secretion retention based on scores of 3-5 on the CAT phlegm domain. Overall, there were significant improvements seen in the CRQ Dyspnoea domain, Emotion domain, mastery domain and total score for the sham group however this was not significant between groups. There was a significant improvement in the CAT chest domain for those receiving the HFAO intervention which was significant over the sham (-0.48 [1.08] HFAO, +0.19 [1.27] sham, p=0.04), however this did not remain significant when baseline differences were accounted for ($FEV_1$ and $PI_{max}$, p=0.06). There were statistically significant improvements in $PI_{max}$ for those receiving the HFAO device (7.61 [12.32] $cmH_2O$) compared to the sham (-0.28 [9.33]) and this was significant (p=0.02). There were statistically

significant improvements in $PE_{max}$ in the HFAO group (7.61 [12.32] $cmH_2O$) comparatively to the sham (6.84 [30.32] $cmH_2O$) however this was not significant between groups. There were no notable improvements in exercise capacity (table 5.12).

*Table 5.12 TIDe subgroup analysis- non sputum producers (CAT Sputum 0-2)*

| | HFAO CAT Sputum 0-2 (n=25) | | | Sham CAT Sputum 0-2 (n=20) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 57.26[21.86] | 60.91[22.16] | 3.65[10.18] | 76.00[19.35] | 77.38[21.77] | 1.38[15.08] | ns |
| $PE_{max}$ ($cmH_2O$) | 103.96[33.04] | 112.74[42.53] | 8.78[22.46] | 131.25[51.73] | 136.38[51.65] | 5.13[28.07] | ns |
| ISWT (m) | 301.36[140.76] | 307.27[133.78] | 5.91[38.01] | 410.63[171.05] | 421.88[161.67] | 11.25[62.28] | ns |
| ESWT (secs) | 281.90[215.86] | 353.90[285.63] | 72.00[142.82]* | 462.95[399.58] | 445.80[278.52] | 17.13[282.01] | ns |
| CRQ-D | 2.89[0.94] | 3.43[1.41] | 0.53[1.26]* | 3.06[1.03] | 3.95[1.47] | 0.90[1.15]** | ns |
| CRQ-Total | 16.20[4.07] | 17.84[4.16] | 1.64[2.13]** | 16.73[3.52] | 18.76[4.73] | 2.04[3.68]* | ns |
| CAT Sputum | 1.28[0.79] | 1.28[1.02] | 0.00[0.87] | 1.45[0.61] | 1.80[1.32] | 0.35[1.18] | ns |
| CAT | 16.68[5.85] | 15.96[6.96] | -0.72[4.84] | 15.25[5.93] | 15.10[6.16] | -0.19[0.84] | ns |
| LCQ | 17.68[2.94] | 18.02[2.53] | 0.34[2.43] | 17.79[2.34] | 18.42[2.05] | 0.42[2.36] | ns |
| LCADL | 28.72[10.48] | 28.08[12.73] | -0.64[9.57] | 25.32[10.02] | 24.79[12.22] | -0.53[5.72] | ns |
| HADS-A | 6.80[3.93] | 6.28[3.92] | -0.52[2.54] | 6.26[4.01] | 6.16[4.23] | -0.11[2.66] | ns |
| HADS-D | 5.84[3.63] | 5.76[4.11] | -0.08[2.60] | 4.74[2.98] | 4.89[2.92] | 0.16[2.04] | ns |
| MDP Total | 28.10[26.15] | 20.95[19.45] | -7.15[16.15] | 26.44[23.51] | 22.81[25.84] | -3.63[16.79] | ns |

*Table 5.12 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p≤0.05, **<0.01 within group, ns not significant*

*Table 5.13 TIDe subgroup analysis- sputum producers (CAT Sputum 3-5)*

| | HFAO CAT Sputum 3-5 (n=25) | | | Sham CAT Sputum 3-5 (n=27) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 65.65[24.80] | 73.26[21.56] | 7.61[12.32] ** | 78.68[25.72] | 78.40[21.50] | -0.28[2.23] | 0.02 |
| $PE_{max}$ ($cmH_2O$) | 110.48[39.56] | 120.96[39.15] | 10.48[15.29]** | 131.04[51.41] | 137.88[44.71] | 6.84[30.32] | ns |
| ISWT (m) | 258.95[144.83] | 263.68[129.92] | 4.74[47.07] | 309.58[51.41] | 292.92[136.72] | -16.67[58.66] | ns |
| ESWT (secs) | 208.78[124.49] | 193.33[100.11] | -12.44[147.69] | 272.46[249.13] | 242.96[156.63] | -29.50[130.33] | ns |
| CRQ-D | 2.70[1.01] | 3.07[1.14] | 0.37[1.18] | 2.69[1.01] | 3.31[1.41] | 0.61[1.04] ** | ns |
| CRQ-Total | 14.89[3.49] | 15.41[3.81] | 0.53[2.56] | 15.27[5.05] | 16.81[4.67] | 1.53[2.25] ** | ns |
| CAT Sputum | 3.64[0.76] | 3.20[1.08] | 0.44[1.16] | 3.63[0.74] | 3.26[1.06] | 0.37[0.84] | ns |
| CAT | 23.78[6.10] | 23.08[6.10] | -0.64[3.76] | 22.93[6.88] | 21.67[8.01] | -1.26[4.07] | ns |
| LCQ | 13.89[3.46] | 14.58[3.69] | 0.69[2.51] | 7.33[2.63] | 8.00[3.42] | 0.67[2.06] | ns |
| LCADL | 28.92[9.85] | 30.52[9.88] | 1.60[7.25] | 29.48[13.16] | 29.11[13.94] | -0.37[8.56] | ns |
| HADS-A | 7.28[3.90] | 7.08[3.93] | -0.20[1.89] | 6.58[4.39] | 5.96[4.19] | -0.62[2.58] | ns |
| HADS-D | 5.72[2.97] | 6.04[3.37] | 0.32[2.75] | 7.12[5.14] | 5.73[4.44] | -1.39[3.51] | ns |
| MDP Total | 46.87[25.52] | 40.26[24.21] | -6.61[23.47] | 35.55[26.82] | 32.05[28.68] | -3.50[15.79] | ns |

*Table 5.13 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05, **p<0.01 within group, ns not significant*

### 5.4.8 Predefined subgroup analysis- frequent exacerbators

Comparisons were made between patients who were considered infrequent exacerbators (0-1 exacerbations over the previous 12 months). There were 18 (34%) participants in the HFAO group and 21 (41%) in the sham group who had zero to one exacerbation in the previous 12 months. There were statistically significant improvements in the CRQ Dyspnoea domain over time for both the HFAO and sham group (0.68 [1.16], 1.03 [0.98] respectively), which meets the MCID, however was not significant between groups. Similarly, the CRQ total score significantly improved over time by 1.15 [2.15] in the HFAO group and 1.87 [3.36] in the sham group however this was not statistically significant between groups. The CRQ mastery domain significantly improved for the HFAO group (0.42 [0.76]) however this was not significant over the effects of the sham. The CAT cough domain and the sleep domain significantly improved in the HFAO and sham group respectively and the sleep domain was significant between groups in favour of the sham. There were statistically significant differences between groups in the CAT confidence domain in favour of the sham however this did not remain significant when adjusted for baseline differences. There were statistically significant improvements in the LCQ psychological domain in the HFAO group which was significant between groups. The MDP affective domain and total score was statistically significant over time in the HFAO group (-4.94 [7.16], -7.78 [14.47] respectively) however this was not significant when compared to a sham (-1.61 [9.06], 3.39 [14.42] respectively). $PE_{max}$ improved significantly in both groups (11.44 [21.19] HFAO, 12.95 [24.86] sham) however this was not significant between groups (table 5.14).

There were 18 (34%) participants in the HFAO that had two or more exacerbations in the preceding 12 months and were considered frequent exacerbators. There were 12 (24%) frequent exacerbators in the sham group. The CRQ dyspnoea domain significantly improved over eight weeks in the sham group (0.83 [0.94] sham, 0.32 [1.26] HFAO) however this was not significant between groups. The sham group had statistically significant improvements in the CRQ mastery domain and the CRQ total score however this was not significant

between groups. The CAT chest domain significantly improved in the HFAO group when compared to a sham (0.61 [1.15], p=0.04). The LCQ social domain was statistically significant between groups however this did not remain significant when adjusted for baseline differences ($FEV_1$ and $PI_{max}$). The LCADL leisure domain and total score significantly improved in the HFAO group however this was not significant between groups. $PI_{max}$ statistically significantly improved in the HFAO group (8.78 [12.22]) compared to a sham (3.00 [10.15], p=0.05). The ISWT improved by 12.67m [40.97] in the HFAO group and worsened significantly by 47.27 [67.54] in the sham, the differences between groups was statistically significant (p=0.02). The differences between group is larger than the reported MCID of 35m[104]. The ESWT increased by 5.07[161.55] seconds in the HFAO group and worsened by 68.18[90.17] seconds in the sham group. This worsening was statistically significant over time but not when compared between groups (table 5.14).

A summary of the sub-group analysis results for the primary outcome (CRQ-Dyspnoea) can be seen in figure 5.15.

*Table 5.14 TIDe subgroup analysis- infrequent exacerbators (<2 in 12 months)*

| | HFAO <2 exacerbations (n=18) | | | Sham <2 exacerbations (n=21) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 67.67[19.51] | 70.22[20.89] | 2.56[11.44] | 73.05[19.84] | 73.32[20.90] | 0.26[10.95] | ns |
| $PE_{max}$ ($cmH_2O$) | 111.28[33.70] | 122.72[35.83] | 11.44[21.19]* | 124.53[36.33] | 137.47[40.14] | 12.95[24.86]* | ns |
| ISWT (m) | 340.59[122.60] | 334.71[113.31] | -5.88[33.92] | 336.00[162.20] | 354.00[167.31] | 18.00[50.43] | ns |
| ESWT (secs) | 238.81[109.06] | 296.64[224.74] | 58.13[142.14] | 344.74[236.88] | 363.47[206.71] | 18.74[206.39] | ns |
| CRQ-D | 3.02[1.13] | 3.69[1.37] | 0.68[1.16]* | 2.80[0.97] | 3.82[1.53] | 1.03[0.98]* | ns |
| CRQ-Total | 16.87[2.90] | 18.01[3.51] | 1.15[2.15]* | 15.82[4.33] | 17.69[5.37] | 1.87[3.36]** | ns |
| CAT | 16.94[5.16] | 15.11[5.54] | -1.83[3.70]* | 19.38[8.08] | 17.33[7.78] | -2.05[3.34]** | ns |
| LCQ | 16.81[3.32] | 17.87[2.31] | 1.07[2.44] | 17.02[3.29] | 17.02[3.38] | 0.00[2.42] | ns |
| LCADL | 23.72[8.66] | 23.50[6.44] | -0.22[2.49] | 28.71[13.36] | 26.24[12.76] | -2.48[8.91] | ns |
| HADS-A | 5.28[3.27] | 5.22[2.90] | -0.06[2.34] | 6.52[4.47] | 7.14[4.08] | 0.62[2.69] | ns |
| HADS-D | 4.89[2.79] | 5.11[3.77] | 0.22[2.49] | 28.71[13.36] | 26.24[12.76] | -2.48[8.91] | ns |
| MDP Total | 30.44[21.82] | 22.67[20.83] | -7.78[14.47]* | 31.67[27.20] | 28.28[30.95] | -3.39[14.42] | ns |

*Table 5.14 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05 within group, ns not significant*

*Table 5.15 TIDe subgroup analysis- frequent exacerbators (≥2 in 12 months)*

| | HFAO ≥2 exacerbations (n=18) | | | Sham ≥2 exacerbations (n=12) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| $PI_{max}$ ($cmH_2O$) | 53.67[26.28] | 62.44[25.19] | 8.78[12.22]** | 84.83[26.98] | 81.83[23.07] | -3.00[10.15] | 0.05 |
| $PE_{max}$ ($cmH_2O$) | 97.39[38.14] | 103.50[41.62] | 6.11[17.94] | 133.00[58.76] | 132.00[39.44] | -1.00[36.95] | ns |
| ISWT (m) | 191.33[102.39] | 214.07[153.59] | 12.67[40.97] | 310.00[120.17] | 262.73[107.62] | -47.27[67.54]* | 0.02 |
| ESWT (secs) | 214.07[153.59] | 209.00[123.18] | 5.07[161.55] | 276.55[176.34] | 208.36[124.78] | -68.18[90.17]* | ns |
| CRQ-D | 2.57[0.92] | 2.88[1.18] | 0.32[1.26] | 2.47[0.77] | 2.20[1.27] | -0.83[0.94] | ns |
| CRQ-Total | 14.31[4.17] | 15.11[4.47] | 0.80[2.75] | 15.20[4.76] | 17.67[4.46] | 2.47[2.11] | ns |
| CAT | 24.11[5.23] | 23.61[5.51] | -0.50[3.85] | 24.17[6.46] | 22.08[8.24] | -2.08[4.25] | ns |
| LCQ | 14.32[3.58] | 15.03[4.00] | 0.71[2.18] | 13.29[3.67] | 15.41[3.93] | 2.11[3.57] | ns |
| LCADL | 33.17[10.07] | 30.61[9.64] | -2.56[4.72] * | 26.00[10.45] | 26.67[12.32] | 0.67[5.66] | ns |
| HADS-A | 8.06[4.09] | 7.22[4.48] | -0.83[1.79] | 6.42[4.46] | 4.67[4.08] | -1.75[2.14]* | ns |
| HADS-D | 6.28[3.64] | 6.11[3.89] | -0.17[2.62] | 7.92[5.60] | 5.92[4.83] | -2.00[3.84] | ns |
| MDP Total | 48.92[32.82] | 36.38[27.41] | -12.54[31.01] | 37.00[27.59] | 25.78[24.68] | -11.22[16.24] | ns |

*Table 5.15 Mean [SD]. HFAO High Frequency Airway Oscillations, $PI_{max}$ Maximal Inspiratory Pressure, $PE_{max}$ Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test, CRQ Chronic Respiratory Questionnaire D Dyspnoea domain, CAT COPD Assessment Test, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living questionnaire, HADS Hospital Anxiety and Depression Scale A Anxiety D Depression, MDP Multidimensional Dyspnoea Profile. *p<0.05, **p<0.01 within group, ns not significant*

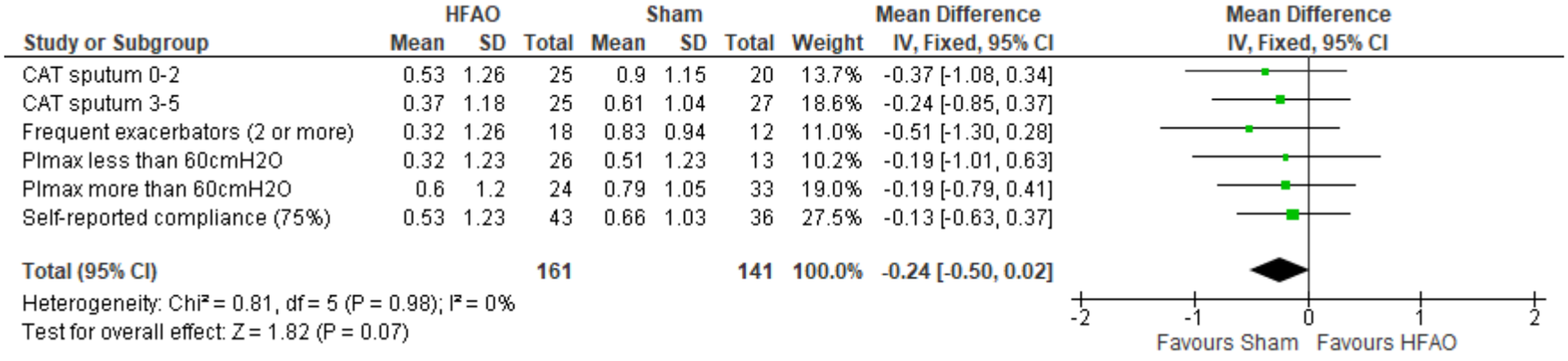



*Figure 5.15 Summery of sub-group analysis primary outcome- CRQ Dyspnoea*

### 5.4.9 Exploratory outcome- Physical activity

Physical activity data was collected in 70 participants pre and post intervention. The overall mean [SD] physical activity step count in this cohort was 3576 [2381] per day, which is comparable to the literature on step count in patients with COPD[188]. Time spent being sedentary and in light moderate or vigorous activity was also captured. At baseline, the time spent in sedentary, light, moderate and vigorous activity were 871.85[217.80] minutes, 239.33 [94.77], 12.45 [23.10], 0.09 [0.36] respectively. There were no significant differences between groups at baseline in relation to their physical activity. After the eight-week intervention the HFAO had a decrease in step count of 285 [1453] compared to the sham which improved by 274 [2167] steps. The HFAO group had a decrease in light moderate and vigorous activity and an increase in sedentary time, showing an overall decrease in activity. The sham group had a reduction in sedentary time and an increase in light activity. Moderate activity decreased and vigorous activity remained the same. Whilst none of these changes were significant over time, there was a statistically significant difference in light activity in favour of the sham group (see table 5.16).

*Table 5.16 Physical activity analysis*

| | HFAO (n=36) | | | Sham (n=34) | | | Between group differences |
|---|---|---|---|---|---|---|---|
| | Baseline | Post intervention | Change | Baseline | Post intervention | Change | p |
| Steps | 3413[2207] | 3127[1844] | -285 [1453] | 3749[2576] | 4023[2538] | 274[2167] | ns |
| Sedentary time (mins) | 861.25[251.95] | 887.34[156.32] | 26.10 [264.25] | 883.07[177.76] | 851.35[200.66] | -31.73 [252.05] | ns |
| Light activity (mins) | 234.48[94.14] | 217.03[81.48] | -17.45 [80.65] | 244.47[96.57] | 267.59[92.74] | 23.72 [73.58] | 0.02 |
| Moderate activity (mins) | 8.91[12.73] | 6.56[8.34] | -2.34 [6.96] * | 16.19[30.26] | 10.25[17.58] | -5.94 [27.23] | ns |
| Vigorous activity (mins) | 0.14[0.49] | 0.00[0.00] | -0.14 [0.49] | 0.04[0.15] | 0.05[0.24] | 0.01 [0.20] | ns |

*Table 5.16 Mean [SD]. HFAO High Frequency Airway Oscillations. *p<0.05, **p<0.01 within group, ns not significant*

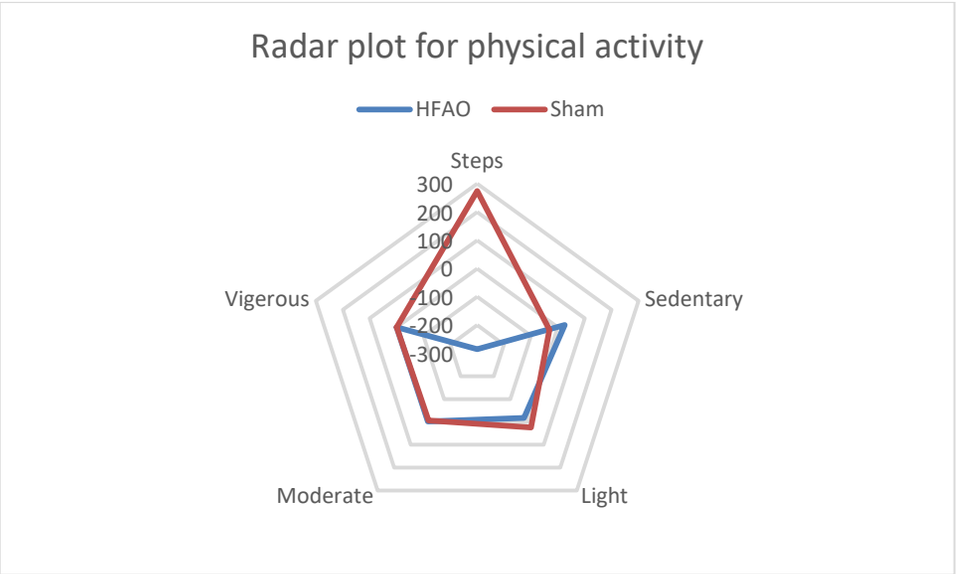



*Figure 5.16 Radar plot of physical activity- time spent in sedentary, light moderate and vigorous activity changes from baseline.*

As the intervention was of eight weeks in duration, it is possible for changes in step count to be dependent on changes in the weather. A one-way ANOVA was carried out to assess the impact of the season at the time of recruitment and their response to step counts. There were no statistically significant differences between baseline step count and season recruited (p=0.32). There were no statistically significant differences between the change from baseline and the season that the participant was recruited to the trial (p=0.08) (table 5.17).

*Table 5.17 One-way ANOVA of physical activity and seasons*

| | Spring (n=17) | Summer (n=34) | Autumn (n=15) | Winter (n=28) | p= |
|---|---|---|---|---|---|
| Baseline steps | 3973.66 [2394.79] | 3537.83 [2536.26] | 4003.34 [3009.44] | 2861.60 [1400.94] | 0.32 |
| Change from baseline Steps | 352.01 [1831.38] | -484.22 [2031.76] | -948.61 [2287.34] | 595.97 [1226.898] | 0.08 |

*Table 5.17 One-Way ANOVA of steps count changes from baseline stratified by seasons. Mean [SD]*

## 5.5 Clinical responders

The CRQ dyspnoea domain has an MCID of 0.5 and there was a total of 51 participants that achieved this, 28 in the sham and 23 in the HFAO group[155]. There were 13 participants that had a worsening of the CRQ dyspnoea domain by 0.5 or more, 6 in the sham and 7 in the HFAO group. The MCID for the CRQ total score is 2 points[155]. There were 21 patients in the sham and 18 patients in the active group that achieved this improvement. There were 2 participants in the sham and 4 in the active group that worsened by more than 2 points in the CRQ total score. There is no official MCID for maximal inspiratory pressures but 13cm$H_2O$ was suggested in a meta-analysis[116]. There were 3 participants in the sham group and 11 in the HFAO group that achieved this improvement. There were 10 participants in the sham group and 7 in the HFAO group that improved the ISWT by the MCID of 35m and 14 that worsened by the MCID (sham= 8, HFAO= 6)[189]. There were 14 in the sham and 15 in the HFAO group that improved by 2 points of the CAT and 18 in the sham and 16 in the HFAO group that worsened by 2 points[133, 190]. There were no statistically significant between group differences in those that met the MCID for the HFAO vs the sham. The improvements across outcomes appear to be variable and it is not necessarily the same participants improving in each outcome. There are no correlations between changes in outcomes, except the CRQ dyspnoea domain and CRQ total (ICC 0.69) however these are derived from

the same questionnaire. The CAT change and CRQ total change appear to correlate moderately (Intraclass Correlation Coefficient -0.41).

*Table 5.18 Patients meeting the Minimal Clinical Important Difference*

| | HFAO (n=50) | | Sham (n=46) | |
|---|---|---|---|---|
| | Improved by MCID | Worsened by MCID | Improved by MCID | Worsened by MCID |
| CRQ Dyspnoea | 23 (46%) | 7 (14%) | 28 (61%) | 6 (13%) |
| CRQ Total | 18 (36%) | 4 (8%) | 21 (46%) | 2 (4%) |
| CAT Total | 15 (30%) | 16 (32%) | 14 (30%) | 18 (39%) |
| $PI_{max}$ ($cmH_2O$) | 11 (22%) | 2 (4%) | 3 (7%) | 4 (9%) |
| ISWT (m) | 7 (14%) | 6 (12%) | 10 (22%) | 8 (17%) |

*Table 5.18 number (%) of patients achieving the MCID Minimal Clinical Important Difference. CRQ Chronic Respiratory Questionnaire, CAT COPD Assessment Test, HFAO High Frequency Airway Oscillating, ISWT Incremental Shuttle Walking Test, $PI_{max}$ Maximal Inspiratory Pressures.*

## 5.6 Three-month follow up

45 patients completed the three months follow up questionnaires at which point all participants were receiving the HFAO device. After the intervention phase all participants were given the HFAO device to use and were followed up by post to assess their usage and any comments. An example survey can be seen in appendix 8. The CRQ and CAT were analysed and stratified by patients who were and were not currently using the device. Comparisons were made between their eight-week follow up visit questionnaires and the three months follow up questionnaires. The baseline characteristics of patients that returned the questionnaires is listed in table 5.19.

*Table 5.19 Baseline characteristics of those three-month follow up*

| | Using HFAO (n=26) | Not using HFAO (n=19) |
|---|---|---|
| Age (years) | 68.31[8.75] | 70.11[6.53] |
| Gender male n (%) | 22 (84.6) | 11 (57.9%) ** |
| Smoking status ex (n) | 21 (80.8) | 17 (89.5%) |
| $FEV_1$ % predicted | 47.50[19.29] | 51.42[19.78] |
| $PI_{max}$ ($cmH_2O$) | 74.20[29.07] | 68.53[22.01] |

*Table 5.19 Mean [SD]. Between group differences reported by *p<0.05 or **p<0.01*

58% of patients were still using the HFAO device after three months. Of the patients that were using the HFAO device eight were using the device two to three times per day, four were using daily and 11 were using it a few times per week. From all the returned questionnaires 49% said they found the device useful, 36% did not find it useful and 16% did not answer. 15 participants that were currently using the device were originally randomised the HFAO and the remaining 11 were randomised to the sham.

*Table 5.20 Randomisation group and device use at three months*

| | HFAO (n=27) | Sham (n=18) |
|---|---|---|
| Currently using device n (%) | 15 (56) | 11 (61%) |
| Stopped using device n (%) | 12 (44) | 7 (39%) |

*Table 5.20 number (%). HFAO High Frequency Airway Oscillations.*

Data were compared from post intervention to three months follow up to assess the impact of device use. There were statistically significant changes in CRQ emotion domain and total scores and in the chest and cough domains of the CAT in those using the device however these scores had worsened. There is a statistically significant worsening on the CAT chest domain for those who were no longer using the device. Overall, the questionnaires appeared to worsen over the three months regardless of device usage (see table 5.21). The CRQ total score and CAT total score appeared to have a greater worsening in those not using the device, however this was not statistically significant. Those not using the HFAO

device had a worsening of the CAT total score that exceeds the minimal clinical important difference.

*Table 5.21 Changes from post intervention to three-month follow up*

| | Using HFAO (n=26) | | Not using HFAO (n=19) | | |
|---|---|---|---|---|---|
| | 8 weeks | 3 months | 8 weeks | 3 months | p value |
| CRQ-Dyspnoea | 3.49[1.26] | 3.19[1.17] | 3.42[1.72] | 3.27[1.81] | ns |
| CRQ-Emotion | 4.80[1.34] | 4.48[1.37] * | 4.66[1.14] | 4.39[1.51] | ns |
| CRQ-Fatigue | 3.73[1.02] | 3.56[1.33] | 3.91[0.95] | 3.77[1.59] | ns |
| CRQ-Mastery | 4.88[1.67] | 4.82[1.60] | 5.05[1.38] | 4.56[1.75] | ns |
| CRQ-Total | 16.89[4.47] | 16.05[4.90]* | 17.04[4.72] | 15.98[6.06] | ns |
| CAT Total | 18.77[6.78] | 19.41[8.22] | 16.95[7.27] | 19.32[8.79] | ns |

*Table 5.21 Mean [SD]. CAT COPD Assessment Test, CRQ Chronic Respiratory Questionnaire*

**p<0.05 within group, ns not significant*

Retrospective comparisons were made between participants that continued using the device and those that terminated its use to assess the effect they had over the intervention phase. This was irrespective of the device that they received during the intervention phase. Those who continued to use the device had significant improvements in the CRQ dyspnoea, emotion and mastery domain, CRQ total, CAT total, MDP total, LCQ total, and $PE_{max}$ over eight weeks. The differences seen in the CAT total exceed the minimal clinical important difference. Those that were no longer using the device had statistically significant improvements in the CRQ fatigue and mastery domain and $PE_{max}$ over the intervention phase (see table 5.22). There were significant between group differences for the CRQ emotion domain and the MDP total score. Those that continued using the device after the intervention phase, up until the three months follow up appeared to have a response to the original intervention phase (regardless of which device they were receiving). Therefore, it appears that the device will be used if there is a perceived benefit.

*Table 5.22 Original response to the intervention phase*

| | Using HFAO (n=26) | | Not using HFAO (n=19) | | Between group |
|---|---|---|---|---|---|
| | Baseline | Eight weeks | Baseline | Eight weeks | p |
| CRQ-D | 2.87[1.03] | 3.62[1.22] ** | 3.15[1.21] | 3.60[1.70] | ns |
| CRQ-E | 4.59[1.27] | 4.94[1.30] ** | 4.88[1.23] | 4.83[1.18] | ns |
| CRQ-F | 3.72[1.02] | 3.88[1.06] | 4.08[0.95] | 4.12[1.02] ** | ns |
| CRQ-M | 4.67[1.50] | 5.03[1.61] ** | 4.88[1.57] | 5.26[1.37] ** | ns |
| CRQ-Total | 15.85[4.27] | 17.47[4.49] ** | 17.02[4.15] | 17.81[4.73] | ns |
| HADS-A | 6.62[4.17] | 5.81[4.25] | 6.32[4.00] | 6.11[3.90] | ns |
| HADS-D | 6.35[3.94] | 5.38[3.40] | 4.79[3.51] | 5.11[4.03] | ns |
| LCQ-Total | 15.34[3.92] | 16.82[3.46] ** | 16.58[3.57] | 17.52[3.21] | ns |
| LCADL-Total | 27.04[10.17] | 26.69[11.19] | 25.74[11.60] | 24.74[8.64] | ns |
| CAT-Total | 21.12[6.58] | 18.77[6.76] ** | 17.53[6.36] | 16.95[7.27] | ns |
| MDP- Total | 39.27[28.30] | 26.42[26.04]** | 30.32[25.03] | 34.84[29.73] | ns |
| $PI_{max}$ ($cmH_2O$) | 75.58[28.84] | 78.04[25.09] | 68.53[22.01] | 70.74[22.48] | ns |
| $PE_{max}$ ($cmH_2O$) | 121.83[42.82] | 133.58[44.97]** | 118.74[36.25] | 131.37[39.84]** | ns |
| ISWT (m) | 323.04[134.75] | 321.30[122.45] | 331.67[145.69] | 326.67[160.33] | ns |
| ESWT (secs) | 315.00[219.03] | 363.48[258.77] | 218.82[93.71] | 201.76[98.43] | ns |

*Table 5.22 Mean [SD]. CRQ Chronic Respiratory Questionnaire D Dyspnoea, E Emotion, F Fatigue, M Mastery, HADS Hospital Anxiety and Depression Scale, A Anxiety, D Depression, LCQ Leicester Cough Questionnaire, LCADL London Chest Activity of Daily Living Questionnaire, CAT COPD Assessment Test, MDP Multidimensional Dyspnoea Profile, MIP Maximal Inspiratory Pressure, MEP Maximal Expiratory Pressure, ISWT Incremental Shuttle Walking Test, ESWT Endurance Shuttle Walking Test. *p<0.05, **P<0.01 within group, ns not significant*

## 5.7 Discussion

This study recruited 104 participants to a double blinded, sham, randomised controlled trial. There was a low attrition rate of 9.2%. There was a self-reported compliance rate of 81% which is deemed high however this was measured subjectively and is subject to bias. There were baseline differences in $FEV_1$ percent predicted, maximal inspiratory muscle pressures and maximal expiratory muscle pressures. Differences in $FEV_1$ and $PI_{max}$ were accounted for in the analysis, the $PE_{max}$ was not accounted for as this highly correlates with $PI_{max}$ and therefore would have been adjusted for. The primary outcome statistically significantly improved in both groups over the intervention phase however this was not significant between groups. It was unexpected to see such a large improvement in the sham group however this demonstrates the impact of participants perception of dyspnoea and the interpretation of breathlessness and confirms that the sham was convincing for participants. There is potential of the Hawthorne effect for trial participants, whereby participants improve due to the nature of being "observed". This is particularly the case in self-reported outcome measures which relies on patient perception. The CRQ was used as the primary outcome as it demonstrated changes in the feasibility study. This is a functional measure of breathlessness and can be difficult to change without functional training, however this study did demonstrate changes in functional dyspnoea. The CRQ dyspnoea domain consistently changed throughout subgroup analysis and in both groups. It is a reliable and validated outcome measure, however a more robust dyspnoea measure exploring different sensations of dyspnoea may be preferable for future studies. During the development of this study design the MDP was not widely available, and does not have an MCID for power calculations, but shows promise as an outcome measure for future dyspnoea interventions.

Overall this study demonstrated statistically significant improvements in $PI_{max}$ in patients using a HFAO device when compared to a sham which demonstrates the devices efficaciousness, however, the improvement is much smaller than the change reported in

the literature (13cm$H_2O$)[191]. This demonstrates that participants received an inspiratory muscle training intervention when receiving the HFAO device however this did not appear to translate into clinical benefits, though the dose received is variable and not specific to a patient's percent of maximum. Although some domains of the COPD assessment test, such as chest tightness and cough demonstrated significant improvements between groups favouring the intervention, it is unconventional to report these domains separately and therefore should be interpreted with caution. Exercise capacity did not improve over the eight weeks. The intervention offered inspiratory muscle training, which may improves patients breathing, however as there were no other training elements for the peripheral limb muscles and therefore it could be that participants were unable to utilise their inspiratory muscle strength improvements as they may become limited by lower limb weakness. This is demonstrated by a greater proportion of patients reporting peripheral limb fatigue as a reason for exercise termination at follow up, however this was a small sample. It is possible that patients with a reduced shortness of breath may either increase their exercise capacity or maintain exercise capacity but feel less breathless while doing so however this was not supported by physical activity analysis.

The multidimensional dyspnoea profile offers a unique way of assessing dyspnoea. Interestingly, there appeared to be a trend in improvement favouring the HFAO group, however, the standard deviations are large, and this might suggest this study is underpowered to detect a change in this outcome. The improvements in the HFAO group were larger than those seen in the sham in terms of the intensity of different sensations of dyspnoea. The baseline intensities of these sensations were higher in the HFAO group and larger improvements were seen in all domains. The mental effort/ concentration sensation had the greatest improvement in the HFAO group. There were also improvements in the muscle effort sensation, which is the expected and intended effect of respiratory muscle training. Additionally, air hunger occurs when respiratory muscles are working near their capacity to meet ventilatory demands and therefore respiratory muscle training could improve this sensation. It is plausible that this improvement would also lead to a reduction in concentration of breathing if participants are perceiving a reduced effort of breathing.

The sham group had the greatest improvements in the sensation of breathing a lot however this was a smaller improvement than seen in the HFAO group. Those using the sham device were instructed to perform the same procedure of deep maximal breathing for five minutes and this could offer some benefits in breathing frequency by increasing depth of breathing and slowing down the rate of breathing. The results of the MDP are opposing the CRQ dyspnoea domain, where participants in the sham group had a larger effect, however, both outcomes assess different aspects of dyspnoea. The CRQ dyspnoea domain explores participants dyspnoea in response to a functional activity, whereas the MDP explored different dyspnoea sensations and the emotional impact they have. As this intervention did not impact functional ability it is not surprising that there were no between group differences noted. The exploration of emotional response to dyspnoea has added value over the assessment of general anxiety and depression (as measured by the HADS). Those using the HFAO device perceived a higher emotional response to dyspnoea at baseline and had a greater improvement following the intervention. The largest improvement was seen in the depression domain in the HFAO despite not seeing these improvements in the HADS. The greatest improvements in the sham group were in the anxiety domain, however this was smaller than seen in the HFAO group. Deep and slowed breathing is a common technique in the presence of anxious episodes and therefore the use of the sham would utilise this technique. Interestingly the addition of respiratory muscle training increased this improvement, possibly due to the overall reduction in dyspnoea sensations. The MDP affective domain had improvements in emotional response, which was not seen in the HADS, this suggests that general anxiety and depression is different to dyspnoea related anxieties and depression. Therefore, it is possible that the use of general tools for anxiety and depression are underestimating the effect of dyspnoea interventions.

The predefined subgroup analysis allows for exploration of which patient group may have the most benefit, however this reduces the sample size and therefore effects the power of the study would no longer be fully powered. The improvements in the primary outcome were greater in those who reported compliance of more than or equal to 75% in the HFAO group. The primary outcome still achieved the MCID and significance in both groups but not

between groups. The CAT cough and chest domains remained significant between groups, as did the $PI_{max}$. In those that had predefined inspiratory muscle weakness there was a significant between group difference on CAT chest, energy and MDP affective domain in favour of the HFAO intervention. Whilst the HFAO group had significant improvements in $PI_{max}$ over time, this was not significant between groups.

It is reasonable to expect those with weakness to have a greater response to the intervention, however that has not been demonstrated with this study. Those with inspiratory muscle weakness had a larger improvement in the $PI_{max}$ following the HFAO intervention however this improvement was smaller for the $PE_{max}$ when compared to those that did not demonstrate baseline inspiratory muscle weakness. Additionally, those without inspiratory muscle weakness at baseline had greater improvements in dyspnoea (measured by the CRQ and MDP). The improvements in the incremental and endurance shuttle walking test was also larger in those without inspiratory muscle weakness when compared to those with inspiratory muscle weakness. However, these differences remained non-significant when compared to the sham, though this analysis is underpowered. This suggests that the level of baseline inspiratory muscle strength is not a factor in determining response to respiratory muscle training which was comparable to the subgroups in the meta-analysis[191]. It is possible that expiratory muscle weakness may have a larger role to play in the assessment of respiratory muscle strength. Whilst there is no definitive cut off for expiratory muscle weakness, further research should explore the impact of expiratory muscle weakness and response to intervention. Future studies could explore a cut off based on a percent of their predicted expiratory muscle strength as demonstrated in the Evans calculation[161].

It is also reasonable to expect greater improvements in participants with sputum retention due to the oscillatory component of the device, however this notion is not supported by these results. Small airway mucus obstruction is a characteristic in COPD even in the absence of excessive mucus. So, it is possible that all patients with COPD would benefit from

airway clearance strategies and could explain why there were no differences when stratified by sputum status[2]. Exploring those with infrequent and frequent exacerbations did not show a clear signal to favour one group over the other. Those that had frequent exacerbations predominantly worsened over the eight weeks which suggests a faster rate of decline compared to those that do not have frequent exacerbations. Those that received the device had better outcomes, and whilst improvements are small, this is amplified by the fact that the sham group worsened. As a result, the changes in ISWT are significant between groups and may suggest an interesting group to target for future trials. Whilst subgroup analysis is underpowered it is useful in determining potential participant groups that may benefit greater from the intervention and is key when developing further research.

Physical activity was explored in this research however this was non-significant. It is possible that whilst this intervention did not increase exercise capacity that patients may do more activity at lighter intensities. The results of this study demonstrated that those with the sham device had a marginal improvement in physical activity and a reduction in sedentary time, whereas the HFAO group had a reduction in step counts and an increase in sedentary time. This highlights the importance of a passive intervention; it is possible that participants used the device in place of normal physical activity and passive interventions often promote sedentary time. There were significant differences in light activity between group and it is possible that this is a result of a type I error, as this is unexpected and not comparable to other presented data. The remaining activity changes in both groups were small and not significant but it may suggest that future work should combine training with a device with other interventions such as exercise or education on physical activity.

The three months follow up demonstrates the continued usage of the HFAO device. It appears that, of those that returned the survey 57% were currently using the device. This is likely to be an over-estimation as it is possible that those that did not return the survey were less likely to be using the device. Interestingly, those that perceived to have a response in the initial intervention phase- regardless of the device they received, were

continuing to use the device. This is based on subjective outcome measures and therefore suggests the need for positive patient perceptions of a device for it to be effective, particularly for subjective outcome measures.

### 5.7.1 Strengths and limitations

This study has some strengths and limitations that should be considered when interpreting the results. Firstly, this is a double blinded, sham controlled, randomised trial which improves its rigour and decreases the risk of bias. There is allocation concealment and the study is fully powered to detect a change in the primary outcome measure. There was low attrition rate and high compliance which strengthens the results of this research. This study includes all patients with COPD who have breathlessness of two or more on the MRC dyspnoea scale and is therefore generalisable. Nevertheless, due to the mechanism of the device and the inability to adjust the resistance, it is reasonable to assume that those with inspiratory muscle weakness will demonstrate the most benefit. Those with inspiratory muscle weakness are often preferably recruited within respiratory muscle training studies which may be considered a weakness of this study design; however, subgroup analysis has allowed exploration of these patients which did not demonstrate a greater response to treatment. The sham used in this study was convincing for patients and allowed for blinding. The resistance of breathing through the sham would be comparable to pursed lip breathing (5cm$H_2O$) and therefore did not deliver a respiratory muscle training intervention. This study is the first interventional study to assess dyspnoea in its multidimensional components using the MDP and supports its use in future trials. This study was supported by patient and public representatives and is generalisable to the COPD population.

### 5.7.2 Comparisons to other literature

The results of this study add to an already conflicted evidence base for inspiratory muscle training. Pooled analysis of studies demonstrated an improvement in inspiratory muscle

strength that was also seen in this research, though the improvements were smaller. The meta-analysis by Gosselink also demonstrated improvements in breathlessness as measured by the Chronic Respiratory Questionnaire Dyspnoea domain when compared to a control[191]. This study demonstrated comparable results in dyspnoea however this was not favourable over sham treatment which is not explored in the current meta-analysis. There were no notable improvements in exercise capacity which was supported by this research. Additional research has not demonstrated improvements in dyspnoea or exercise capacity when compared to a sham and therefore this research adds to this evidence base[181]. The use of the MDP in this study was novel and has not been used in previous trials. The improvements in health-related quality of life for airway clearance devices were larger than was seen in this work, however the majority of the pooled studies compare an airway clearance device to a control (chapter 2). Similarly, the improvements in the COPD Assessment Test are much greater in the meta-analysis of airway clearance devices but were predominantly compared to a control.

The results of this study do not demonstrate clinical significance over a sham device however there is a signal in improving different sensations of breathlessness. These results are comparable to other inspiratory muscle training studies and demonstrates an improvement in muscle strength that is not translated into clinical outcomes. This research was not able to identify a clinical responder group. Those that are considered frequent exacerbators appeared to have a greater response to this treatment, however this sample is too small to infer any clinical implications. These results highlight areas that may be interesting to research further such as frequent or current exacerbators and combining HFAO with an exercise intervention.

# 6 The use of Lung Clearance Index as an outcome measure

## 6.1 Lung Clearance Index Validity Study

### 6.1.1 Introduction

Physiotherapeutic techniques for sputum clearance are notoriously difficult to demonstrate effectiveness, and there is a lack of reliable outcome measures which is a barrier to the development of the evidence base for all areas of respiratory physiotherapy[192]. Previously research utilises a variety of outcome measures, including, but not exclusive to, sputum volume (wet or dry weight), respiratory function tests (commonly $FEV_1$ and FVC), blood gas analysis and auscultation. However, the use of these techniques has a number of limitations. Typically, these measures are inaccurate and insensitive to the management of sputum which limits the evidence base for what is perceived as a clinically effective technique. Sputum wet/dry weight is particularly labour intensive for both the participant and the researcher, and the results are difficult to interpret. Post interventional sputum weight has the desired outcome of increasing sputum as it implies better airway clearance. However, over a longer duration sputum weight is expected to decrease as it suggests a reduction in sputum production. $FEV_1$ as performed by spirometry, is insensitive to sputum clearance and has a large daily variance of 10%[193]. Auscultation has a low inter-rater reliability and is not quantifiable and therefore makes this an unreliable and insensitive outcome which indirectly reports sputum[192]. Patient reported outcome measures are often utilised in adjunct to or in place of objective outcome measures. There are many patients reported specific and non-specific outcome measures used to assess the impact of sputum clearance. Specific measures often explore ease of expectoration and quantity of sputum; however, this is a crude and subjective way to quantify a difficult concept. The variation in

preferred outcome measures results in difficulty with data synthesis and meta-analyses[120]. The assessment and treatment of sputum clearance is often a treatment priority for physiotherapists as patients with large volumes of sputum tend to have poorer outcomes including poorer lung function. The presence of sputum, as well as bronchial obstruction and emphysematous changes lead to abnormal gas distribution and results in lung inhomogeneity. The Lung Clearance Index (LCI) is a non-invasive measure of lung heterogeneity in the peripheral airways that holds promise as a physiological endpoint and may offer insight into the impact of secretion clearance.

The use of the LCI, via multiple breath washout, has been utilised among participants with Cystic Fibrosis, Asthma, Bronchiectasis and paediatric lung disease[83, 84, 87, 194, 195]. There is a preference to its use in paediatrics as the technique requires little coordination and is non-exertional. LCI is potentially useful in early diagnosis as it is likely to be abnormal long before spirometry detects any changes (further exploration of this research can be found in chapter 1). The reliability of the LCI has been demonstrated among adults and children with Cystic Fibrosis. The LCI is reproducible and more sensitive than $FEV_1$ in identifying early stage disease in paediatrics[91]. This is further raised in children infected with Pseudomonas Aeruginosa and is an early predictor of lung function decline[88, 90]. Horsley et al demonstrated the reproducibility and repeatability of the LCI in adults with Cystic Fibrosis[83]. Over 85% of their subjects were able to perform the washout manoeuvre. Critiques of the LCI surround the duration of the test, with each test lasting approximately 10 minutes (dependant on disease population and/or severity), with the test being performed in triplicate. As technology advances the equipment for the performance of the LCI is becoming less bulky and easier to use, and therefore its integration into clinical practice is becoming more likely. The use of MBW tests can give additional insight into the function of the conducting zone and the peripheral airways ($S_{cond}$, $S_{acin}$ respectively). This has seldom been reported in the literature but may offer value. Further explanation of this can be found in chapter 1. The evidence for the use of the LCI in patients with COPD is lacking. Gas mixing and ventilation heterogeneity is known to be abnormal in patients with COPD and therefore the LCI will provide insight into the severity of ventilation heterogeneity and its

responsiveness to treatment. As sputum retention is likely to affect gas mixing and ventilation heterogeneity, the LCI has potential as a surrogate outcome measure for sputum clearance in response to physiotherapeutic management. The use of the LCI within COPD is not fully understood. Previous research has demonstrated repeatability in a short-term assessment using a nitrogen washout system (>24hours apart) however this research did not explore within visit or longer term follow up or the repeatability of an $SF_6$ washout. There was no exploration of phase III slope analysis that could be useful in the assessment of patients with COPD[93]. This work will explore the potential added benefit of the LCI over and above the use of spirometry and its repeatability within visit and between visit. The MBW test is often criticised for its duration and therefore this study will explore the possibility of shortening the test by reducing the washout phase (to a $1/20^{th}$ washout).

The aims of this study are to understand whether the use of the LCI is reproducible in patients with COPD. The objectives are outlined as follows:

- To understand the correlation between spirometry and LCI in patients with COPD.
- To understand whether the LCI is reproducible in patients with COPD on a single visit.
- To understand whether the LCI is reproducible in patients with COPD between two separate visits.
- To explore the feasibility and repeatability of a shortened LCI to $1/20^{th}$ of the starting concentration comparatively to $1/40^{th}$.
- To predict the effect size estimates for $1/20^{th}$ and $1/40^{th}$ washout tests at 80% and 90% power.

### 6.1.2 Methods

This research is an extension the feasibility trial in chapter 4 and TIDe study in chapter 5. Ethical approval was obtained by the National Health Service Health Research Authority and the Local Research Ethics Committee. ISRCTN trial number: ISRCTN81979106. 86 participants were recruited to participate in the correlation cohort in order to perform spirometry and multiple breath washout. A subgroup of 20 participants were recruited from the feasibility study to assess the repeatability of the LCI within visit and over eight weeks. Participants were recruited from consensual research databases and respiratory clinics. Participants were included if they were symptomatic with a diagnosis of COPD, confirmed by spirometry testing as outlined by the GOLD standards ($FEV_1$/FVC ratio <0.70)[21]. Participants were at least 40 years old and not contraindicated to testing (such as pneumothorax, rib fractures etc.). Further details of inclusion criteria can be found in chapter three.

86 participants completed MBW and spirometry from both the feasibility and TIDe study combined, in order for correlation comparison. Twenty participants attended for repeatability testing of the LCI. All participants completed spirometry using a Vitalograph and in line with ERS/ATS quality standards[196]. Participants also performed the MBW test in order to calculate the LCI. The MBW was performed using a modified, open circuit, photoacoustic Innocor device and 0.2% Sulphur Hexafluoride ($SF_6$). Evidence of equipment calibration can be found in appendix 9. The tests were performed in upright sitting and in line with the ERS/ATS standards[163]. Participants were instructed to perform tidal volume breathing through the mouthpiece with a nose clip in situ. Tidal volumes were calculated based on 7-12mls per kg of the participant's actual body weight. This may differ if using their predicted body weight however the results of the test will not be affected if this is kept consistent for the participant. Once the $SF_6$ was suitably washed in, the gas was disconnected during exhalation and the washout phase began. The test was stopped when the concentration had reached $1/40^{th}$ of the starting concentration for three consecutive breaths. Each participant performed the MBW in triplicate and tests that varied more that

10% Functional Residual Capacity (FRC) were excluded. A minimum of two tests were required to be included in the analysis. Further description of the MBW test can be found in chapter three. The LCI is calculated using the below formula and the mean of the acceptable tests was used. Phase III slopes were analysed in a pooled slope analysis.

$$LCI = \frac{Cumulative\ exhaled\ volume}{FRC}$$

Participants involved in the repeatability cohort repeated the MBW after a 20-minute break to determine within visit repeatability. Participants returned eight weeks later to perform a final three tests allowing for between visit data analysis. Spirometry was also repeated after eight weeks. Study visits can be seen in figure 6.1.

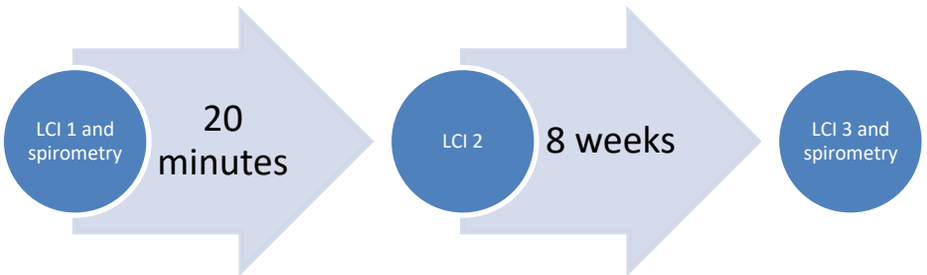



*Figure 6.1 Visit schedule for Lung Clearance Index repeatability study*

Washout tests were interpreted using a customised algorithm on MatLab (2019) and analysis was performed on SPSS v23. The LCI and FRC are presented as mean of the three tests performed for each time point. If one test was outside of the 10% variance, the mean

of the remaining two tests were used. The $S_{cond}$ and $S_{acin}$ were assessed using a pooled phase III slope analysis. The $LCI_{1/20th}$ was retrofitted using the same washout test. This was performed in MatLab using an earlier cut off. Repeatability for within visit and between visit data was determined via Cronbach's Alpha and presented as intraclass correlation coefficients. A correlation coefficient of less than 0.5, between 0.5 and 0.74, between 0.75 and 0.9 and values above 0.9 are considered poor, moderate, good, and excellent repeatability, respectively[197]. Bland Altman plots were performed in order to determine the upper and lower limits of agreement. This will provide insight into the normal variance of the test and highlight any systematic bias. Regression analysis will further develop the identification of systematic bias of the test. The correlation between spirometry and LCI will be explored. The repeatability of a shortened test will be explored with a post hoc analysis. All tests will be re-analysed with a $1/20^{th}$ concentration and assessed for the within and between visit repeatability. Comparisons will be made between the $1/20^{th}$ and $1/40^{th}$ washout tests.

### 6.1.3 Results

84 participants were recruited to explore correlations between spirometry and multiple breath washout measurements (male 62%, mean [SD] age 70[7.3], $FEV_1$ percent predicted 51[17]). 80 tests were suitable for analysis due to an error in the analysis programme (n=2) or not having 2 tests within 10% FRC (n=2). 20 participants were included in the repeatability cohort (mean [SD] age 69 years [7], $FEV_1$ percent predicted 50[15]) (figure 6.2, table 6.1). One participant was excluded as they did not have two reproducible tests (within 10% variance FRC).

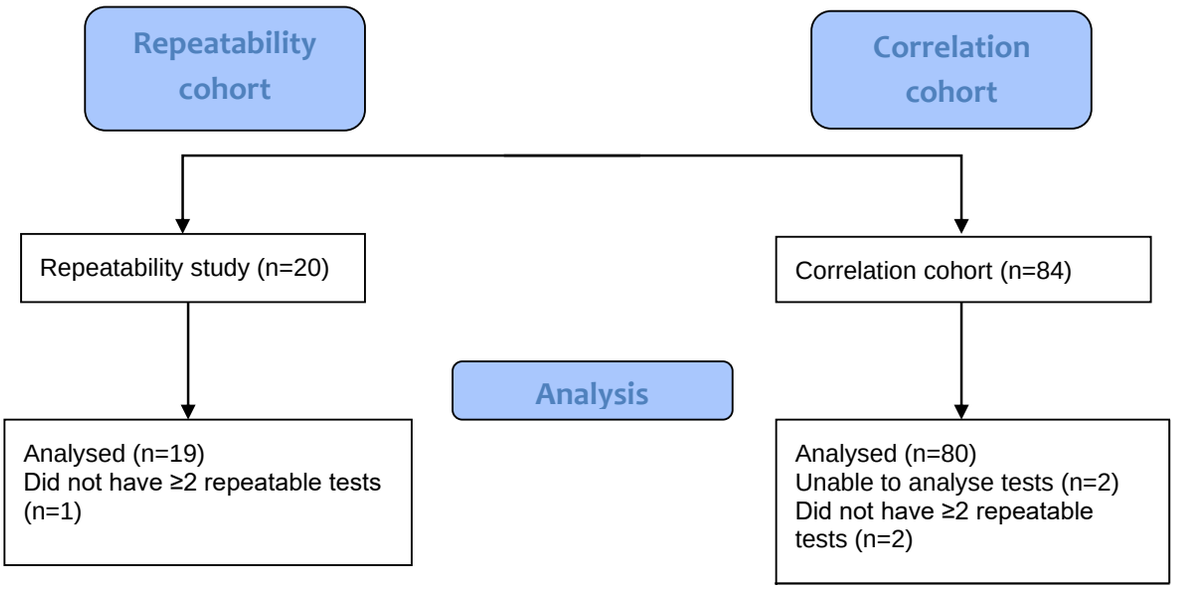



*Figure 6.2 Consort diagram for repeatability and correlation cohorts.*

*Table 6.1 Baseline characteristics of Lung Clearance Index testing cohort*

| | Repeatability cohort (n=20) | Spirometry correlation cohort (n=84) |
|---|---|---|
| Gender (male: female) | 15:5 | 62:22 |
| Age (years) | 69[7.0] | 70[7.3] |
| $FEV_1$ % predicted | 50[15] | 51[17] |
| $FEV_1$ (l) | 1.35[0.43] | 1.36[0.53] |
| FVC (l) | 2.57[0.55] | 2.70[0.86] |
| $FEV_1$/FVC ratio | 0.52[0.13] | 0.49[0.13] |
| CAT score | 21.14[7.15] | 16.30[6.89] |
| BMI ($kg/m^2$) | 29.0[6.6] | 29.0[63.6] |

*Table 6.1 Baseline characteristics presented as mean [SD] unless otherwise stated. $FEV_1$ Forced Expiratory Volume in 1 second, FVC Full Vital Capacity, CAT COPD Assessment Test, BMI Body Mass Index.*

There were statistically significant, weak correlations between $FEV_1$ and $LCI_{1/40th}$ (-0.31, $p<0.01$) (figure 6.3), BMI and $LCI_{1/40th}$ (-0.36, $p<0.01$) and $LCI_{1/40th}$ and GOLD staging (-0.31, $p<0.01$). There were statistically significant moderate correlations between $S_{acin}$ and $FEF_{25-75}$ (-0.45, $p<0.01$) (figure 6.4) There were no notable correlations between $S_{cond}$ and measurements of spirometry. One-way ANOVA demonstrated statistically significant differences of the $LCI_{1/40th}$ when stratified by their level of airflow obstruction. Significance was noted between GOLD stage II and GOLD stage IV (table 6.2). There were no significant correlations between exacerbation frequency and measurements of the MBW. There was a high correlation (0.86, $p<0.01$) between washouts performed at $1/20^{th}$ and $1/40^{th}$ of the starting concentration (figure 6.5).

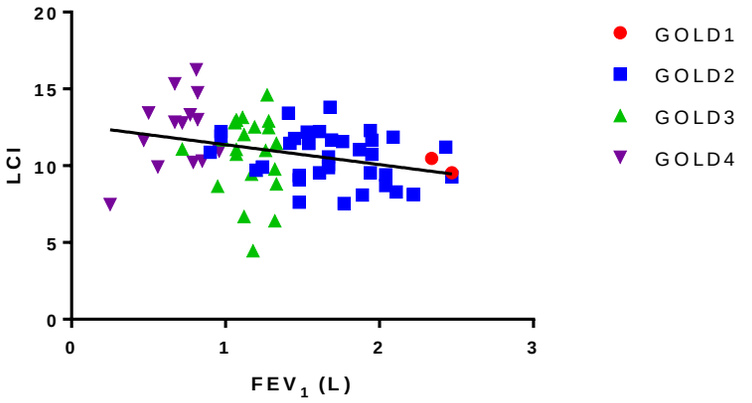



*Figure 6.3 Correlations of Lung Clearance Index and $FEV_1$*

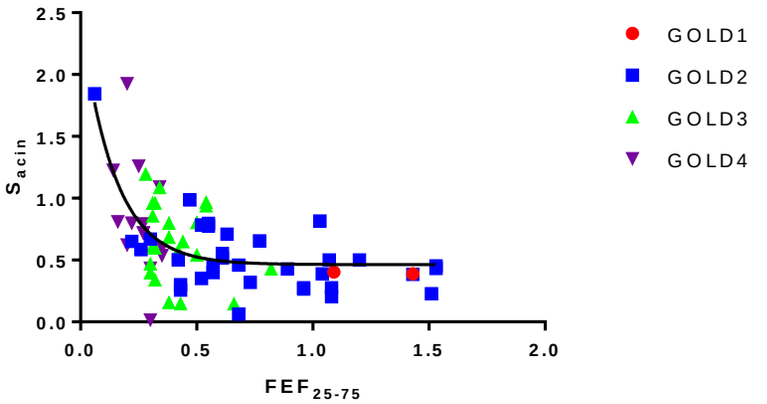



*Figure 6.4 Correlations of $S_{acin}$ and $FEF_{25-75}$*

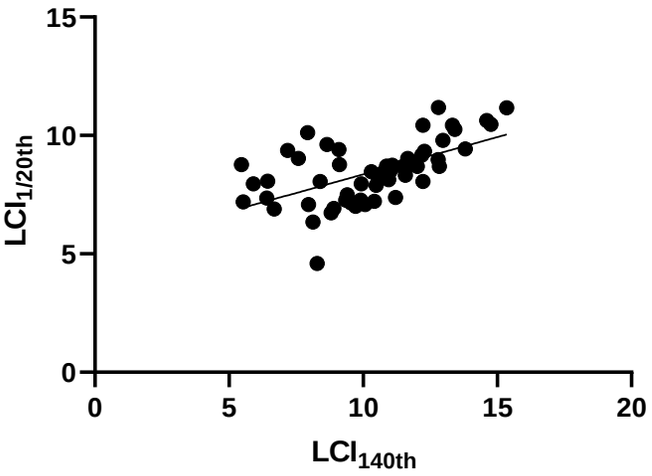



*Figure 6.5 Correlations of $LCI_{1/20th}$ and $LCI_{1/40th}$*

*Table 6.2 One-way ANOVA of Lung Clearance Index and COPD severity*

| | GOLD 1 (n=2) | GOLD 2 (n=38) | GOLD 3 (n=25) | GOLD 4 (n=14) | p |
|---|---|---|---|---|---|
| $LCI_{1/40th}$ | 10.01[0.67] | 10.46[1.62] | 10.88[2.42] | 12.31[2.38] | 0.04 |

*Table 6.2 Mean [SD] of LCI and GOLD staging. LCI Lung Clearance Index, GOLD Global Institute for Lung Disease.*

*Repeatability results*

19 of the 20 participants completed the protocol and were eligible for within visit repeatability analysis. One participant was excluded from the analysis as the MBW tests were outside of the accepted 10% variance in FRC. The within visit repeatability was deemed high with Intraclass Correlation Coefficients >0.9 for all measures. Bland-Altman plots detected no systematic bias (figure 6.6 and 6.7). Over eight weeks the repeatability of the multiple breath washout remained high with correlations above 0.8 for the $LCI_{1/40th}$, $LCI_{1/20th}$, $S_{acin}$ and FRC. $S_{cond}$ had a lower ICC of 0.52 which demonstrates moderate correlations (table 6.3).

*Table 6.3: Within and between visit intraclass correlation coefficients*

| N=19 | Mean [SD] (within visit) | Within visit ICC | Mean [SD] (between visit) | Between visit ICC |
|---|---|---|---|---|
| $FEV_1$ (l) | 1.36 [0.47] | | 1.35 [0.43] | 0.92 |
| $FEV_1$ % | 51.45[14.86] | | 52.94[16.71] | 0.92 |
| $FEF_{25-75}$ (l/sec) | 0.58[0.36] | | 0.62[0.26] | 0.64 |
| FVC (l) | 2.58 [0.63] | | 2.57 [0.55] | 0.74 |
| $LCI_{1/40th}$ | 11.24 [2.25] | 0.92 | 11.42 [2.03] | 0.88 |
| $FRC_{1/40th}$ | 3.51 [1.11] | 0.96 | 3.50 [0.89] | 0.92 |
| $S_{cond}$ | 0.06 [0.11] | 0.94 | 0.04 [0.03] | 0.52 |
| $S_{acin}$ | 0.784 [0.46] | 0.95 | 0.698 [0.40] | 0.80 |
| $LCI_{1/20th}$ | 8.587[1.43] | 0.96 | 8.528[1.18] | 0.80 |
| $FRC_{1/20th}$ | 3.40[1.05] | 0.90 | 3.38[1.01] | 0.91 |

*Table 6.3 Mean [SD] of the multiple breath washout and spirometry tests and the correlations. $FEV_1$ Forced Expiratory Volume in 1 second, $FEF_{25-75}$ Forced Expiratory Flow 25-75%, FVC Forced Vital Capacity, LCI Lung Clearance Index, FRC Functional Residual Capacity, $S_{cond}$ Conducting zone slope, $S_{acin}$ acinar zone slope.*

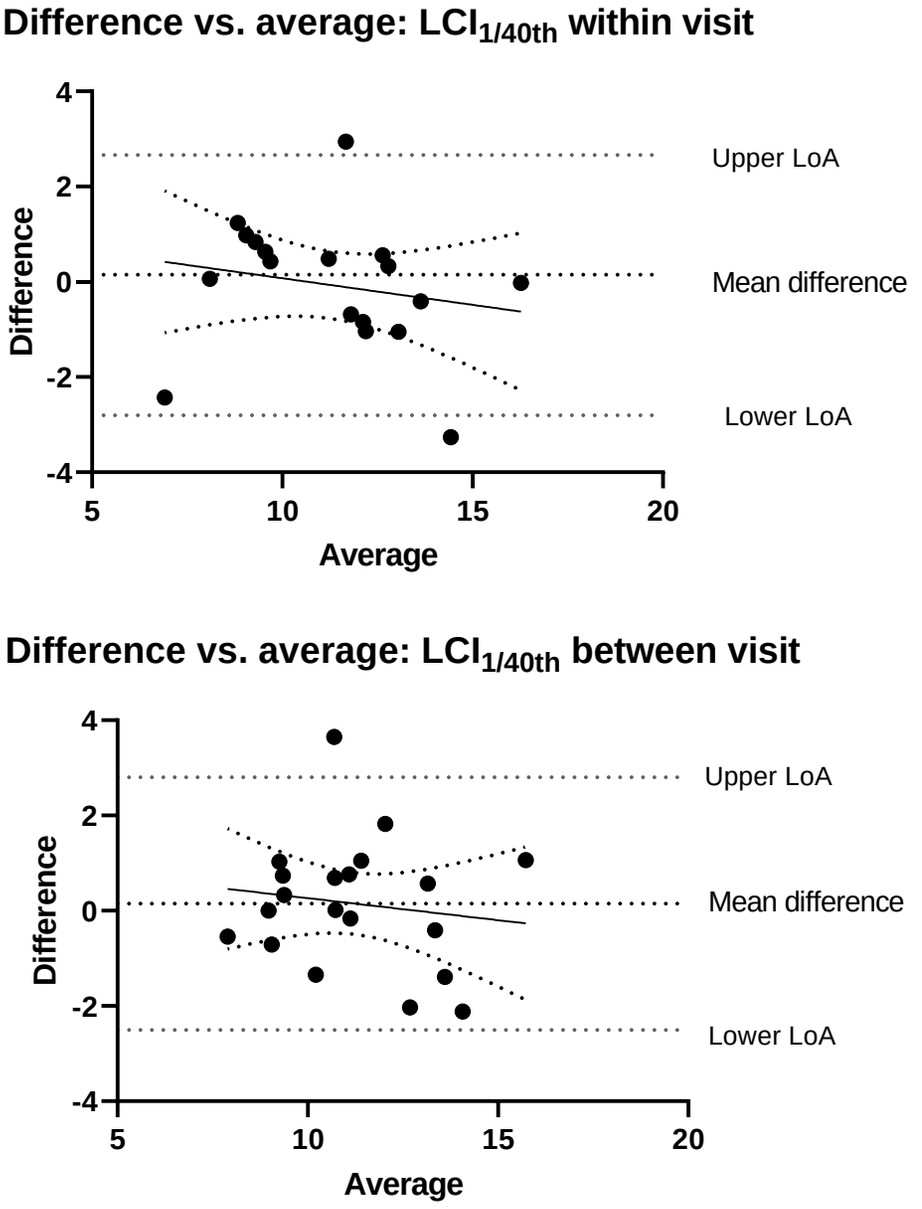



*Figure 6.6 Bland-Altman plots for $LCI_{1/40th}$ within visit (top) and between visit (bottom)*

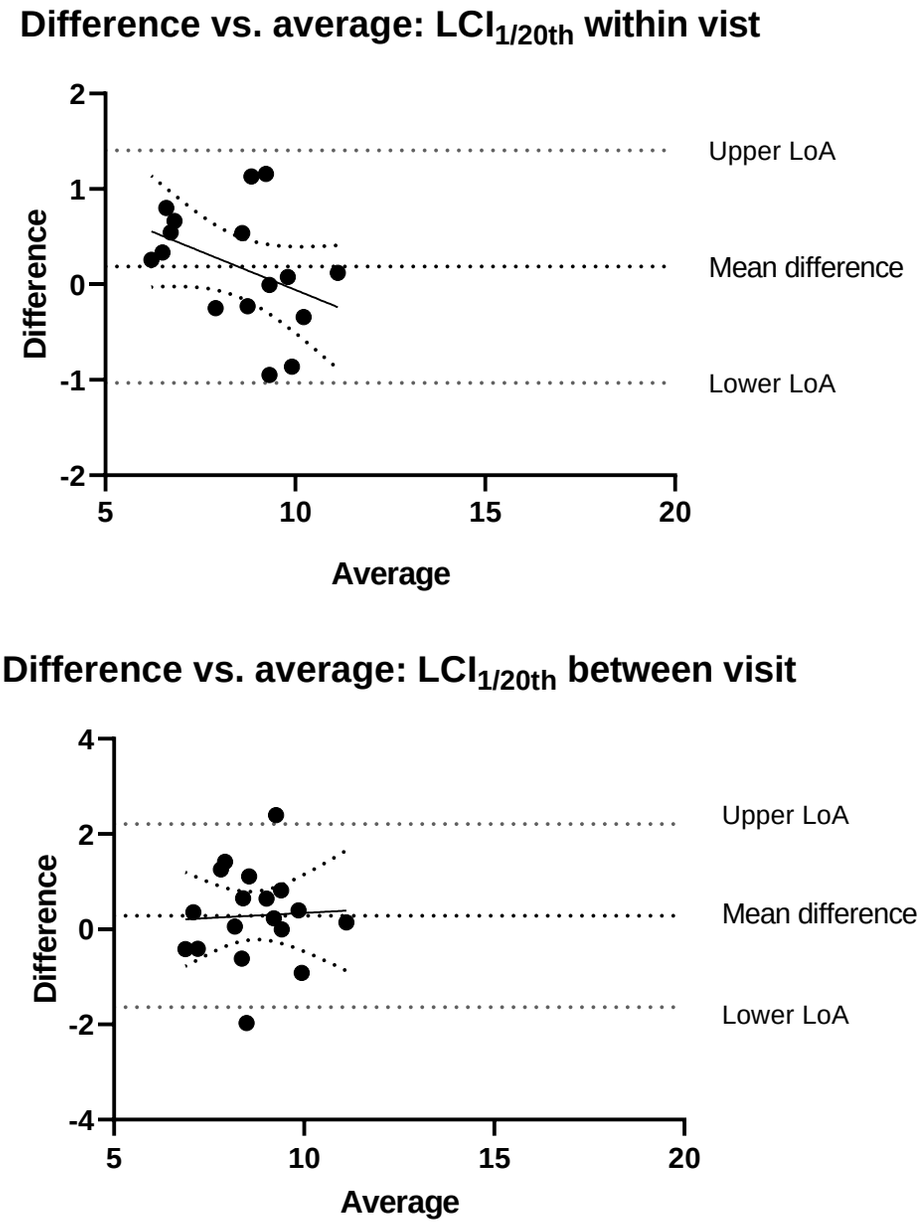



*Figure 6.7 Bland-Altman plots for $LCI_{1/20th}$ within visit (top) and between visit (bottom)*

The Bland-Altman plots determine the bias and limits of agreement between the measures. For the $LCI_{1/40th}$ within visit repeatability the level of bias [SD] is -0.07[1.40]. The limits of agreement are from -2.803 and 2.664 (figure 6.6). There are two participants that lie outside of these set limits of agreement. The participant that sits outside of the upper limit of agreement demonstrated a worsening of the $LCI_{1/40th}$ by 3.26. There was a reduction in their FRC by 0.435 which may account for this variance, given that the LCI is derived from the cumulative exhaled volume divided by the FRC. The patient that sits outside of the lower limit of agreement however has a 2.94 improvement in LCI and a reduction in FRC by 0.518 which does not explain the variance. It is plausible that the conduction of the first MBW could open previously collapsed airways, reducing gas trapping and leading to an improvement in ventilation for the second test. This participant also had a reduction in $S_{acin}$ and therefore supports the notion of better peripheral ventilation, additionally there was very little difference between baseline and over eight weeks ($LCI_{1/40th}$ +0.41) and therefore this discrepancy could be attributed to the MBW test itself. For the between visit repeatability the bias [SD] is 0.15[1.35]. The limits of agreement range from -2.503 to 2.805 which is comparable to the within visit limits of agreement (figure 6.7). There is one outlier in this dataset, this patient had an improvement of 3.65 in the $LCI_{1/40th}$ and an increase in FRC by 0.183 which may explain the variance. Regression analysis predicts a best fit slope [95% CI] of -0.112 [-0.412, 0.188] within visit and -0.093 [-0.419, 0.234] between visit (table 6.4). There is a greater variance between visit when compared to within visit however are both are considered to be repeatable. Exploration of outliers can be seen in table 6.5.

The $LCI_{1/20th}$ within visit repeatability had a bias of 0.29[0.98] with the limits of agreement ranging from -1.640 to 2.212. The limits of agreement are comparable to what was seen on the $LCI_{1/40th}$ analysis. Between visit there is a bias of 0.19[0.62] and limits of agreement of -1.031, 1.4106 The limits of agreement are lower than what was seen in the $LCI_{1/40th}$ analysis. Linear regression predicts a best fit slope [95% CI] of -0.162[-0.377, 0.053] within visit and 0.043[-0.432, 0.518] between visit.

Table 6.4 Bland-Altman with linear regression.

| | Bias [SD] | Slope [95% CI] | Model p-value | Model R2 |
|---|---|---|---|---|
| $LCI_{1/40th}$ within visit | -0.07[1.40] | -0.12[-0.41, 0.19] | 0.44 | 0.04 |
| $LCI_{1/20th}$ within visit | 0.29[0.98] | -0.16[0.38, 0.05] | 0.13 | 0.16 |
| $LCI_{1/40th}$ between visit | 0.15[1.35] | -0.09[-0.42, 0.23] | 0.56 | 0.02 |
| $LCI_{1/20th}$ between visit | 0.19[0.62] | 0.04[-0.43, 0.52] | 0.85 | 0.00 |

Table 6.4 Bias [SD], slope angle [95% CI] for Bland Altman plot and linear regression. LCI Lung Clearance Index

*Table 6.5 Outlier analysis on $LCI_{1/40th}$*

| | $LCI_{1/40th}$ change | FRC change | $S_{acin}$ change |
|---|---|---|---|
| Outlier 1 (within visit) | +0.33 | -0.44 | 0.29 |
| Outlier 2 (within visit) | -2.94 | -0.52 | 1.00 |
| Outlier 3 (between visit) | -3.65 | +0.18 | 0.30 |

*Table 6.5 LCI Lung Clearance Index, FRC Functional Residual Capacity, $S_{acin}$ acinar slopes*

The Bland Altmann analysis of $LCI_{1/40th}$ and $LCI_{1/20th}$ has shown a bias of 3.017[0.698]. The lower and upper limits of agreement are 1.648 and 4.385, respectively. The larger the LCI the greater the difference between the $LCI_{1/40th}$ and $LCI_{1/20th}$ washouts, however the linear regression suggests that this bias is proportionate. The linear regression slope [CI] is 0.252 [0.136, 0.368] which was applied to the $LCI_{1/20th}$ to provide an estimated $LCI_{1/40th}$ washout. This was then compared to the original $LCI_{1/40th}$ and assessed for bias (figure 6.8). This demonstrates a bias of 0.884[0.678] with a lower and upper limit of agreement of -0.444, 2.211. The line of best fit slope is 0.018.

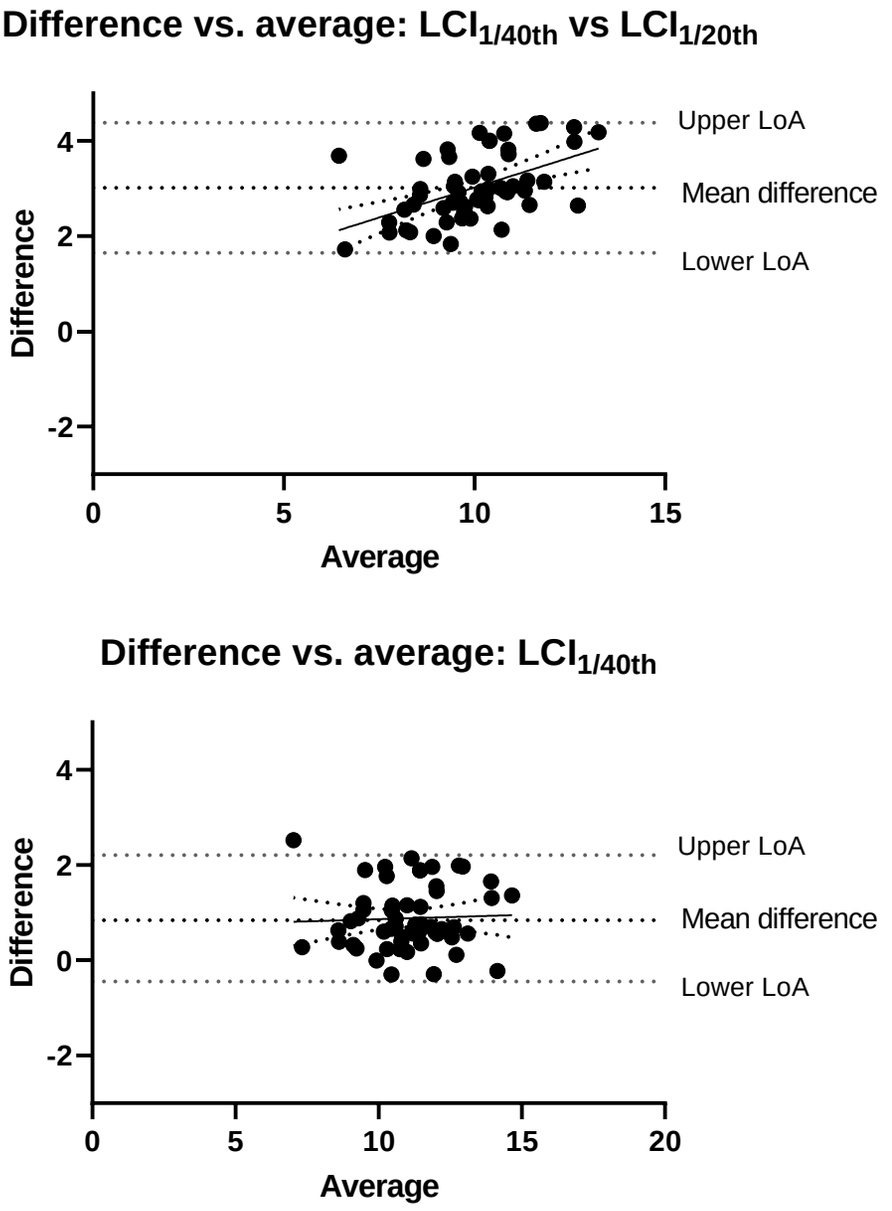



*Figure 6.8 Bland-Altman plot $LCI_{1/40th}$ and $LCI_{1/20th}$ (top) with regression (bottom)*

The mean [SD] test time for a $LCI_{1/40th}$ washout test was 204[93] seconds and 613[278] seconds if performed in triplicate. A shortened washout to $LCI_{1/20th}$ starting concentration has a mean [SD] test time of 140[61] seconds or 420[183] in triplicate. Using a $LCI_{1/20th}$ washout results in a shortened test of 31.5% compared to $LCI_{1/40th}$ washout test (figure 6.9).

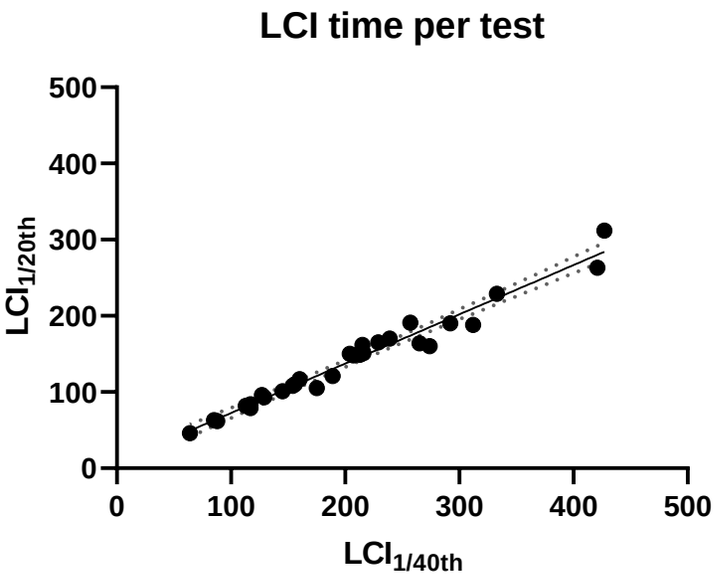



*Figure 6.9 $LCI_{1/40th}$ and $LCI_{1/20th}$ washout duration*

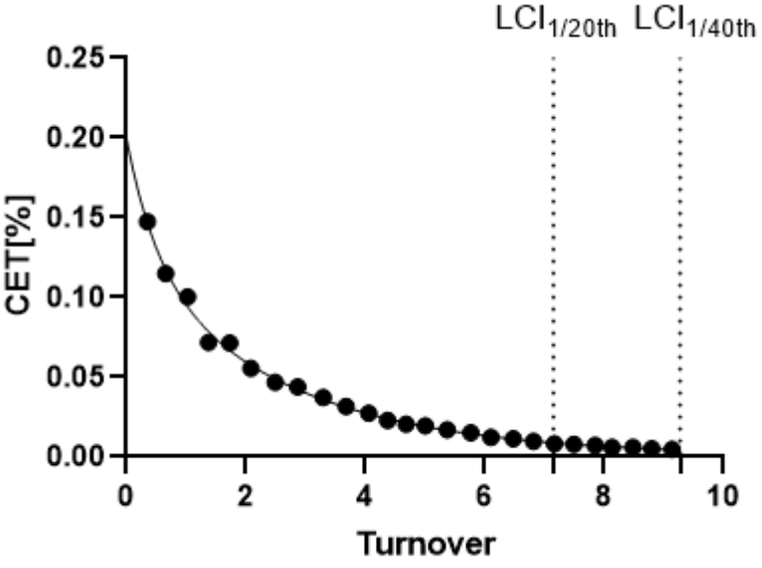



*Figure 6.10 Example $LCI_{1/20th}$ and $LCI_{1/40th}$ washout time. CET End Tidal Concentration.*

There is no known minimal clinically important difference (MCID) available for the LCI however there was a response of -2.16 in the Cystic Fibrosis Ivacaftor interventional study[198]. Based on this treatment effect and the reported standard deviation in the repeatability cohort [2.25] the required sample size would be 18 per group. For a longer follow up and the standard deviation in the COPD cohort of 2.03 the required sample size would be 14 participants per group. It is likely that this effect size is larger than would be seen in a COPD cohort and as there is limited data on the LCI in patients with COPD, the effect sizes were estimated to determine sample sizes per group in table 6.6. Table 6.6 shows the sample size estimates at 80% and 90% power based on a 5% type II error using standard deviations seen in the repeatability cohort.

*Table 6.6 predicted effect sizes for $LCI_{1/40th}$*

| | Within visit | | Between visit | |
|---|---|---|---|---|
| Effect | 80% | 90% | 80% | 90% |
| 1.0 | 80 | 107 | 65 | 87 |
| 1.2 | 56 | 74 | 45 | 61 |
| 1.4 | 41 | 55 | 34 | 45 |
| 1.6 | 32 | 42 | 26 | 34 |
| 1.8 | 25 | 33 | 20 | 27 |
| 2.0 | 20 | 27 | 17 | 22 |
| 2.2 | 17 | 22 | 14 | 18 |
| 2.4 | 15 | 19 | 12 | 16 |

*Table 6.6 Predicted effect size based on 80% and 90% power, 0.05 type II error and SD demonstrated in repeatability study for within and between visit study designs.*

### 6.1.4 Discussion

Comparisons between spirometry and MBW measures demonstrated significant correlations however these measurements were weakly correlated. This supports the notion that the LCI and spirometry are measuring different elements of lung function and

therefore is an appropriate outcome measure that may add value over and above the results of spirometry. The $S_{acin}$ and $FEF_{25-75}$ have moderate correlations as these are both aiming to measure the peripheral airways, however the $FEF_{25-75}$ is not a pure measure of the peripheral airways and is often argued that this is not the intent of the measure. The $FEF_{25-75}$ is calculated using the FVC and therefore the additional information gleamed from this measure is not of clinical benefit. As it is derived from FRC it is not a true measure of small airways and this could explain why the correlation with $S_{acin}$ remains moderate. This study demonstrates the feasibility of conducting the MBW in patients with stable COPD. All participants were able to complete the tests without any concerns. 95% of patients had tests that were suitable for analysis (FRC within 10% variance). $LCI_{1/40th}$, $LCI_{1/20th}$, FRC, $S_{cond}$ and $S_{acin}$ were highly repeatable within visit with an ICC of over 0.9. Over an eight-week period; $LCI_{1/40th}$, $LCI_{1/20th}$, FRC and $S_{acin}$ remained highly repeatable (>0.80), however the $S_{cond}$ demonstrated only moderate correlation (0.52) and therefore demonstrated a higher variance than other measures. There is a large amount of noise in this measurement which may affect its variability. The variability seen in the $S_{cond}$ is larger than what has previously been demonstrated in other conditions[84]. This variation should be considered when interpreting results from clinical trials. These results are comparable to spirometry repeatability, however the $FEF_{25-75}$ demonstrated lower repeatability than the $S_{acin}$. As the $S_{acin}$ has demonstrated higher repeatability and is a more specific measure of peripheral airway function, this would be preferable in the assessment of small airway ventilation.

This study demonstrates the repeatability and validity of using measurements of the MBW as an outcome measure in clinical trials. The $S_{cond}$ may demonstrate larger variances than other measures of the MBW however this is still considered moderately correlated and therefore its use is appropriate. Due to the differences in spirometry and MBW measurements, it is possible that the MBW test may add additional value in the investigation of patients with COPD. It is feasible to shorten the LCI to a washout at $1/20^{th}$ of the starting concentration. This has demonstrated similar repeatability to a $1/40^{th}$ washout. The washout phase can be shortened by an average of 31.5%. MBW tests that utilise an inert tracer gas such as sulphur hexafluoride require a wash in phase. The use of an inert

tracer gas typically requires a 300 second wash in phase per test, however if the washout is shortened it is feasible to shorten the wash in concentration. Reducing this by approximately 31.5% would shorten the wash in phase to 206 seconds per test. The total test time for $LCI_{1/40th}$ would be 504 seconds per test or 1512 seconds in triplicate (25 minutes, 12 seconds), whereas the $LCI_{1/20th}$ test time would be 346 seconds or 1038 seconds in triplicate (17 minutes 8 seconds). It is possible that this time is an overestimation of wash in durations however is generalizable to the entire COPD population regardless of severity. The time saving is greater for those with severe disease. This duration is comparable to quality assured spirometry which takes around 20 minutes[199].

Spirometry is the gold standard for diagnosis in respiratory disease however the use of the LCI can offer an alternative to spirometry testing, particularly in early disease, or those who would have difficulties generating the effort required for an exertional spirometric test. The LCI may have added value in the assessment of small airways and may be particularly useful in clinical trials, where spirometry is insensitive to change. A shortened washout may be appealing for clinicians; however, it is important to consider a shortened test will reduce the assessment of the more peripheral airways and should be considered when the research question does not require an as in-depth analysis of the far peripheral airways. For the purpose of this research the washout will remain at $1/40^{th}$ in keeping with current guidelines. Further research is needed to explore the differences between response to treatments for a $1/40^{th}$ and $1/20^{th}$ washout test.

## 6.2 Exploratory analysis of TIDe study- Lung Clearance Index

### 6.2.1 Introduction

As the LCI measured via MBW has demonstrated feasibility and repeatability in patients with COPD it is appropriate for the use during clinical effectiveness trials. There have been few interventional trials investigating the use of LCI in response to therapies and is more

commonly used in early diagnosis and paediatrics. A study was conducted in Cystic Fibrosis investigating the response of the LCI to Ivacaftor drug (a Cystic Fibrosis Transmembrane Conductance Regulator drug) where they demonstrated a mean improvement of -2.2 [95% CI -3.0 to -1.3] at one month which was sustained at six months (-2.1[-2.7 to -1.5]) on the LCI[198]. Research has also explored response to airway clearance techniques in patients with bronchiectasis, however due to the nature of the disease patients were unable to reliably complete the washout due to excessive coughing. They noted a decline in LCI, which may be a result of removing sputum plugs which would paradoxically worsen the LCI. The COPD population generally produce less sputum than those with bronchiectasis and Cystic Fibrosis, and therefore are less affected by sputum plugging, however this is an important issue that should be considered with airway clearance therapies and LCI response. It is reported in that literature that up to 22% of patients with COPD experience issues with sputum retention however, this is typically poorly reported due to difficulties in quantifying sputum.

This study is an exploratory analysis of the TIDe study, methods are described in chapter 5. The use of oscillations in a HFAO device can assist in the clearance of sputum from the lungs. Sputum plugging and retention could lead to ventilation heterogeneity and therefore clearing secretions may impact the LCI in patients with COPD. Patients with sufficient sputum clearance would have improved ventilation and therefore the hypothesis is that the use of a HFAO device for eight weeks could improve ventilation heterogeneity as measured via the MBW. The aims of this study are:

- To understand the burden of sputum retention in patients with COPD as measured by the COPD Assessment Test.
- To explore the impact of airway clearance on ventilation in patients with stable COPD.
    - Demonstrate the impact of airway clearance via the HFAO on ventilation as measured by MBW tests, exploring the LCI, $S_{cond}$ and $S_{acin}$.

- To determine the impact of an exacerbation during the trial period on the MBW and its response to therapy.
    - Subgroup analysis comparing the response to treatment for patients with and without an exacerbation during the trial period.
- To explore the response to airway clearance when stratified by sputum producers and non-sputum producers
- To compare the response to airway clearance in relation to the MBW at 1/40$^{th}$ and 1/20$^{th}$ washouts.

### 6.2.2 Methods

The results of this chapter are derived from the randomised controlled trial (TIDe) described in detail in chapter five. The MBW was performed prior to the intervention period and after the eight weeks and performed at the same time of day where possible to do so. Each participant performed three tests at each time point and the test was performed in line with the ERS/ATS statement, further information can be found in chapter three. Participants performed the washout at tidal volumes (as calculated by 7-12mls per kg of their weight) pre and post intervention phase. The tests were analysed using a custom MATLAB algorithm and at least two tests had to fulfil the criteria of falling within 10% variance of the FRC. Tests that did not fulfil that criteria were excluded case by case. The mean of the included tests was used for analysis. As this outcome was added as an amendment to the initial TIDe research, the MBW was not performed on all participants. Spirometry was performed pre and post intervention according to the ERS/ATS guidelines, participants best test was taken and included in the analysis. Due to the initial aims of TIDe to assess the devices impact on dyspnoea, participants were not recruited based on their level of sputum production. Therefore, participants were categorised as “non-sputum producers” if they scored between 0-2 on the COPD Assessment Test (CAT) and “sputum producers” is they scored 3-5 on the CAT.

The results were analysed using STATA statistical package and SPSS version 23. This was analysed by a paired t-test and mixed model. Subgroup analysis was performed to compare non-sputum producers to sputum producers and to assess the impact of an exacerbation during the study phase and compared to those who did not have an exacerbation.

### 6.2.3 Results

A subset of 63 participants from the TIDe study performed the MBW test at baseline and therefore were included in the analysis. These patients were predominantly male (73%) with a mean [SD] $FEV_1$ percent predicted of 53 [18]. Participants had a high BMI of 29.32 [6.58] and a raised $LCI_{1/40th}$ of 10.26 [2.38]. There were 13 exacerbations during the study period, 6 in the HFAO group and 4 in the sham group. There were no significant differences at baseline (table 6.7).

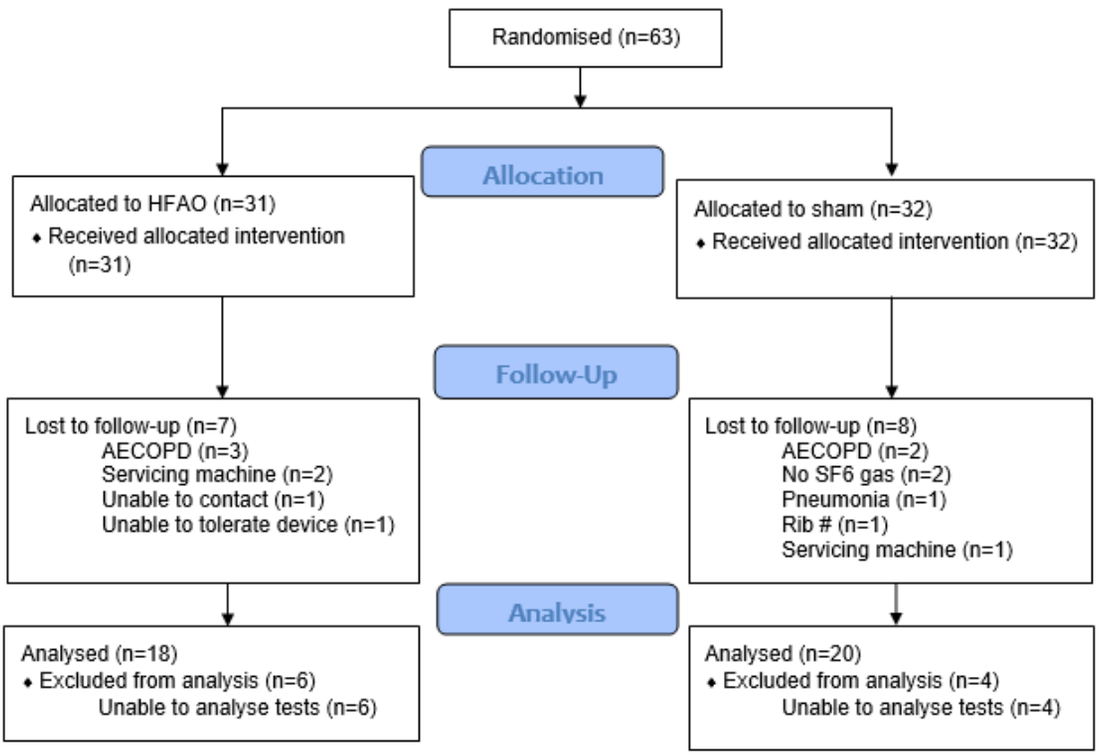



*Figure 6.11 Consort diagram LCI exploratory analysis*

*Table 6.7 Baseline characteristics for response to treatment cohort*

| | HFAO (n=31) | Sham (n=32) | Total |
|---|---|---|---|
| Gender male n (%) | 22 (71) | 23 (74) | 45 (73) |
| Age (years) | 69.58[8.71] | 70.45[6.48] | 70.02[7.62] |
| $FEV_1$ %predicted | 46.45[18.03] | 52.54[18.57] | 49.54[18.41] |
| $FEV_1$ (l) | 1.30[0.56] | 1.36[0.54] | 1.33[0.55] |
| FVC (l) | 2.76[0.87] | 2.59[0.75] | 2.67[0.81] |
| $FEV_1$/FVC ratio | 0.52[0.12] | 0.46[0.13] | 0.49[0.13] |
| CAT score | 20.42[7.37] | 19.34[7.23] | 19.87[7.26] |
| BMI ($kg/m^2$) | 27.63[5.45] | 31.00[7.23] | 29.32[6.58] |

*Table 6.7 $FEV_1$ Forced Expiratory Volume in 1 second, FVC Full Vital Capacity, CAT COPD Assessment Test, LCI Lung Clearance Index, BMI Body Mass Index. *p<0.05*

56% of participants reported issues with sputum clearance based on the CAT sputum domain (scores between 3 and 5). There were no differences between those with or without sputum retention in the $LCI_{1/40th}$ (CAT sputum 0-2 11.30 [1.86], CAT sputum 3-5 11.26 [1.76]) (p=0.94). Those with sputum retention had higher $S_{acin}$ (0.52 [0.26] CAT sputum 0-2, 0.71 [0.70] CAT sputum 3-5) however these differences were not statistically significant (p=0.37).

Over the eight-week intervention phase, both groups had a worsening of their $LCI_{1/40th}$ by 0.426 [1.463] in the sham and 0.757 [1.233] in the HFAO group. There was a worsening of 0.019 [0.085] of the $S_{cond}$ in the sham group and an improvement of -0.016 [0.157] in the HFAO group. The $S_{acin}$ improved by -0.046 [0.308] and -0.195 [0.588] in the sham and HFAO groups, respectively. The $LCI_{1/20th}$ had a worsening in both groups of 0.071 [0.731] in the sham and 0.343 [0.754] in the HFAO group. These changes were not statistically significant over time or between group (table 6.8). Figure 6.12 demonstrates changes in the $LCI_{1/40th}$ between visit, figure 6.13 compares the changes in FRC between visit.

*Table 6.8 Changes in Multiple Breath Washout*

| | HFAO n= 22 | | Sham n=20 | | |
|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | p= |
| $LCI_{1/40th}$ | 11.589[1.008] | 12.346[1.520]* | 11.344[1.906] | 11.771[1.867] | 0.18 |
| $FRC_{1/40th}$ | 4.074[1.280] | 3.737[1.337] * | 3.371[0.807] | 3.140[0.800] | 0.75 |
| $S_{cond}$ | 0.052[0.035] | 0.035[0.039] | 0.041[0.033] | 0.060[0.095] | 0.79 |
| $S_{acin}$ | 0.734[0.750] | 0.539[0.379] | 0.525[0.095] | 0.479[0.276] | 0.45 |
| $LCI_{1/20th}$ | 8.702[1.143] | 9.044[1.112] | 8.734[1.044] | 8.806[1.252] | 0.36 |
| $FRC_{1/20th}$ | 3.609[1.067] | 3.603[1.078] | 3.234[0.828] | 3.126[0.813] | 0.37 |

*Table 6.8 HFAO High Frequency Airway Oscillations, LCI Lung Clearance Index, $S_{cond}$ conducting slope, $S_{acin}$ acinar slope.*

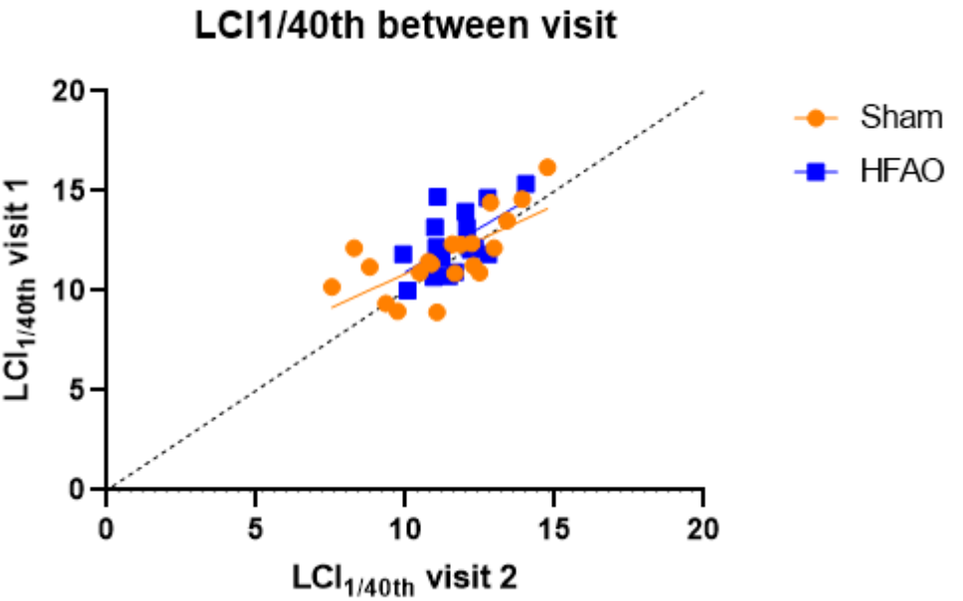



*Figure 6.12 $LCI_{1/40th}$ visit one and visit two*

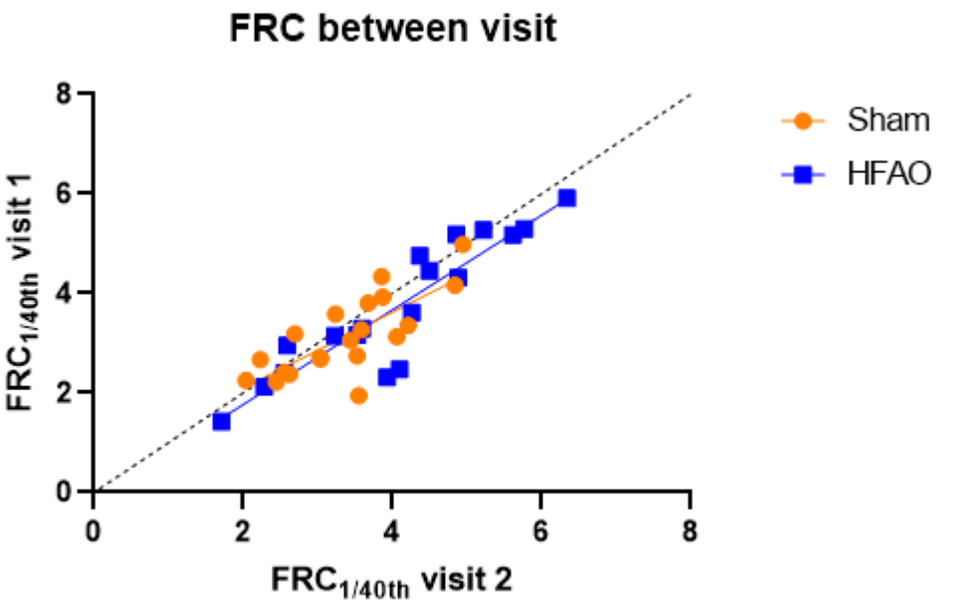



*Figure 6.13 $FRC_{1/40th}$ visit one and visit two*

Participants were stratified based on their level of sputum retention on the CAT sputum domain. There were 9 participants in the sham and 8 in the HFAO group that reported 0-2 on the CAT sputum domain had an improvement of the $LCI_{1/40th}$ of -0.039 [1.717] in the sham and a worsening of 0.548 [1.145] in the HFAO group. There were improvements in the $S_{cond}$ of -0.011 [0.030] in the sham and -0.042 [0.082] in the HFAO group. The $S_{acin}$ improved by -0.012 [0.035] in the sham and -0.081 [0.476] in the HFAO group. The $LCI_{1/20th}$ improved by -0.003 [0.746] and worsened by 0.755 [0.724] in the sham and HFAO group, respectively. The changes in the $LCI_{1/20th}$ for the HFAO group were statistically significantly different over time however this was not significant between groups (table 6.9).

There were 11 participants in the sham and 14 in the HFAO group that reported CAT sputum score of 3-5. There was a worsening of the $LCI_{1/40th}$ by 0.807 [1.165] in the sham and 0.900 [1.322] in the HFAO group. The worsening of $LCI_{1/40th}$ was statistically significant over time in both groups. The $S_{cond}$ worsened in the sham group (0.044 [0.108]) but improved in the HFAO group (-0.002 [0.188]). The $S_{acin}$ improved for both groups (-0.073 [0.281] sham, -0.260 [0.653] HFAO). The $LCI_{1/20th}$ worsened by 0.128[0.766] in the sham and 0.051[0.335] in the HFAO group. There were no statistically significant differences between groups (table 6.10, figure 6.14).

*Table 6.9 Lung Clearance Index analysis- non-sputum producers (CAT sputum 0-2)*

| | HFAO n=8 | | Sham n=9 | | |
|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | P= |
| $LCI_{1/40th}$ | 11.762[0.601] | 12.309[1.483] | 10.794[1.434] | 10.755[1.395] | 0.21 |
| $FRC_{1/40th}$ | 3.820[0.991] | 3.235[0.980] | 3.275[0.884] | 2.822[0.774] * | 0.77 |
| $S_{cond}$ | 0.071[0.087] | 0.029[0.012] | 0.054[0.042] | 0.043[0.034] | 0.43 |
| $S_{acin}$ | 0.579[0.347] | 0.498[0.388] | 0.463[0.163] | 0.451[0.294] | 0.83 |
| $LCI_{1/20th}$ | 8.610[0.655] | 9.365[0.888] * | 7.933[0.807] | 7.930[0.807] | 0.11 |
| $FRC_{1/20th}$ | 3.091[0.432] | 3.161[0.264] | 3.319[0.803] | 3.355[0.820] | 0.04 |

*Table 6.9 LCI Lung Clearance Index, FRC Functional Residual Capacity, $S_{cond}$ conducting slope, $S_{acin}$ acinar slope. *p<0.05*

*Table 6.10 Lung Clearance Index analysis- sputum producers (CAT sputum 3-5)*

| | HFAO n=14 | | Sham n=11 | | |
|---|---|---|---|---|---|
| | Pre | Post | Pre | Post | P= |
| $LCI_{1/40th}$ | 11.479[1.215] | 12.369[1.615]* | 11.795[2.183] | 12.601[1.837]* | 0.70 |
| $FRC_{1/40th}$ | 4.235[1.457] | 4.057[1.475] | 3.449[0.772] | 3.401[0.754] | 0.60 |
| $S_{cond}$ | 0.041[0.206] | 0.039[0.048] | 0.030[0.021] | 0.074[0.125] | 0.82 |
| $S_{acin}$ | 0.823[0.907] | 0.563[0.387] | 0.576[0.271] | 0.503[0.274] | 0.46 |
| $LCI_{1/20th}$ | 8.755[1.377] | 8.858[1.221] | 9.335[0.853] | 9.462[1.139] | 0.89 |
| $FRC_{1/20th}$ | 3.912[1.220] | 3.861[1.291] | 3.319[0.803] | 3.355[0.820] | 0.56 |

*Table 6.10 LCI Lung Clearance Index, FRC Functional Residual Capacity, $S_{cond}$ conducting slope, $S_{acin}$ acinar slope. *p<0.05*

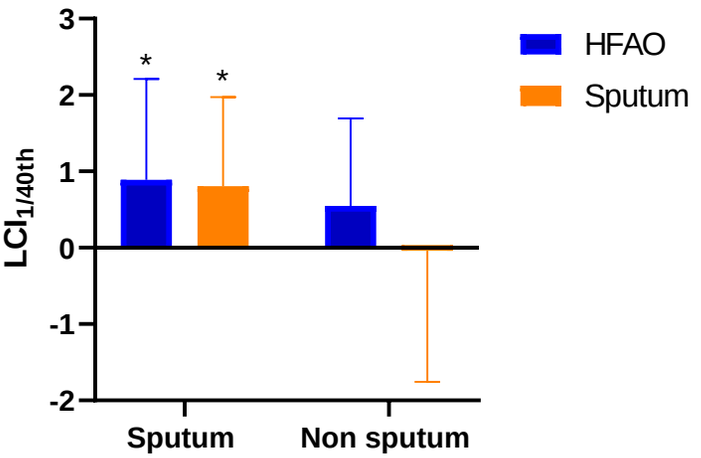



*Figure 6.14 Changes in $LCI_{1/40th}$ for sputum and non-sputum producers*

There were nine participants that experienced at least one exacerbation during the intervention phase (4 in the sham and 5 in the HFAO group). In the patients that experienced an exacerbation the $LCI_{1/40th}$ worsened by a mean [SD] of 1.521 [1.141]. Those that did not experience an exacerbation had a smaller worsening of their $LCI_{1/40th}$ of 0.371 [1.313]. Those in the HFAO group who had at least one exacerbation had a statistically significant worsening of their $LCI_{1/40th}$ when compared to those who did not exacerbate (table 6.11).

*Table 6.11 One-way ANOVA of Lung Clearance Index and exacerbations*

| | 0 exacerbations n=29 | ≥1 exacerbation n=9 | p |
|---|---|---|---|
| HFAO | 0.386[1.000] | 2.054[1.181] | 0.01 |
| Sham | 0.357[1.587] | 0.987[0.940] | 0.46 |
| Total | 0.371[1.313] | 1.521[1.141] | 0.03 |

*Table 6.11 HFAO High Frequency Airway Oscillations*

There were 15 participants in the sham group and 14 in the HFAO group that did not experience an exacerbation during the intervention phase. The $LCI_{1/40th}$ and $LCI_{1/20th}$ worsened over the eight weeks. In those that had one or more exacerbations over the intervention phase, this worsening was much greater in for those in the HFAO group and this difference was statistically significant. The $S_{acin}$ improved in all participants irrespective of their exacerbation history, the improvement in the HFAO group was statistically significantly larger in those that had an exacerbation during the intervention phase compared to those who had zero exacerbations. This was not seen in those using the sham device. There were no statistically significant differences between groups (figure 6.15, table 6.12).

*Table 6.12 Lung Clearance Index analysis- exacerbations vs no exacerbations*

| | 0 exacerbations | | | ≥1 exacerbation | | |
|---|---|---|---|---|---|---|
| | HFAO (n=14) | Sham (n=15) | p | HFAO (n=4) | Sham (n=4) | p |
| $LCI_{1/40th}$ | 0.386[1.000] | 0.358[1.587] | 0.50 | 2.054[1.181] * | 0.987[0.940] | 0.10 |
| $FRC_{1/40th}$ | -0.336[0.633] | -0.283[0.614] | 0.98 | 0.336[0.145] * | -0.003[0.163] | 0.04 |
| $S_{cond}$ | -0.037[0.121] | 0.032[0.095] | 0.06 | 0.077[0.272] | -0.017[0.019] | 0.31 |
| $S_{acin}$ | -0.056[0.331] | -0.076[0.325] | 0.97 | -0.822[1.081] | -0.053[0.150] | 0.27 |
| $LCI_{1/20th}$ | 0.117[0.652] | 0.026[0.778] | 0.77 | 1.189[0.474] * | 0.237[0.629] | 0.04 |
| $FRC_{1/20th}$ | -0.024[0.328] | -0.013[0.403] | 0.35 | 0.063[0.390] | -0.022[0.185] | 0.82 |

*Table 6.12 LCI Lung Clearance Index, $S_{cond}$ conducting slope, $S_{acin}$ acinar slope. *p<0.05 in changes from baseline.*

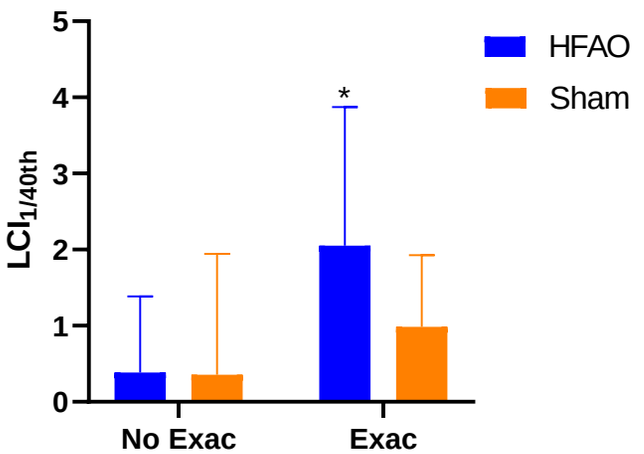



*Figure 6.15 Changes in $LCI_{1/40th}$ in patients with and without an exacerbation during the intervention phase.*

Correlation of changes

The change from baseline in the $LCI_{1/40th}$ and $LCI_{1/20th}$ is listed below in table 6.13. The magnitude of change between the $1/40^{th}$ and $1/20^{th}$ analysis differs between the sham and the HFAO group. The correlation coefficient of change between $LCI_{1/40th}$ and $LCI_{1/20th}$ is 0.726 ($p<0.01$). Figure 6.16 demonstrates the change from baseline for the $LCI_{1/40th}$ and $LCI_{1/20th}$. The ratio of change between the $LCI_{1/40th}$ and $LCI_{1/20th}$ is 0.453 in the HFAO group and 0.167 in the sham. There were no changes seen in spirometry measurements following treatment.

*Table 6.13 Changes in Lung Clearance Index $1/40^{th}$ and $1/20^{th}$ washouts*

| | HFAO change from baseline | Sham change from baseline | p |
|---|---|---|---|
| $LCI_{1/40th}$ | 0.757[1.233] | 0.426[1.463] | 0.21 |
| $LCI_{1/20th}$ | 0.343[0.173] | 0.071[0.731] | 0.11 |
| $FEV_1$ (l) | -0.18[0.13] | 0.00[1.18] | 0.77 |
| $FEV_1$ % predicted | -0.90[4.60] | 0.52[6.75] | 0.64 |

*Table 6.13 Changes from baseline in the $LCI_{1/40th}$ and $LCI_{1/20th}$ for HFAO and Sham groups. $FEV_1$ Forced Expiratory Volume in 1 second, LCI Lung Clearance Index, HFAO High Frequency Airway Oscillating device.*

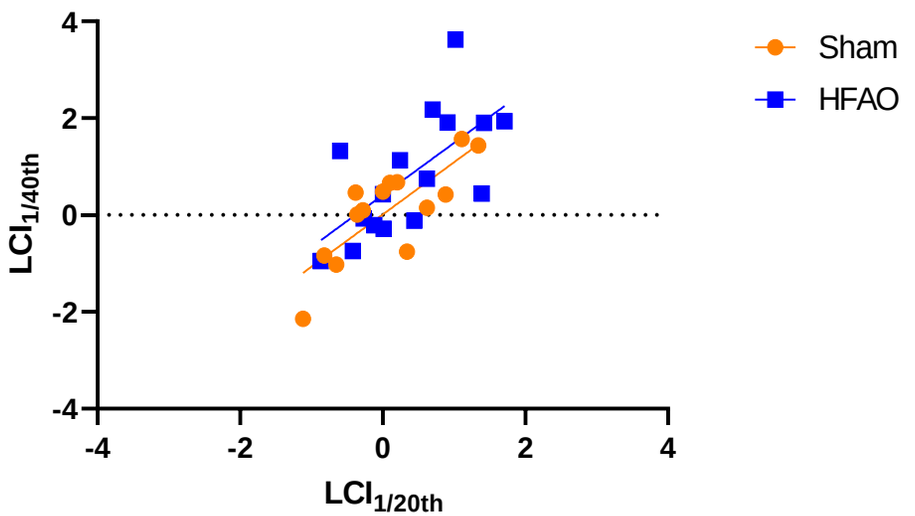



*Figure 6.16 Changes in $LCI_{1/40th}$ and $LCI_{1/20th}$*

### 6.2.4 Discussion

This was an exploratory analysis of the TIDe study which examined the use of the LCI in response the HFAO compared with a sham. This has potential as a surrogate measure of sputum clearance and explored the conducting and acinar zones as well as shortening the LCI to a $1/20^{th}$ washout. 56% of participants in this study demonstrated high sputum burden as measured by the CAT sputum score (3-5) which is higher than reported in the literature. Both groups had a worsening of the LCI after the eight-week intervention phase, however there were observed greater improvements in the $S_{cond}$ and $S_{acin}$ in the HFAO group. There was a larger worsening of the LCI in those who had predefined sputum retention compared to those who had minimal sputum, which could be explained by ventilating previously closed areas of the lungs. Exacerbation frequency worsened the LCI in the HFAO group.

Spirometry is not responsive to physiotherapeutic techniques however these results have demonstrated some changes in ventilation heterogeneity following an intervention. Both groups demonstrated a worsening over the eight-week intervention period which is greater than the reported variance in the repeatability testing. Those receiving the intervention had a larger worsening of the LCI however this was not statistically significant. The $S_{acin}$ had a greater improvement in the HFAO group and it is plausible that an improvement in peripheral ventilation has led to improved airway recruitment, which were previously non-ventilating areas of the lung. Opening new areas of ventilation in the lung would increase the LCI as these areas would not have previously been utilised in testing. Additionally, exacerbations have been demonstrated to worsen LCI in Cystic Fibrosis, which may contribute to the mean worsening[200]. In those that did not exacerbate during the trial period the LCI worsening was lesser however this was marginally larger than the usual variance. The $LCI_{1/20th}$ showed a comparable direction of change and therefore may be useful in the assessment of airway clearance techniques, though the magnitude of change differs for the sham and HFAO group. This could be explained by the improvements in peripheral ventilation as demonstrated by the $S_{acin}$ analysis. It is possible that the improvements were a result of increasing airway recruitment of previously non-ventilated

areas of the lungs which would increase LCI overall but improve the peripheral ventilation. Whereas the sham group had a smaller improvement in $S_{acin}$ and therefore a smaller worsening in the LCI. The LCI has demonstrated an overall worsening as a response to the intervention, which may be explained by improved diffusion-convection-dependant inhomogeneity as noted in the $S_{acin}$. The use of the $LCI_{1/20th}$ would not provide a reliable $S_{cond}$ and $S_{acin}$ measurement and therefore the assessment of peripheral airway ventilation would not reliably be possible. Without phase III slope analysis, the interpretation of the results would differ.

## 6.3 Strengths and limitations

This study demonstrates some strengths in that it is the first to explore the repeatability of the $LCI_{1/40th}$ and $LCI_{1/20th}$ washout points. It offers a long term follow up of eight weeks in participants with COPD. The LCI, and phase three slope analysis has not previously been used as a therapeutic outcome measure in response to an intervention in patients with COPD and is the first of its kind to explore the impact physiotherapeutic techniques on ventilation heterogeneity. This was a double blinded, sham, randomised controlled trial and therefore has a low risk of bias. There are some limitations to this study, in that sputum volume was not reported and therefore comparisons were not able to be made. The use of the LCI is an indirect measure of sputum clearance and can be influenced by many other factors however as the intervention aimed to assist sputum clearance, it is reasonable to attribute differences between groups to enhanced airway clearance. The $LCI_{1/20th}$ assessment was performed via a retrofit and therefore the feasibility of conducting a $1/20^{th}$ washout is currently unknown. The use of the $LCI_{1/20th}$ results in a different conclusion and therefore its use as an outcome measure may not be appropriate. A shortened LCI may not capture all the effects on peripheral ventilation and therefore is not an appropriate endpoint for physiotherapeutic interventions where peripheral ventilation may be affected. This research would recommend the use of a $LCI_{1/40th}$ washout in order to capture

peripheral ventilation however, this is dependent on the mechanism of action and primary aim of the study.

## 6.4 Comparisons to other literature

The results of this research strengthen the repeatability literature of the use of the LCI in patients with COPD, of which the data is limited[90]. It is the first to explore a long term follow up of the LCI and the addition of phase III slope analysis. This research is the first to explore the use of the LCI as a potential outcome measure for patients with COPD, however the results were comparable to the bronchiectasis data[89]. The use of the $S_{cond}$ and $S_{acin}$ as outcome measures have not been explored in patients with COPD or other respiratory conditions and this is a novel finding for this work. This research provides a theoretical underpinning for the impact of sputum clearance techniques in patients with COPD, however future research would be useful to strengthen the knowledge base. This research makes suggestions of the potential sample size necessary to detect a change based on different effects sizes.

# 7 Discussion

## 7.1 Summary of Findings

Dyspnoea and sputum retention are both common symptoms in COPD and are the key priorities for treatment for respiratory physiotherapists. Whilst there are a vast number of treatment modalities, devices for both dyspnoea and sputum management are often overlooked, particularly in the UK due to cost implications. Inspiratory muscle training devices offers promise in the treatment of breathlessness as a result of respiratory muscle dysfunction and the evidence has demonstrated an improvement in inspiratory muscle strength, dyspnoea and quality of life. The use of expiratory muscle training is infrequently employed however offers a theoretical potential for improvement, given that patients with COPD are characterised by an expiratory flow limitation. It is also believed that patients with COPD demonstrate stronger respiratory muscles due to the higher demand on the respiratory system however evidence has demonstrated inspiratory and expiratory muscle weakness in parallel. This research has demonstrated a presence of inspiratory muscle weakness. Furthermore, laboured breathing causes a higher oxygen cost and increases breathlessness and therefore strengthening these muscles may reduce the overall oxygen cost of breathing. The use of respiratory muscle training has not been recommended in the COPD guidance due to lack of robust evidence[3]. Conversely sputum clearance devices have been recommended in the NICE guidance if participants have excessive sputum however, the availability and application of these devices clinically is sparse[3]. The evidence for airway clearance devices is subject to large amounts of bias and evidence predominantly favours breathing exercises[120]. The lack of rigorous evidence is partly due to a lack of reliable outcome measures for sputum clearance. The use of sputum weight can be unreliable, labour intensive and difficult to interpret, whereas patient reported outcomes are open to large variability due to their subjectivity. The use of devices is appealing for clinicians due to their ease of application and potential added benefit over and above other techniques (such

as breathing exercises). The Aerosure medic is a device developed to address dyspnoea and sputum and is the first duel functioning device for patients with COPD. This thesis aimed to explore the effect of sputum clearance devices on common outcomes in COPD through the conduction of a systematic review. The use of the Aerosure device was explored for its feasibility and effectiveness in relation to dyspnoea, quality of life, exercise capacity and respiratory muscle strength. Finally, this thesis explored the use of the Lung Clearance Index as a surrogate measure of sputum clearance in patients with COPD.

The systematic review (chapter 2) undertaken within this thesis explores the evidence of devices as an airway clearance technique. The results demonstrated an increase in sputum volume immediately after treatment which suggests an enhanced sputum clearance. Long term follows up showed a reduction in overall sputum volume when compared to a control which suggests a reduction in the production of sputum; however, these results are not statistically significant. The use of sputum volume as an outcome measure provides some difficulties in interpretation as it may suggest a change in either sputum production or sputum clearance. The use of patient reported sputum clearance is vastly different amongst cohorts and therefore provides a high variability. The use of airway clearance devices in stable COPD can significantly reduce exacerbation rates by 30% at 30 days and 50% at six months. This was statistically significant and meets the known minimal clinical important reduction in exacerbation frequency of 20%[155]. There was a lack of evidence regarding exacerbation frequency in patients experiencing a current hospitalisation and/or exacerbation of COPD. The use of devices did not translate into statistically significant improvements in health-related quality of life as measured by the SGRQ however this met the MCID of four points[155]. Measurements of symptoms by the CAT and BCSS were statistically significant in favour of the intervention which exceeds the established MCID for these outcomes (CAT -2, BCSS -1)[155]. These results support the use of airway clearance devices in the management of exacerbations and symptoms in patients with stable COPD. The included research predominantly explores the use of devices within patients who demonstrate hypersecretion of sputum defined as 20ml or more of sputum in one day. There were too few studies to compare the impact of recruiting patients based on their

level of sputum production (chronic mucus secretion compared to all COPD patients) however results appear heterogeneous between studies that predefined chronic mucus secretion as an inclusion criteria and studies that recruited regardless of sputum status (as demonstrated on the $I^2$ statistic). Small airway mucus obstruction is characteristic in COPD even in the absence of excessive mucus and therefore airway clearance could benefit all patients with COPD[2]. The evidence for devices in patients with an acute exacerbation is much less convincing and therefore further research is required. This is conflicting to the current NICE guidelines which recommend airway clearance devices to those with excessive sputum during an exacerbation. The provision of airway clearance devices in the UK are low due to cost implications, however the large reduction in exacerbation frequency may provide a cost saving in the administration of antibiotics and hospital bed days and healthcare utilisation costs.

Whilst the use of airway clearance devices is poor in the UK, the provision of respiratory muscle training is absent in patients with COPD. Although there has been evidence to suggest improvements in walking capacity and health related quality of life, the use of inspiratory muscle training is not recommended by national guidelines[3]. The flow resistance of the HFAO device offers a form of combined inspiratory muscle training and the addition of oscillations allows for secretion clearance. At the time of this thesis there was no evidence for the use of the HFAO device in patients with COPD and therefore its feasibility and acceptability were unknown. This research demonstrated the feasibility of using this device in participants with COPD, with high recruitment rate and low attrition rate (chapter 4). The self-reported compliance rate was high with 90% of patients meeting the 75% compliance threshold. This study demonstrated trends in improving respiratory muscle strength, incremental shuttle walking test and health related quality of life, however the sample size was underpowered to imply clinical benefits. Public and patient involvement was utilised in order to develop a clinical effectiveness trial, gaining insight into outcomes, intervention duration and sham device development.

The recruitment and retention rate were echoed in the randomised control trial which was powered based on the CRQ dyspnoea domain. The results of the double blinded sham-controlled trial showed significant improvements in inspiratory muscle pressure when compared to the sham and therefore the device intervention has been delivered (chapter 5). These changes were consistent with the changes in the feasibility trial however; the improvement in inspiratory muscle strength was smaller compared to the systematic review by Gosselink[191]. There were no significant improvements in walking capacity or quality of life compared to the sham however there was a trend in improving breathlessness as measured by the MDP. There was a large standard deviation of this measurement which suggests the study was underpowered to detect the between group differences. At present there is no MCID for the MDP; however it has been suggested that questionnaires using a 10-point Visual Analogue Scale (VAS) can be considered clinically meaningful if a change in 1 point is demonstrated[201]. As the sensory and affective domains explore five components on a VAS, a five-point change in each domain would be required. The MDP total score utilises both sensory and affective domains plus an immediate response on a 10-point Likert scale and therefore it is expected that a total change of 11 points would be clinically meaningful. Based on the standard deviations seen in this study an 11 point change with 80% power would require 53 participants per group (106 participants in total) to detect a change, though this clinically meaningful change is estimated and further research into the MCID would be useful. However, based on this estimated MCID, this research did not demonstrate clinically a meaningful improvement in the MDP however was underpowered to detect a change. There are very few studies that have explored measuring different sensations of dyspnoea and therefore it is unclear how significant this finding is but has demonstrated added value in the assessment of dyspnoea. The CRQ-dyspnoea domain was the primary outcome as it is validated in COPD and has a known MCID; however, it does not capture the complexity of the symptom. There has been development of more complex measures of dyspnoea (such as the MDP) since this project development which may be more appropriate outcome measures for future trials, however the development of an MCID would inform sample size and interpretation of results. These findings contribute to a conflicting body of literature which has simultaneously demonstrated small and no

improvements in the use of inspiratory muscle training in the management of dyspnoea in COPD, either as an adjunct to pulmonary rehabilitation or an individual intervention. It is reasonable to assume that those with predefined inspiratory muscle weakness would have a greater benefit to the intervention however this was not demonstrated with subgroup analysis in this study, which is comparable to the literature where additional benefits were not seen in participants with weaker inspiratory muscles[191]. Additionally, those with sputum retention may have a better response to the airway clearance element of the device; however, this was not the case. Those that had frequent exacerbations preceding the trial (≥2 in 12 months) appeared to have a greater response, in that the walking capacity was preserved in the treatment group however significantly reduced in the sham group. This was statistically significant between groups and the difference met the known MCID of 35m. This suggests a faster decline in function in those that have frequent exacerbations and may be an interesting group to target for future research. The potential mechanism for this difference in the incremental shuttle walking test is that in those with frequent exacerbations, participants receiving the HFAO device were able to maintain their respiratory muscle strength, feel less breathless and as a result were able to maintain their walking distance. Whereas, participants using the sham may have reduced strength that increased breathlessness and limited their exercise tolerance. Whilst subgroup analysis is useful in identifying potential areas for further research, it is underpowered and therefore there is a possibility of a type I error.

As previously mentioned, sputum clearance is difficult to capture, and the current outcome measures are hugely variable or difficult to interpret. Therefore, this research explored the potential use of LCI as a surrogate measure for sputum clearance. The LCI has previously demonstrated repeatability in patients with mild disease however this has not been explored throughout the severities or for a long duration follow up[93]. The use of the LCI is repeatable within visit and over the course of eight weeks and provides a stable outcome measure for the assessment of ventilation heterogeneity (chapter 6). Phase III slope analysis give insight into the conducting and peripheral zones and may provide added value in the assessment of small airways. The $S_{cond}$ and $S_{acin}$ demonstrated high repeatability within visit;

however, the $S_{cond}$ is less repeatable at eight weeks. This could be attributed to instrument noise or disease specific changes and is comparable to the asthma literature[84]. The duration of the LCI is often criticised, particularly for patients with severe disease and this limits its clinical application. This research explored the potential of a shortened LCI to 1/20$^{th}$ of the starting concentration and this demonstrated excellent repeatability within and between visits. This can offer a time cost saving of 31.5% and reduces the average duration to 17 minutes 12 seconds which is comparable to quality assured spirometry. This promotes the clinical application of the LCI.

The response of the LCI was explored in relation to an intervention. The LCI increased in both the sham and HFAO group. The increase was larger in those that received the intervention however this was not statistically significant between groups. The $S_{acin}$ had a greater improvement in patients that received the HFAO when compared to the sham. It is possible that the use of the HFAO device increased ventilation to previously closed airways. Airways not actively participating in ventilation would not be captured by the LCI, however if these airways opened up and began ventilating again this would increase the overall LCI. This is supported by an improvement in $S_{acin}$ that suggests improved diffusion-convection-dependant inhomogeneity. This improvement in $S_{acin.}$ was greater in those that demonstrate sputum retention and a greater increase in their LCI compared to those that do not report sputum retention. Those that experience an exacerbation during the intervention phase had a worsening of the LCI compared to those who did not have an exacerbation; however, this was a small sample size. The $LCI_{1/20th}$ demonstrated feasibility as an outcome measure, offering an attractive time saving, and has been shown to be equally as sensitive as $LCI_{1/40th}$ in patients with Cystic Fibrosis, however, would not allow for phase III slope analysis as this would provide an unreliable estimate[202].

## 7.2 Strengths and limitations

This research utilises rigorous techniques and attempts to minimise bias in order to derive reliable conclusions. The evidence was systemically reviewed and synthesised the available evidence on airway clearance devices. There were wide inclusion criteria and utilised second reviewers to strengthen the data extraction. Authors were contacted where data was not available in text which strengthens this research. There is a pooled sample size of 866 participants with varying severity of diseases. The included studies are predominantly subject to moderate bias and therefore results must be interpreted in relation to the quality and quantity of the available evidence. Where possible, sensitivity analysis was explored to understand the impact of specific devices, patient characteristics and study duration.

The HFAO device was assessed for feasibility prior to the development of a clinical effectiveness trial. Public and patient involvement was key in the development and interpretation of the randomised controlled trial. Clinical effectiveness was assessed using a fully powered, double blind, randomised, sham controlled trial. Allocation concealment was employed and there were no episodes of unblinding throughout the trial. This strengthens the quality of the research and minimises the exposure to bias. The sham used in the randomised controlled study was convincing as participants were not aware of the device they had received, and did not offer any additional training, which is demonstrated by the lack of improvements in $PI_{max}$. The use of the LCI as a surrogate outcome measure for sputum clearance offers a novel approach in the assessment of physiotherapeutic interventions. This offers a non-exertional alternative to spirometry which is known to be insensitive to treatments. The MBW tests are quality checked and were only included if they are within the set variance of 10% in FRC.

Whilst this research made every attempt to minimise bias, there are some inevitable limitations. Sputum volume was not captured in this cohort and therefore are unable to compare sputum volume changes to changes in LCI. However, as previously noted sputum

volume is difficult to interpret as the volume of sputum is not reflective of the amount of sputum in the lungs, can be labour intensive and is difficult to interpret. The HFAO device is a flow resistive device providing resistance of a maximum 40cm$H_2O$ with 100l per minute flow rate. Therefore, it is possible that participants with a high baseline inspiratory muscle strength will not receive the recommended 30-50% resistance to achieve a training response. Participants were not recruited based on a presence of inspiratory muscle weakness; however, the use of subgroup analysis did not show greater improvements in those that had predefined inspiratory muscle weakness and therefore the exclusion of participants without weakness is futile. These results are comparable to the meta-analysis by Gosselink[191]. Whilst the use of subgroup analyses is interesting in identifying a potential responder groups and offering insight into areas of further research, the splitting of the sample means this analysis is underpowered to detect a change. Additionally, interesting results were seen with the use of the MDP to assess the complexity of differing sensations and emotional responses to dyspnoea; however, the large standard deviations of this measure suggest this study was underpowered to detect a change. Furthermore, this research demonstrated a high compliance rate to the intervention; though this was self-reported and should be interpreted with caution. Whilst the sham was considered an effective sham device, participants demonstrated improvements in symptoms, likely due to the Hawthorne effect whereby participants improve outcomes due to the awareness of being observed, which has been demonstrated in other studies. This is particularly important in self-reported outcomes such as health related quality of life. The difference between the sham and the HFAO group is the true benefit of the device as both groups will be influenced by the Hawthorne effect. Lastly, the systematic review highlighted improvements in 30 day and 6-month exacerbation frequency; the clinical effectiveness trial did not include 6-month follow up exacerbation data and therefore cannot be compared to the literature.

## 7.3 Implications

The systematic review in this thesis supports the use of airway clearance devices in patients with stable COPD, particularly in those that have mucus hypersecretion. This may be useful in reducing exacerbations and improving symptoms of COPD. The use of the HFAO device (Aerosure) did not demonstrate comparable improvements in symptoms however did show trends in improving dyspnoea. It is possible the those who have frequent exacerbations may have the most benefit particularly in maintaining exercise capacity however due to the small sample size and secondary sub analysis, these results are not generalizable. Based on the primary outcome, the use of the HFAO device in patients with COPD cannot be recommended to significantly reduce breathlessness over and above a sham device.

The use of the LCI may offer value over spirometry in clinical practice. The use of the $S_{acin}$ offers insight into the assessment of the small airways and has potential in adjunct with the LCI for the assessment of sputum clearance. It is feasible to perform a shortened washout at $1/20^{th}$ of the starting concentration and is repeatable over a period of eight weeks. This could improve the implementation of the MBW test as it a shorter alternative, however the assessment of the $S_{cond}$ and $S_{acin}$ are less reliable at a $1/20^{th}$ cut off. This research supports the use of the LCI in patients with COPD for the assessment of ventilation heterogeneity at $1/40^{th}$ and $1/20^{th}$ washout concentrations, and the use of $S_{cond}$ and $S_{acin}$ from a $1/40^{th}$ washout.

This research contributes to the evidence in respiratory muscle training and airway clearance in patients with stable COPD; however, it also raises some interesting areas for potential research.

Firstly, the systematic review supports the use of airway clearance devices in COPD and can reduce exacerbation frequency by up to 50%. However, the evidence is subject to moderate bias and therefore there is a need for evidence with low risk of bias. Similarly, the evidence

during an acute exacerbation, or immediately after an exacerbation is sparse and further research would be useful in this area. This would require recruiting participants during, or at the end of, an admission and offering airway clearance device or a sham. This research would recommend longer intervention in patients with an acute exacerbation of COPD and preferably compared to a sham device. Finally, implementation research in the clinical environment would be useful to understand whether these interventions can be mimicked in clinical practice and an economic analysis to understand the cost benefits of this intervention if clinical gains have been demonstrated.

The use of the HFAO device demonstrated small improvements in cough and sputum based on domains of the COPD Assessment Test, in patients over and above the sham device; however, this is a sub-domain of the COPD Assessment Test and therefore is underpowered to detect a change. Sub-group analysis failed to identify a responder group; however, it is possible that those with frequent exacerbations may have benefits in incremental shuttle walking test that was not seen in the larger analysis and this would be an interesting group of patients to research. This change has not been demonstrated in previous research and is an important and difficult group of patients to treat. This is supported by the significant differences seen in $PI_{max}$ of this subgroup. The assessment of exacerbation frequency at 30 days and 6 months for the HFAO and sham group would be useful and would allow for comparison to airway clearance device literature (chapter 2).

This research utilises a novel use of the MDP questionnaire to assess dyspnoea in patients with COPD. The use of the MDP demonstrated improvements in the HFAO group and suggests a change in the sensation of breathlessness. There appeared to be a shift in the type of perceived breathlessness however the clinical impact of this is not known. This is a new outcome measured which is used little clinically and the evidence base of this outcome measure is small and therefore further research would be useful. Further research could target interventions dependant on their type of breathlessness perceived, for example the HFAO may address work of breathing or air hunger where pulmonary rehabilitation may

impact hyperventilation, work of breathing and concentration. Further research into this area would provide insight into precision treatment of dyspnoea. Research exploring the minimal clinical important difference in response to known effective interventions for breathlessness, such as pulmonary rehabilitation, would be useful in interpreting this research. Qualitative analysis of changes in breathlessness sensation would give insight into the interpretation of breathlessness for future studies. In response to treatment, larger sample sizes may be necessary to detect a change in this outcome.

The use of the LCI as an outcome measure may be useful in research studies and would provide a novel insight into physiotherapy teaching. The use of phase III slope analysis, particularly the $S_{acin}$ is recommended for studies assessing the response to airway clearance devices. It is likely that sputum and/or sputum plugs would limit ventilation to the peripheral airways and as a result clearing sputum can result in improvements in $S_{acin}$ hence its importance to be included as an outcome measure. In these study designs, a $1/40^{th}$ washout test would be favourable. Comparisons of the LCI and sputum volume would enhance the interpretation of the LCI as a surrogate measure of sputum clearance. Patient reported sputum clearance measures have a large variation and therefore may not be reliable in response to sputum clearance devices.

## 7.4 Contributions to literature

This research contributes to the wider literature in numerous ways. The systematic review adds to the 2011 Cochrane review which predominantly explored breathing exercises for airway clearance. This updates the evidence in which there has been a large increase in airway clearance device research. It adds the exploration of symptoms and quality of life. This systematic review strengthens the NICE guidance which suggests the consideration of airway clearance devices in patients with persistent secretions. However, this review does not support the recommendation of airway clearance devices in patients during an acute exacerbation of COPD.

Current evidence of the HFAO device explores healthy volunteers only and therefore this initiates the evidence into to the COPD literature. The results seen in healthy volunteers were greater in the sham group that the HFAO group however the authors attribute this to the ineffectiveness of the sham. The sham used in the young healthy volunteers' study differs to the one seen in this work and was developed with this in mind. The young healthy volunteers had an improvement of 2.4cm$H_2O$ in the $PI_{max}$, which is slightly smaller than what was seen in the COPD population. As expected, those with COPD have a reduced baseline $PI_{max}$ and therefore you may expect a larger increase in response to treatment. This is because the HFAO devices offers flow resistance which has an upper limit of resistance that would not meet 30% of healthy volunteers baseline maximum and as a result there is a ceiling effect. There is a large body of evidence for the use of inspiratory muscle training devices which is already conflicting. The body of evidence for combined respiratory muscle training is much smaller and this study is comparable to other research that did not demonstrate improvements in health-related quality of life[118].

The use of the LCI in patients with COPD has been previously demonstrated to be repeatable over a short time period and an $SF_6$ washout was recommended[90]. This research adds to the currently small body of literature of the LCI in patients with COPD. The repeatability is sustained at a longer follow up of eight weeks and offers potential as an outcome measure for further research. The use of the LCI in response the therapy has been explored in response the Ivacaftor in Cystic Fibrosis and in response to airway clearance in patients with bronchiectasis[89, 191]. The response of the LCI is larger in patients with Cystic Fibrosis in response to Ivacaftor in comparison to seen in this research$_{191}$. The use of the LCI in bronchiectasis was difficult to interpret due to the poor repeatability as a result of excessive coughing in the patient population. The LCI worsened in response to airway clearance techniques for patients with bronchiectasis which is comparable to what is seen in this research[89]. These changes were relatively small and not significant between group. The $S_{cond}$ and $S_{acin}$ are seldom reported in the literature however this research has demonstrated that it may offer additional value in the assessment of small airway changes. This offers a theoretical explanation as to why the LCI worsened in response to an

intervention. This research contributes to a currently small body of evidence for the LCI in response to treatment, which previously has not been explored in patients with COPD.

## 7.5 Future work

The positive results from the systematic review conducted in this thesis supports future work to explore the implementation of airway clearance devices in patients with stable COPD. As this work demonstrates the effectiveness of airway clearance devices in managing exacerbations at 30 days and 6 months, improved symptoms and enhance sputum clearance. Further work should make every attempt to reduce bias and therefore should be double blinded and sham controlled. The addition of the LCI as measured by the MBW test would add to the current evidence base in airway clearance, and the addition of sputum weight would be a useful supplement to this work. As the provision of devices in the UK is poor, an economic cost analysis would be beneficial to further support the case for its use.

The evidence synthesised in the systematic review for airway clearance devices for patients experiencing an exacerbation of COPD is sparse and therefore further trials exploring the impact of devices on the management of acute exacerbations would be beneficial. Additionally, comparisons of devices may provide added value. This can be categorised as positive expiratory pressure devices, oscillating positive expiratory pressure devices, and chest wall vibrations. This work would be supplemented by the addition of qualitative research to understand the patient's perception of using devices for airway clearance.

Further research into the HFAO device is crucial. From what was found in this thesis, those experiencing frequent exacerbations (2 or more a year) may have an additional benefit. Similarly, the use on patients who are experiencing an exacerbation would be useful. The feasibility of recruiting those with an acute exacerbation is not known and considerations to timing and duration of the intervention would be necessary. It is likely that recruitment rate and compliance would be lower with a higher attrition rate and therefore sample size

calculations should accommodate this. Device studies for airway clearance have recruited patients as an inpatient in a “real world study” which demonstrates improvements in all-cause mortality and readmission. However this was for participants following cardiothoracic or abdominal surgery and had a low recruitment rate[203]. Therefore, the calculated sample size should account for expected inflated attrition and recruitment rates.

The use of the MDP has offered valuable insight into the management of dyspnoea which has not previously been explored. The use of this measure would be useful in other interventional studies aimed at treating and managing dyspnoea. It would be useful to understand its response pulmonary rehabilitation and response to other common treatment modalities. For a deeper understanding and interpretation of these results, an exploration of the differences of dyspnoea between disease population (such as asthma, interstitial lung disease, Cystic Fibrosis etc.), and stages of their disease (acute, mild, severe, very severe etc.). Research should prioritise the calculation of a minimal clinically important difference in order to assist in the interpretation of results.

Further research into the LCI is vital in order to assist in the understanding of the impact physiotherapeutic treatments, specifically airway clearance techniques, are having on lung physiology. Whilst this research demonstrated the $LCI_{1/20th}$ was feasible and repeatable, this was calculated in the analysis phase and therefore would require testing in vivo. This research demonstrated the repeatability of the LCI in stable COPD and therefore this would need to be tested in patients during an acute exacerbation. As recommendations suggest airway clearance devices for patients during an acute exacerbation of COPD further research that utilises a sham and the LCI, $S_{cond}$ and $S_{acin}$ would be of clinical interest. As sputum is produced in the conducting zone and often pools or blocks the acinar zones, the assessment of $S_{cond}$ and $S_{acin}$ are vital in the assessment of sputum clearance[195]. Other airway clearance techniques such as manual therapies (I.e. percussions and vibrations) and High Frequency Chest Wall Oscillations may also improve clearance and LCI measurements in the short and long term. Additionally, the use of the LCI, $S_{cond}$ and $S_{acin}$ in response to

airway clearance therapies would be useful in other disease populations where sputum clearance is a hallmark of treatment such as Cystic Fibrosis and Bronchiectasis. It would be useful to understand the correlations between the LCI and sputum volume, though this would be a labour-intensive study.

In general, there should be a larger focus on non-medical management of dyspnoea which can extend from physical techniques to psychological interventions. It is important to research ways to reduce dyspnoea but also how to cope with persistent dyspnoea. These interventions can be targeted at a variety of respiratory conditions and across various severities. However, researchers should be mindful of the burden of treatment and this balance may require the attention of researchers.

# 8 Appendices

## Appendix 1

## Benchmark report provided by Kings College London, further data.

Summary report provided by Dr Caroline Jolley on behalf of Kings College London.

**Summary report for Actegy 100913**

**Dr Caroline Jolley, King's College London**

**Bench testing of PEP devices:**

1. Aerosure Medic (PEP mode i.e. low frequency setting) x 3 devices, 5 runs per device at each flow rate

2. Flutter at 0-degree tilt and 30-degree tilt x 3 devices, 5 runs per device at each flow rate

3. Acapella Blue ("A Blue") at low, mid and high resistance x 3 devices, 5 runs per device at each flow rate

4. Acapella Green ("A Green") at low, mid and high resistance x 3 devices, 5 runs per device at each flow rate

All devices were tested at 10L/min, 20 L/min and 30 L/min (data collected at 50L/min subsequently excluded as out of operating range of Flutter and Acapella; Acapella Blue tested at 10L/min and 20L/min as not intended for use by patients who can generate flow rates above 15L/min).

**Analysis**

The following variables have been reported for each device:

1. Oscillation frequency (Hz)

2. Max-min pressure per oscillation ($cmH_2O$) i.e. the amplitude of each oscillation produced

3. Mean pressure per oscillation ($cmH_2O$)

4. Peak pressure per oscillation ($cmH_2O$)

**Data selection**

Each "run" was at least 4 seconds long, and the final complete 1 second of recorded data was used for analysis.

**Statistical analysis and data presentation**

Data from the three devices were pooled at each flow rate. The mean, standard deviation (SD), and standard error of the mean (SEM) for each variable recorded at each flow rate were calculated. The only exception to this was Acapella Blue low resistance at 10L/min: one of the devices did not oscillate and so data from the remaining two devices only are included for this flow rate.

**Summary of results**

Table 1 summarises data collected at 10L/min.

Table 2 summarises data collected at 20L/min

Table 3 summarises data collected at 30L/min.

Data in the tables are presented as mean, standard deviation (SD), number of oscillations analysed (n) and the standard error of the mean (SEM).

Following these tables are plots of the mean (SD) of oscillation frequency, max-min pressure per oscillation, mean pressure per oscillation and peak pressure per oscillation.

The matrices following these plots indicate whether the values recorded using the Medic devices fall within the range (mean+/-SD) * of values recorded using the other PEP devices for each variable analysed. *(*please indicate what statistical criteria you would like to be used for equivalence).*

It was noted that for the Aerosure Medic devices, the oscillation waveform was not sinusoidal, with additional oscillations superimposed at peak pressures.

**Conclusion**

Although the operating characteristics of the Aerosure Medic devices were not wholly equivalent to any one device at specific flow rates, across the range of flow rates 10-30L/min, Aerosure Medic used in low f PEP mode operated within the range of oscillation frequency, oscillation max-min pressure, mean oscillation pressure and peak oscillation pressure produced by the Flutter, Acapella Blue and Acapella Green PEP devices.

Table 1: 10L/min

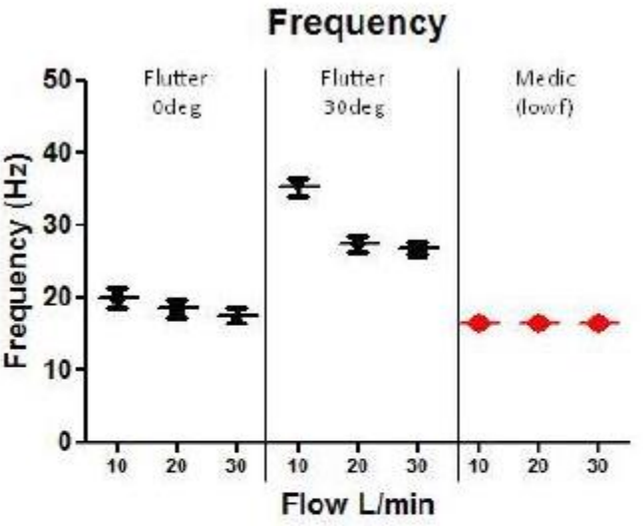
| Frequency (Hz) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 19.81 | 35.21 | 15.08 | 14.00 | 14.15 | 8.93 | 8.45 | 16.34 | 16.42 |
| SD | 1.27 | 1.28 | 0.73 | 0.37 | 0.61 | 0.46 | 0.91 | 1.88 | 0.22 |
| n | 297 | 348 | 151 | 206 | 212 | 133 | 118 | 241 | 248 |
| SEM | 0.07 | 0.07 | 0.06 | 0.03 | 0.04 | 0.04 | 0.08 | 0.12 | 0.01 |
| | | | | | | | | | |
| **Max-min P (cmH2O)** | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 17.03 | 18.76 | 17.68 | 19.43 | 21.04 | 13.65 | 16.60 | 18.28 | 11.83 |
| SD | 1.24 | 3.26 | 2.37 | 1.16 | 4.80 | 1.09 | 2.49 | 3.54 | 1.37 |
| n | 300 | 348 | 153 | 211 | 216 | 138 | 123 | 243 | 248 |
| SEM | 0.07 | 0.17 | 0.19 | 0.08 | 0.33 | 0.09 | 0.22 | 0.23 | 0.09 |
| | | | | | | | | | |
| **Mean P (cmH2O)** | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 8.87 | 14.40 | 7.04 | 7.53 | 9.36 | 2.82 | 2.97 | 7.13 | 4.79 |
| SD | 1.33 | 0.87 | 0.31 | 0.42 | 0.59 | 0.26 | 0.44 | 0.80 | 0.44 |
| n | 300 | 348 | 153 | 211 | 216 | 138 | 123 | 243 | 248 |
| SEM | 0.08 | 0.05 | 0.03 | 0.03 | 0.04 | 0.02 | 0.04 | 0.05 | 0.03 |
| | | | | | | | | | |
| **Peak P (cmH2O)** | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 19.79 | 24.23 | 18.21 | 20.60 | 22.89 | 13.43 | 16.33 | 19.71 | 8.73 |
| SD | 0.76 | 1.80 | 1.12 | 0.39 | 3.38 | 0.81 | 1.68 | 1.90 | 1.17 |
| n | 300 | 348 | 153 | 211 | 216 | 138 | 123 | 243 | 248 |
| SEM | 0.04 | 0.10 | 0.09 | 0.03 | 0.23 | 0.07 | 0.15 | 0.12 | 0.07 |

Table 2: 20L/min

| Frequency (Hz) | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 18.50 | 27.38 | 17.86 | 18.50 | 22.18 | 9.64 | 11.15 | 12.56 | 16.39 |
| SD | 1.27 | 1.13 | 1.83 | 1.35 | 1.24 | 0.60 | 0.44 | 1.15 | 0.20 |
| n | 278 | 272 | 246 | 274 | 327 | 143 | 165 | 190 | 248 |
| SEM | 0.08 | 0.07 | 0.12 | 0.08 | 0.07 | 0.05 | 0.03 | 0.08 | 0.01 |
| | | | | | | | | | |
| Max-min P ($cmH_2O$) | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 35.50 | 28.44 | 12.69 | 21.47 | 25.98 | 19.09 | 26.87 | 33.98 | 28.13 |
| SD | 1.68 | 5.26 | 5.51 | 1.82 | 3.76 | 1.65 | 1.65 | 3.10 | 3.08 |
| n | 278 | 272 | 247 | 275 | 330 | 147 | 166 | 191 | 248 |
| SEM | 0.10 | 0.32 | 0.35 | 0.11 | 0.21 | 0.14 | 0.13 | 0.22 | 0.20 |
| | | | | | | | | | |
| Mean P ($cmH_2O$) | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 9.78 | 15.41 | 13.93 | 16.10 | 22.70 | 5.28 | 6.77 | 8.76 | 11.57 |
| SD | 0.91 | 1.40 | 1.57 | 1.57 | 1.15 | 0.34 | 0.37 | 0.98 | 1.23 |
| n | 278 | 272 | 247 | 275 | 330 | 147 | 166 | 191 | 248 |
| SEM | 0.05 | 0.09 | 0.10 | 0.09 | 0.06 | 0.03 | 0.03 | 0.07 | 0.08 |
| | | | | | | | | | |
| Peak P ($cmH_2O$) | | | | | | | | | |
| | Flutter 0deg | Flutter 30deg | A blue low | A blue mid | A blue high | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 33.73 | 31.74 | 21.46 | 29.24 | 37.63 | 19.93 | 26.91 | 34.59 | 20.72 |
| SD | 1.30 | 3.91 | 4.55 | 1.94 | 2.09 | 1.34 | 0.79 | 1.25 | 2.66 |
| n | 278 | 272 | 247 | 275 | 330 | 147 | 166 | 191 | 248 |
| SEM | 0.08 | 0.24 | 0.29 | 0.12 | 0.11 | 0.11 | 0.06 | 0.09 | 0.17 |

Table 3: 30L/min

| Frequency (Hz) | | | | | | |
|---|---|---|---|---|---|---|
| | Flutter 0deg | Flutter 30deg | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 17.42 | 26.74 | 17.48 | 29.06 | 25.30 | 16.37 |
| SD | 1.04 | 0.91 | 4.18 | 13.61 | 4.70 | 0.22 |
| n | 257 | 268 | 265 | 449 | 364 | 243 |
| SEM | 0.06 | 0.06 | 0.26 | 0.64 | 0.25 | 0.01 |
| | | | | | | |
| Max-min P ($cmH_2O$) | | | | | | |
| | Flutter 0deg | Flutter 30deg | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 46.51 | 39.70 | 5.84 | 11.05 | 25.10 | 47.41 |
| SD | 3.55 | 5.87 | 2.79 | 4.39 | 11.64 | 5.03 |
| n | 257 | 268 | 266 | 449 | 365 | 244 |
| SEM | 0.22 | 0.36 | 0.17 | 0.21 | 0.61 | 0.32 |
| | | | | | | |
| Mean P ($cmH_2O$) | | | | | | |
| | Flutter 0deg | Flutter 30deg | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 10.48 | 16.49 | 13.72 | 29.01 | 22.70 | 20.13 |
| SD | 0.75 | 1.87 | 0.69 | 18.82 | 4.03 | 2.04 |
| n | 257 | 268 | 266 | 449 | 365 | 244 |
| SEM | 0.05 | 0.11 | 0.04 | 0.89 | 0.21 | 0.13 |
| | | | | | | |
| Peak P ($cmH_2O$) | | | | | | |
| | Flutter 0deg | Flutter 30deg | A green low | A green mid | A green high | Medic lowf PEP |
| mean | 43.05 | 40.75 | 16.86 | 35.11 | 38.01 | 35.57 |
| SD | 3.11 | 5.03 | 1.86 | 18.18 | 5.11 | 4.67 |
| n | 257 | 268 | 266 | 449 | 365 | 244 |
| SEM | 0.19 | 0.31 | 0.11 | 0.86 | 0.27 | 0.30 |


Frequency
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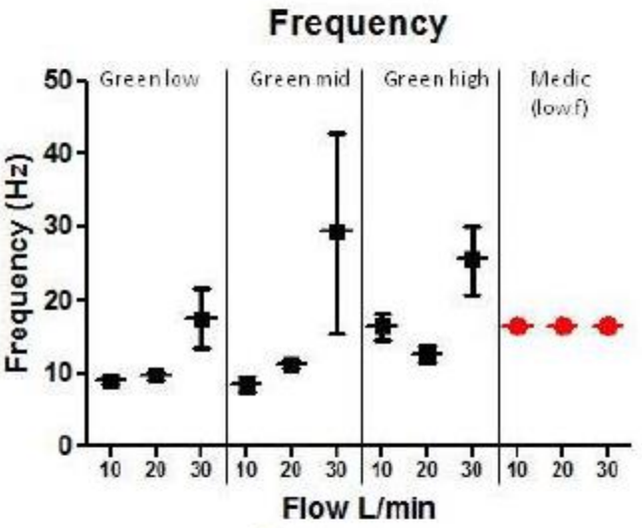
Flutter 30deg
Medic (low f)
Frequency (Hz)
0
10
20
30
40
50
10 20 30 10 20 30 10 20 30
Flow L/min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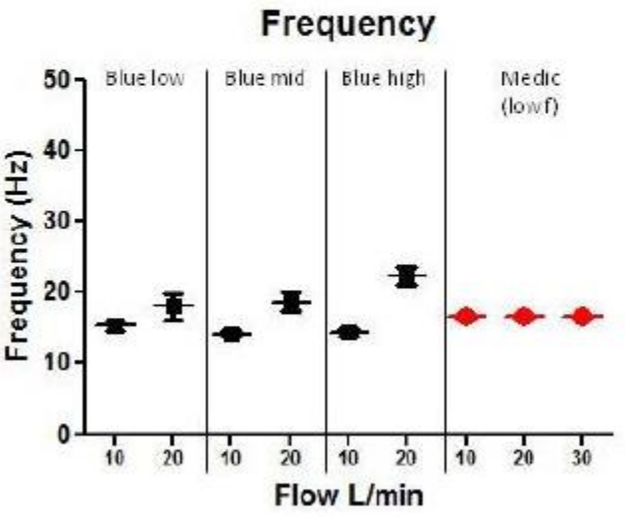
Frequency
Blue low
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Medic (low f)
Frequency (Hz)
0
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40
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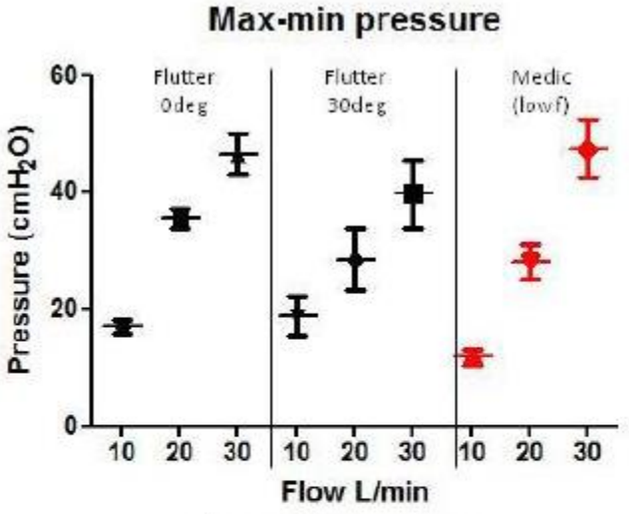
10 20 10 20 10 20 10 20 30
Flow L/min


Max-min pressure
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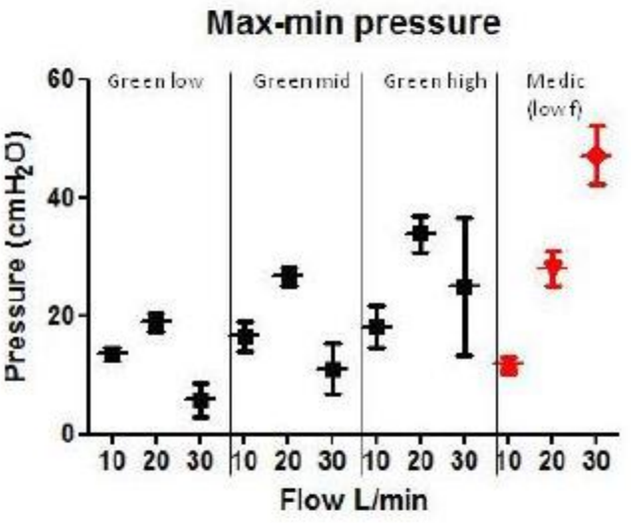
Max-min pressure
Green low
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Medic (low f)
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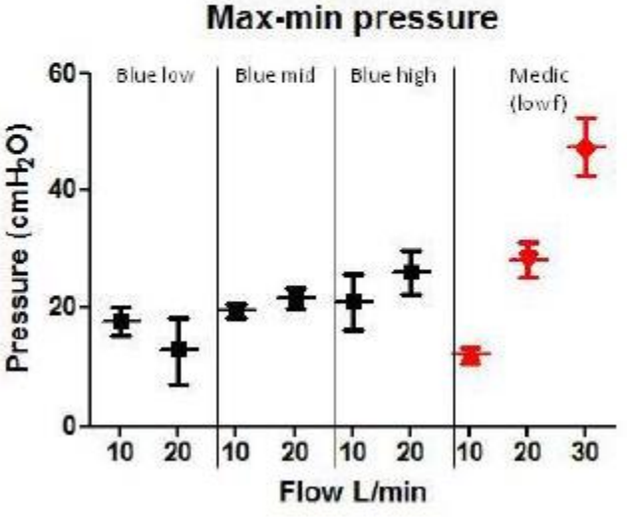
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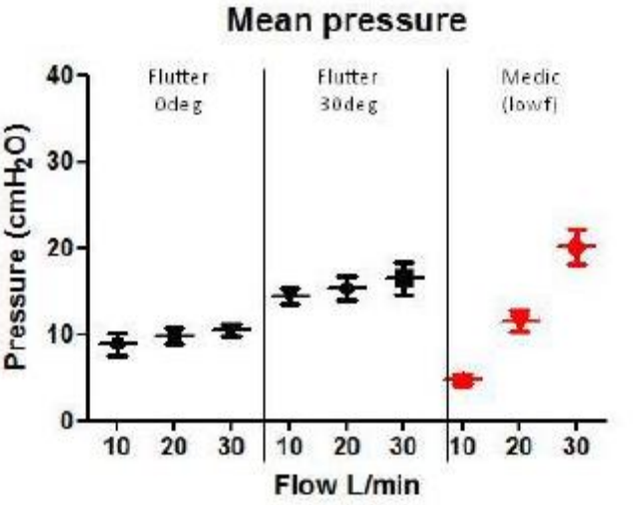
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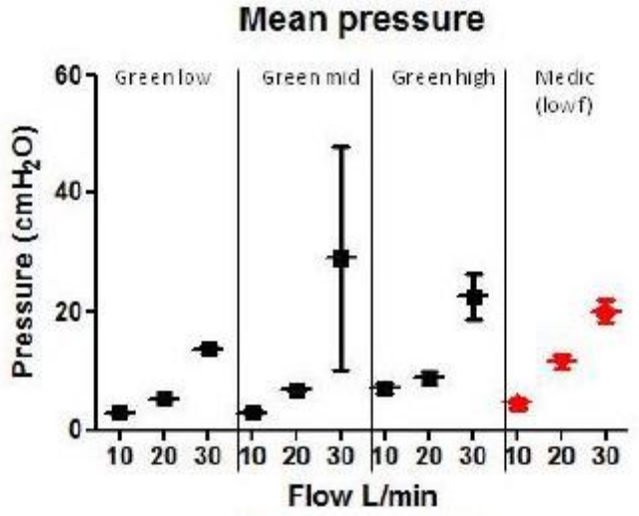
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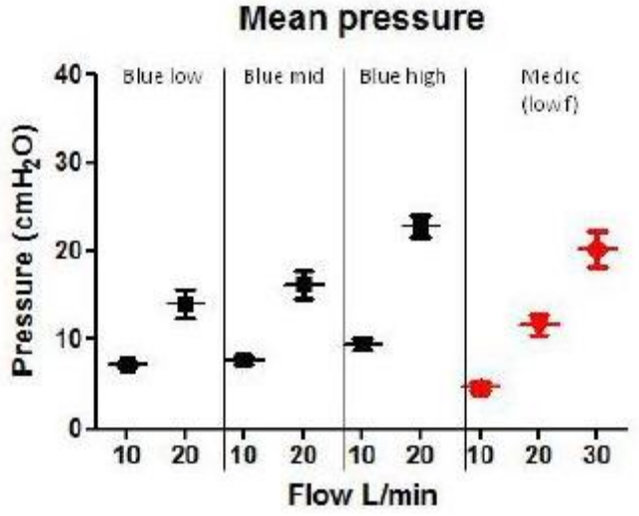
Mean pressure
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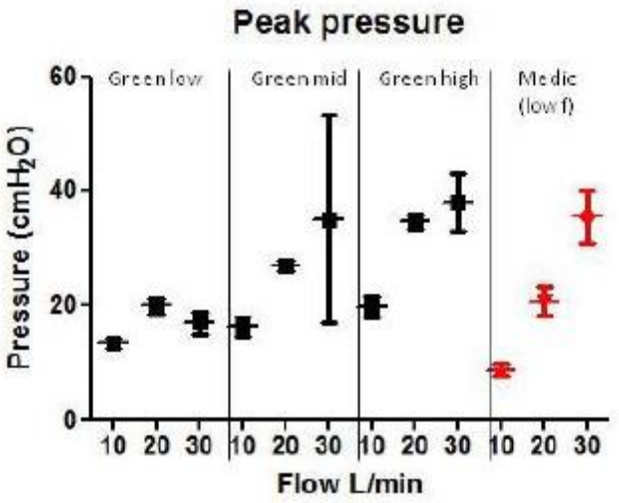
Peak pressure
Green low
Green mid
Green high
Medic (low f)
Pressure (cmH2O)
60
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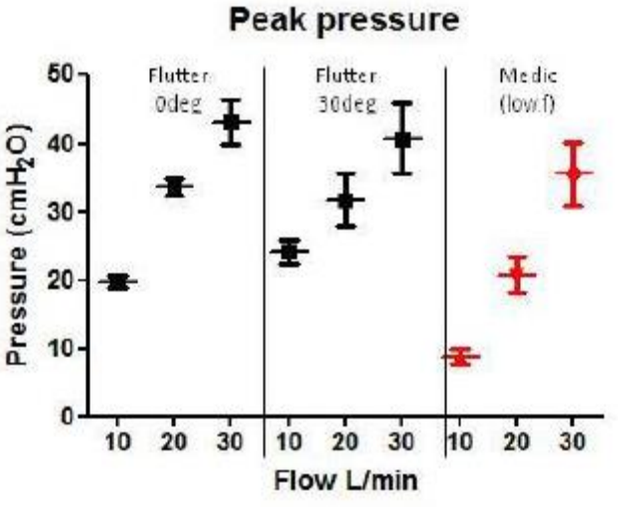
Flow L/min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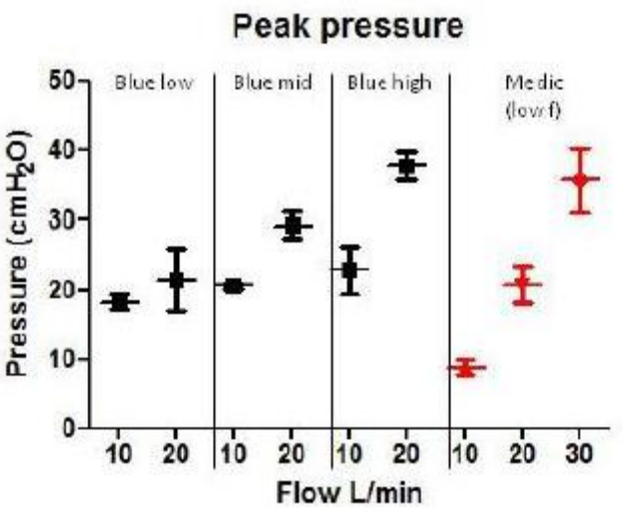
Peak pressure
Blue low
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Blue high
Medic (low f)
Pressure (cmH2O)
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Flow L/min

| Matrix 1: Medic low f vs other PEP devices: Oscillation frequency. "Y" indicates in range | | | |
|---|---|---|---|
| Flow rate L/min | 10 | 20 | 30 |
| Flutter 0 degree tilt | Y | Y | |
| Flutter 30 degree tilt | | | |
| Blue low resistance | Y | Y | |
| Blue mid resistance | Y | Y | |
| Blue high resistance | Y | | |
| Green low resistance | | | Y |
| Green mid resistance | | | |
| Green high resistance | Y | | |

| Matrix 2: Max-min pressure per oscillation | | | |
|---|---|---|---|
| Flow rate L/min | 10 | 20 | 30 |
| Flutter 0 degree tilt | | | Y |
| Flutter 30 degree tilt | | Y | Y |
| Blue low resistance | | | |
| Blue mid resistance | | | |
| Blue high resistance | | Y | |
| Green low resistance | Y | | |
| Green mid resistance | | Y | |
| Green high resistance | | Y | |

| Matrix 3: Mean pressure per oscillation | | | |
|---|---|---|---|
| Flow rate L/min | 10 | 20 | 30 |
| Flutter 0 degree tilt | | Y | |
| Flutter 30 degree tilt | | | Y |
| Blue low resistance | | Y | |
| Blue mid resistance | | | |
| Blue high resistance | | | |
| Green low resistance | Y | | |
| Green mid resistance | Y | | Y |
| Green high resistance | | Y | Y |

| Matrix 4: Peak pressure per oscillation | | | |
|---|---|---|---|
| Flow rate L/min | 10 | 20 | 30 |
| Flutter 0 degree tilt | | | Y |
| Flutter 30 degree tilt | | | Y |
| Blue low resistance | | Y | |
| Blue mid resistance | | | |
| Blue high resistance | | | |
| Green low resistance | | Y | |
| Green mid resistance | | | Y |
| Green high resistance | | | Y |

# Appendix 2

# Protocol for TIDe

ERJ open research

STUDY PROTOCOL
COPD

# A randomised controlled trial to investigate the use of high-frequency airway oscillations as training to improve dyspnoea in COPD

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ABSTRACT

**Introduction:** Chronic obstructive pulmonary disease (COPD) is characterised by expiratory flow limitation resulting in symptomatic dyspnoea, sputum retention and ventilation heterogeneity. Changes in breathing mechanics affect the ability of respiratory muscles to respond to the ventilatory demands, increasing the sensation of dyspnoea. A high-frequency airway oscillating device has been developed to combine respiratory muscle training and oscillations to improve dyspnoea and sputum retention within COPD.

**Methods and analysis:** Patients with symptomatic COPD (Medical Research Council Breathlessness scale grade ⩾2) will be recruited to a double-blind, randomised, sham-controlled trial. Both groups will follow an 8-week intervention phase using the device three times per day for 5 min at a time. This will be recorded in a self-reported diary. The device applies a flow resistive load and oscillations for combined training. Those receiving the sham device will follow the same protocol; however, the mechanism of action will be removed from the device. Improvements in the Chronic Respiratory Questionnaire-Dyspnoea domain will be the primary outcome measure. Secondary outcomes will explore respiratory muscle function, health-related quality of life, exercise capacity and physical activity. The Lung Clearance Index will be an exploratory outcome. Outcomes will be explored using the most appropriate statistical test, dependent on the sample distribution. Focus groups will be an exploratory outcome and analysed by thematic analysis.

**Ethics and dissemination:** Ethical approval has been obtained from the East Midlands-Leicester South Research Ethics Committee and the trial has been registered through the ISRCTN Registry. The study results will be disseminated to the appropriate stakeholders through presentations, conferences and peer-reviewed journals.

@ERSpublications
**A double-blind, placebo-controlled, randomised trial investigating the effects of high-frequency airway oscillations on dyspnoea, sputum, quality of life and exercise capacity in #COPD.** http://bit.ly/2F8bQ6s

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This study is registered at www.isrctn.com with identifier number ISRCTN45695543. All individual participant data collected during the trial after de-identification will be available on request by researchers who provide a methodologically sound protocol.

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## Introduction

Chronic obstructive pulmonary disease (COPD) is characterised by expiratory flow limitation that results in excessive dyspnoea, reduced exercise tolerance and reduced health-related quality of life. Dyspnoea is a multidimensional symptom with many mechanisms contributing to the perception of dyspnoea. It is known that respiratory muscle dysfunction can contribute to dyspnoea and that this may be a result of the inability of respiratory muscles to meet the demands of the mechanical load and capacity, leading to respiratory muscle dysfunction and an increased sensation of dyspnoea [1]. Persistent and recurrent dyspnoea impacts activity levels and the ability of patients to perform activities of daily living, which impacts quality of life. Respiratory muscle training can be used to address this mechanism of dyspnoea. Research primarily explores the use of inspiratory muscle training in COPD, demonstrating improvements in inspiratory muscle strength and endurance, functional exercise capacity, and health-related quality of life when compared with a control group [2]. These improvements appear meaningful in terms of quality of life, dyspnoea and muscle strength [3].

Combined inspiratory and expiratory respiratory muscle training is an additional technique for the management of dyspnoea; however, this technique is used much less frequently. This may be due to the opinion that patients with COPD do not demonstrate expiratory muscle weakness, although it has been suggested that up to 50% of patients with moderate to severe COPD exhibit expiratory muscle weakness in parallel with inspiratory muscle weakness [4]. Inspiratory muscle weakness is defined by a maximal inspiratory pressure generating capacity of $\leqslant$60 $cmH_2O$. This value has some limitations in that it is not adjusted for age, height and weight. The values for expiratory muscle weakness are not definitive. Evans and Whitelaw [5] present a calculation that may be useful in identifying patients who demonstrate expiratory muscle weakness; however, lack of consensus on expiratory muscle weakness definitions limits targeted therapy [6]. Percentages of predicted values can be calculated for both inspiratory and expiratory muscle strength based of the Evans and Whitelaw [5] formula. There is a small evidence base for combined respiratory muscle training; however, it has been demonstrated to improve respiratory muscle strength and endurance, with an increase in 6-min walk distance when compared with inspiratory muscle training alone [7]. The mechanism and effectiveness of combined respiratory muscle training are not fully accepted as a treatment strategy for patients with COPD. The Joint American College of Chest Physicians/American Association for Cardiovascular and Pulmonary Rehabilitation Committee declared that a stimulus or load applied to the respiratory muscles during training is sufficient to augment respiratory muscle strength training and is associated with increased exercise capacity and decreased dyspnoea [8]. However, this is not included in the National Institute for Clinical Excellence guidelines due to disparity in the research [6, 8].

Sputum retention is commonly reported alongside dyspnoea as an unsettling symptom for patients with COPD. Additional therapy is available for the management of sputum retention, and can include manual therapies, breathing exercises and devices as an adjunct [9]. Management of sputum has been demonstrated to reduce hospital admissions, need for ventilatory assistance and quality of life through various methods of sputum clearance, including manual therapies, breathing exercises and positive expiratory pressure devices in patients with COPD [10]. The use of devices has a smaller evidence base compared with other techniques. This is even more limited within COPD management; however, oscillatory devices aim to break down the enzymes in the sputum and vibrate the secretions of the chest wall, making them easier to clear. There is a disparity in the current literature base due to the inability to reliably capture sputum clearance. Sputum wet and dry weight measurements are labour intensive and difficult to translate into meaningful results. Patient-reported outcome measures may provide some insight into the impact of sputum, but this can be variable. Therefore, we propose the use of the Lung Clearance Index (LCI) as a surrogate measure of sputum clearance.

The LCI has been used in cystic fibrosis, paediatrics and early lung disease, and has been identified as more sensitive than conventional spirometry and is responsive to inhaled treatment [11]. The LCI is calculated *via* a multiple breath washout system using an inert gas and is determined by the cumulative exhaled volume divided by the functional residual capacity. This technique gives insight into the unevenness of ventilation due to pathological changes in lung structure. Ventilation heterogeneity assesses the gas mixing properties of the lungs, which are known to be affected in COPD. Other measures of the multiple breath washout provide further insight into large and small airways disease. Sputum plugging can occur at different anatomical levels within both the large and small airways, and therefore phase 3 slope analysis gives insight into the ventilation heterogeneity in the conducting ($S_{cond}$) and acinar ($S_{acin}$) airways, respectively. It is plausible that an improvement in sputum clearance could impact the gas mixing properties and therefore impact on the LCI. The LCI is repeatable over short and long time periods (up to 8 weeks) in a cohort of COPD patients; however, its response to therapy is yet to be explored [12–14].

The Aerosure Medic is a dual-function device for dyspnoea management and secretion clearance. It is a high-frequency airway oscillation (HFAO) device that offers flow resistance to inspiration and expiration in order to provide respiratory muscle training with the aim to reduce dyspnoea and improve breathing

efficiency [15]. The device also offers oscillations for mucociliary clearance on inspiration and expiration that may contribute to improved quality of life and reduction of dyspnoea by addressing airflow obstruction [15]. This device is commercially available for patients; however, there are limited data on its clinical effectiveness. A feasibility study was conducted prior to the proposed randomised controlled trial in order to further understand the mechanism of action and effect on symptoms, quality of life and study procedures [15]. The study recruited 24 participants, and the results demonstrated its feasibility with high recruitment rate, compliance and low attrition. Trends were noted in improving dyspnoea, respiratory muscle strength and health-related quality of life. The trial protocol was deemed appropriate and the training intervention was manageable, and therefore the results of the feasibility study encouraged a clinical effectiveness trial.

The objectives for the clinical effectiveness trial are: 1) to determine the effects of a HFAO device on dyspnoea, lung function, health-related quality of life, exercise capacity and physical activity in participants with COPD when compared with a sham device; 2) to explore if there is a subgroup of patients who receive the most benefit from this therapy; 3) to explore the LCI and other measures of multiple breath washout as a measure of sputum clearance in participants with COPD and its response to an intervention; 4) to explore the impact of oscillatory positive expiratory pressure on the LCI; and 5) to explore patients' experience and beliefs of using a device for the management of COPD.

## Methods and analysis

This is a double-blind, randomised controlled trial comparing a HFAO device with a sham device. The trial is registered with the ISRCTN Registry (identifier ISRCTN45695543) and has been adopted onto the UK National Institute for Health Research (NIHR) Clinical Research Network portfolio.

A flow diagram of the study procedures is shown in figure 1.

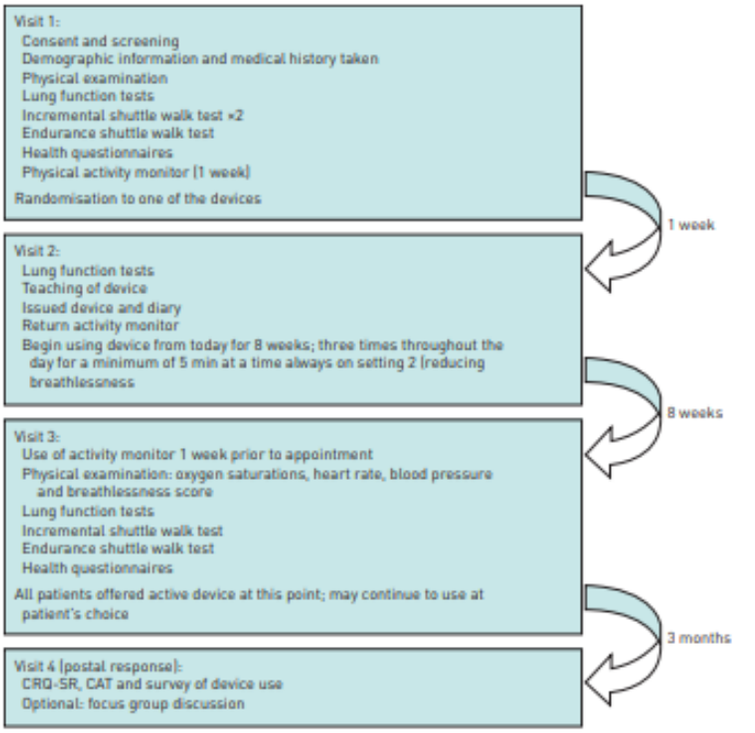


FIGURE 1 Flow diagram of study procedures in patients with symptomatic chronic obstructive pulmonary disease (COPD). CRQ-SR: self-reported Chronic Respiratory Questionnaire; CAT: COPD Assessment Test.

### Participants

Participants are considered eligible if they have an established diagnosis of COPD, confirmed by spirometry as defined by a forced expiratory volume in 1 s/forced vital capacity ratio <0.7 [16]. Participants must also report significant dyspnoea identified on the Medical Research Council Breathlessness scale (grade 2–5) [17]. Participants must be willing to be randomised to either arm of the study. They will be excluded if they have had an exacerbation in the last 4 weeks that required antibiotic or steroid therapy (including hospitalisations), recent or current pneumothorax or haemoptysis, and recent thoracic, gastric or facial surgery, or trauma. Participants must be able to communicate sufficiently well in English in order to provide informed consent.

The sample size was calculated based on a 0.5 point change in the Chronic Respiratory Questionnaire-Dyspnoea domain, with a standard deviation of 0.85 accounting for a type 1 error of 0.05 and 80% powered. This requires a sample size of 94 participants to complete the protocol (n=47 per group). This was inflated by 13% as seen in the previous feasibility study to account for dropout; therefore, we anticipate recruiting 106 participants to the study [15]. The recruitment phase will run for a period of up to 3 years and will be terminated by December 2020 or once adequate power is achieved.

### Setting

Participants in this study will be primarily recruited from research databases at the NIHR Leicester Biomedical Research Centre – Respiratory (Leicester, UK). Participants will also be identified by COPD clinics and Pulmonary Rehabilitation clinics at the University Hospital of Leicester NHS Trust. All potentially suitable participants will receive an invitation letter on behalf of the study team that includes the patient information sheet about the study. Potential participants will be given at least 24 h to review the information and consider their participation in the trial.

### Intervention

This study will compare the Aerosure Medic (a HFAO device) with a sham control device.

The Aerosure Medic was developed by Actegy (Bracknell, UK). It is a battery-operated, dual-action device providing oscillations at either 15 or 25 Hz and flow resistance. The resistance applied ranges from 0 to 50 $cmH_2O$ dependent on the patient's flow rate; however, the specific resistance cannot be set through this device. The device requires participants to inhale and exhale through a mouthpiece deeply for a minimum of 5 min at a time and repeat this three times per day. The oscillation will be performed on the 25 Hz setting. This is comparable to respiratory muscle training literature and is required for a minimum of 6 weeks in order to demonstrate effectiveness. As many of the outcome measures require a 2-week recall, the intervention phase was set at 8 weeks in order to capture changes that may have taken place. Participants will record each session in a self-reported diary and score each session on their perceived exertion based on a 0–10 visual analogue scale. The intervention will be administered by a respiratory physiotherapist and the technique will be checked. Patients will be able to call the research department with any queries or problems with using the device.

The sham device appears identical to the active HFAO; however, the valve is removed and therefore provides no flow resistance or oscillations (figures 2 and 3).

Participants will receive the device intact, and will be instructed on its use and necessary cleaning requirements. Participants will be unaware of the device mechanics, and therefore will be unable to distinguish between the sham and active device. Participants and the outcome assessor will remain blinded to the treatment group. After the 8-week intervention phase each participant will be given the active HFAO device to retain.

Randomisation will be performed using a web-based programme and allocated on a 1:1 ratio (www.sealedenvelope.com). Randomisation will be allocated by an unblinded assessor and concealed from the patient and the outcome assessor.

### Outcomes

The outcomes measures will be administered at baseline prior to commencement of the intervention phase. All outcome measures will be repeated 8 weeks later. Upon completion of the follow-up, all participants will be issued the HFAO device to use according to their own requirements. At 3 months after their final visit, participants will receive a postal follow-up that will consist of the self-reported Chronic Respiratory Questionnaire (CRQ-SR) and the COPD Assessment Test (CAT) alongside a form to collect average device use. Outcomes will explore lung function, health-related quality of life, exercise capacity and physical activity.

FIGURE 2 Top (left to right): Aerosure Medic active device, and device aerosol head anterior and inferior views. Bottom (left to right): Aerosure Medic sham device, and device aerosol head anterior and inferior views. Note mechanism removed from sham device.

*Primary outcome*

The primary outcome measure is the CRQ-SR dyspnoea domain administered at baseline, after the 8-week intervention phase and 3 months after the intervention phase [18]. The primary end-point is after the 8-week intervention phase.

*Lung function*

Lung function will be assessed by spirometry (Vitalograph ALPHA, Maids Moreton, UK) to confirm diagnosis, performed in line with American Thoracic Society (ATS)/European Respiratory Society (ERS) standards [19]. While it is unlikely that the device will have an impact on spirometry, it will be repeated at follow-up in order to compare with other measurements. Spirometry is to be repeated a minimum of three times and up to seven times where the forced vital capacity falls outside of a 10% variance [16]. The best attempt will be recorded.

Respiratory muscle strength will be assessed on inspiration and expiration. Participants will perform this test from residual volume or full vital capacity for inspiratory and expiratory pressures, respectively. Patients will be instructed to inhale/exhale forcefully and sustain this for 2 s. This is to be repeated a minimum of four times and up to seven attempts if participants continue to improve [20]. The measured best will be recorded. Participants will be considered to exhibit inspiratory muscle weakness if the results are <60 $cmH_2O$. Predicted values will be calculated for both inspiratory and expiratory pressures. Planned subgroup analysis will be performed on those who demonstrate inspiratory muscle weakness based on a cut-off of 60 $cmH_2O$.

*Health-related quality of life*

Participants will complete questionnaires on their perceived health status and health-related quality of life. These will be completed independently with a researcher on hand to resolve any difficulties. The CRQ-SR,

FIGURE 3 Patient using the Aerosure Medic.

CAT, Leicester Cough Questionnaire, London Chest Activity of Daily Living questionnaire, Multidimensional Dyspnoea Profile, and Hospital Anxiety and Depression Scale will be used [18, 21–24]. All questionnaires will be scored individually and repeated at follow-up (8 weeks). The CRQ-SR and CAT will be repeated *via* a postal follow-up 3 months post-completion of the intervention phase. These two questionnaires and a survey asking about device use will be administered 3 months post-intervention phase to understand the long-term benefits of using the device. A subgroup analysis of "sputum producers" and "non-sputum producers" as stratified by the CAT sputum score will be explored.

### *Exercise capacity*

Exercise capacity will be measured by the incremental shuttle walk test (ISWT) and the endurance shuttle walk test (ESWT) [25, 26]. These are standardised and validated tests of maximal performance. Each participant will perform a familiarisation of the ISWT on visit 1 which is to be repeated after adequate rest, this will be at least 30 min and will require participant's baseline measurements to return to their pre-exercised state (blood pressure, oxygen saturations, heart rate and Borg breathlessness). The maximum distance performed on the ISWT will be used to calculate the appropriate speed for the ESWT, walking at 85% maximum. Both the ISWT and ESWT will be performed at baseline and follow-up post-intervention phase, and in line with ERS/ATS standards [27].

### *Physical activity*

Physical activity is an exploratory outcome and participants will be required to wear an ActiGraph GT3X activity monitor (ActiGraph, Pensacola, FL, USA) for 1 week prior to randomisation and 1 week before visit 3 at the end of the intervention phase. The ActiGraph GT3X is to be worn around the waist, above the right hip, for 7 days and nights to the participant's tolerance. The ActiGraph GT3X is not to be worn during water-based activities. Data collected will be analysed using ActiLife software (ActiGraph).

### *Ventilation heterogeneity*

Ventilation heterogeneity as measured *via* a multiple breath washout will be used as an exploratory outcome. This test is performed using an inert tracer gas (sulphur hexafluoride ($SF_6$)) and measuring the

washout phase. The patient is required to inhale and exhale through the mouthpiece with a nose clip *in situ* at tidal volumes. Initially patients will be breathing $SF_6$ and then this will be disconnected once the desired concentration is achieved, leaving the patient to breathe room air through the mouthpiece until the $SF_6$ gas is washed out to 1/40th of the starting concentration (figure 4). This is performed in triplicate and analysed for the mean of the three tests. Analysis is performed using a customised MATLAB algorithm. Each test must be within 10% functional residual capacity (FRC) to be included in the analysis. In the event one test is outside of this variance, the two remaining tests will be used [28, 29]. This analysis will produce the LCI, functional residual capacity (FRC), $S_{cond}$ and $S_{acin}$. LCI and FRC are calculated as the mean of the eligible tests, and $S_{cond}$ and $S_{acin}$ will be calculated by a pooled slope analysis of the eligible tests using an automated MATLAB algorithm for phase 3 slope identification. This measure will be used to explore the impact of sputum clearance on ventilation heterogeneity and may provide clinical insight into the physiological implications of sputum retention. Each participant will perform this test at baseline and following the intervention phase.

### *Compliance*

Compliance to the intervention will be analysed by a self-reported diary. Participants will complete the diary daily alongside the device use. This will record the duration and frequency of sessions alongside the perceived exertion and any other comments the participant may have. Participants completing ⩾75% of the allocated treatments will be considered compliant [15]. A subgroup analysis will explore the impact of compliance on the results of the study.

### *Qualitative focus groups*

Participants of the randomised control trial will be invited to participate in focus groups after the completion of the trial. This will provide insight into the experiences of using a device for the management of symptoms, which is an area of little research. The aim of the focus groups will be to provide an understanding of the use of the device for the management of COPD. This may also give insight into the compliance of the device during and after the trial. Both the intervention and the sham group will be invited to participate, as from the completion of the study all groups will be given an active device to retain. Those who express interest at the time of consent will be invited to participate. We will aim to conduct a minimum of two focus groups with around 5–10 participants per group. The topic of discussion has been developed with an experienced qualitative researcher and members of the Centre of

FIGURE 4 Patient performing a multiple breath washout measurement.

Exercise and Rehabilitation Sciences Public and Patient Involvement advisory group. This will explore device use and impact on symptoms as well as patient preferences. The focus groups will be performed by a member of the team not directly involved with the randomised controlled trial, but who has experience in qualitative methods. The focus groups will be conducted in a hospital setting.

### *Data analysis plan*

Baseline characteristics will be described and compared using the appropriate statistical tests (*e.g.* independent t-test, Mann–Whitney test or Chi-squared test). Changes pre- and post-intervention will be described for all of the aforementioned outcome measures, and also at 3 months for CRQ-SR and CAT. Differences between groups will be described, with the primary outcome being CRQ-SR at 8 weeks. Differences between groups will be compared using linear mixed models. Participants will need to complete the primary outcome measure after the intervention phase to be included in the analysis.

Pre-defined subgroup analyses will be performed on: 1) adherent *versus* non-adherent (defined as <75 or ⩾75% self-reported use), 2) those with inspiratory muscle weakness (<60 $cmH_2O$), 3) "sputum producers" *versus* "non-sputum producers" (defined using the CAT subscale) and 4) those with ventilation heterogeneity (defined using the LCI). Further exploratory analyses will be performed on physical activity measures and multiple breath washout measures.

Qualitative focus groups will be recorded with consent and later transcribed. Transcriptions will be analysed using thematic analysis, whereby they will be coded for the development of the main themes [30]. Themes will be checked with the participants involved in the focus groups to ensure the discussion was accurately captured.

## Ethics and dissemination

Ethical approval was gained on the June 7, 2017. The findings from this study will determine the clinical effectiveness of the HFAO device. Results will be disseminated widely to target key audiences, including healthcare professionals working in respiratory care, patients and members of the public, and academics and external organisations. We aim to disseminate nationally and internationally. The dissemination strategy will be developed alongside the Centre of Exercise and Rehabilitation Sciences Patient and Public Involvement advisory group (Glenfield Hospital, Leicester, UK). The results of this study will be presented at appropriate national, international and regional respiratory and physiotherapy conferences. Results will be published in a timely manner and are anticipated to be publically available during 2020.

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Author contributions: All authors co-developed the protocol. The manuscript was prepared by E. Daynes.

Conflict of interest: E. Daynes reports grants from Actegy Ltd during the conduct of the study. N. Greening has nothing to disclose. S. Sidiqqui has nothing to disclose. S. Singh reports grants from Actegy Ltd during the conduct of the study.

Support statement: This work was supported by Actegy Ltd (Bracknell, UK).

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# Appendix 3

# Ethical approvals for feasibility and TIDe study

NHS
Health Research Authority
East Midlands - Leicester South Research Ethics Committee
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

**Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval**

07 June 2017

Professor Sally Singh
Respiratory Biomedical Research Unit
Glenfield Hospital
Groby Road
LE3 9QP

Dear Professor Singh,

| | |
|---|---|
| **Study title:** | **A Randomised Controlled Trial to Investigate the Use of High Frequency Airway Oscillations as Training to Relieve Dyspnoea in COPD.** |
| **REC reference:** | **17/EM/0156** |
| **Protocol number:** | **1** |
| **IRAS project ID:** | **220947** |

Thank you for your letter of 02 June 2017, responding to the Committee's request for further information on the above research and submitting revised documentation.

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

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to make a request to postpone publication, please contact hra.studyregistration@nhs.net outlining the reasons for your request.

**Confirmation of ethical opinion**

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

**Conditions of the favourable opinion**

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

*Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).*

*Guidance on applying for NHS permission for research is available in the Integrated Research Application System, www.hra.nhs.uk or at http://www.rdforum.nhs.uk.*

*Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.*

*For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.*

*Sponsors are not required to notify the Committee of management permissions from host organisations*

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will

be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

**It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).**

**Ethical review of research sites**

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

The Committee has not yet completed any site-specific assessment (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. We will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

**Approved documents**

The final list of documents reviewed and approved by the Committee is as follows:

| *Document* | *Version* | *Date* |
|---|---|---|
| GP/consultant information sheets or letters [GP Letter] | 1 | 09 December 2016 |
| Instructions for use of medical device [Aerosure user manual] | | 07 October 2015 |
| Interview schedules or topic guides for participants [Topics to explore for TIDe study] | 1 | 31 March 2017 |
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| Validated questionnaire [LCADL] | 4 | 02 December 2016 |
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**Statement of compliance**

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

**After ethical review**

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

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

**User Feedback**

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

**HRA Training**

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

| | |
|---|---|
| **17/EM/0156** | **Please quote this number on all correspondence** |

With the Committee's best wishes for the success of this project.

Yours sincerely,

**Mr John Aldridge**
**Chair**

Email:NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *Mrs Carolyn Maloney*

NHS
Health Research Authority
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**Mr John Aldridge**
**Chair**

Email:NRESCommittee.EastMidlands-LeicesterSouth@nhs.net

*Enclosures:* "After ethical review – guidance for researchers"

*Copy to:* *Mrs Carolyn Maloney*

# Appendix 4

# Patient information sheet for feasibility study, LCI repeatability sub study and TIDe

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road
Leicester
LE3 9QP

Tel: 01162502758
Fax: 0116 258 3950

# PATIENT INFORMATION SHEET

***An eight week pilot study to investigate the effect of high-frequency airway oscillation breathlessness in patients with chronic obstructive pulmonary disease***

## *Invitation*

You are being invited to take part in the above research study conducted by the respiratory research team. Prior to agreeing in participating in the research, please take time to read the following information carefully and discuss it with friends, relatives and your Respiratory Consultant if you wish. Ask a member of the research team if you have any questions or if you would like any further information. Take time to decide whether or not you wish to take part. Thank you for reading this information sheet.

## *What is the purpose of this study?*

Patients with Chronic Obstructive Pulmonary Disease (COPD) often experience breathlessness at rest or on exertion. The aim of this study is to investigate whether airflow oscillation (vibration) can assist in the reduction of breathlessness and increase exercise capacity in COPD, alongside sputum clearance. The airflow oscillation will be delivered using a device called Aerosure.

About the device: Aerosure is a small, hand-held, battery-operated device that vibrates air as you breathe in and out through it. It is intended to be used for five minutes daily, then as and when required throughout the day. Although Aerosure is new, devices that vibrate air have been available for many years and are known to be safe. Aerosure is designed for use in your own home. If you require oxygen, Aerosure should be used in a room that is well-ventilated.

This is a pilot study that has been designed to test whether the use of the Aerosure device is a feasible and acceptable device for COPD patients who are suffering with breathlessness.

## *Why have I been chosen?*

We are inviting people with COPD who are suffering with breathlessness and who feel limited by this during daily tasks. To be eligible to take part you must have a confirmed diagnosis of COPD and report episodes of breathlessness which are limiting your walking abilities.

## *Do I have to take part?*

It is your decision whether or not you take part. If you agree to participate you will be given this information sheet to keep and once you have had suitable time (at least 24 hours) to consider your involvement and discuss with your family or GP if necessary you will be asked to sign a consent form. Your participation is voluntary and you may withdraw from the study at any time without giving reason. A decision to withdraw at any time or a decision not to take part will not affect the standard of care you receive. The data collected to the point of withdrawal may still be used.

## *What will happen if I take part?*

A member of the medical research team in the Respiratory Biomedical Research Unit at Glenfield Hospital will contact you to explain the study and invite you to take part. The researcher will re-contact you by telephone to answer any questions you may have, and to ask whether or not you would like to take part. He/she will also arrange a convenient time and date for you to come to the Respiratory Biomedical Research Unit, at Glenfield Hospital for your initial visit. You will have a follow up visit after 8 weeks. During both visits you will be expected to complete the following:

Basic details: The researcher will take your basic details (age, gender, current medication, ethnicity, social situation, employment). Previous medical history will also be discussed. This will only occur on visit one.

Physical examination: The researcher will take the following measurements: height, weight, oxygen saturations, heart rate, blood pressure and breathlessness score. This will occur on visit one and two.

Lung function: You will be required to perform three breathing tests to assess your lung capacity and respiratory muscle strength. The test of lung capacity will only occur on visit one.

Exercise capacity: There are two tests that need to be completed to gauge your exercise tolerance. This will involve walking between two cones at a set pace (recorded as bleeps on CD) until you feel you need to stop. This may take up to 15 minutes dependent on your walking ability. Your breathlessness score will be taken before and after performing the tests and your heart rate and oxygen saturations will be monitored throughout. If you require oxygen then you will be required to use this at your prescribed rate.

Questionnaires: You will be asked to complete some questionnaires regarding your quality of life, anxiety and depression, and symptoms related to your COPD.

Diary: You will be asked to keep a diary of adherence and symptoms daily. The researcher will contact you via telephone at pre-arranged intervals to keep up to date with your progress and allow you to raise any concerns you may have.

Meeting: After participating in the study you will also be invited to a dissemination session. This gives you the opportunity to discuss and feedback about the device and your involvement in the study. This will help us identify areas in which we can improve. This will also give the researchers the opportunity to share the results of the study with you. Refreshments will be provided.

If new information or evidence becomes available regarding the device, you will be informed and you remain the right to withdraw at any time.

## *What are the possible disadvantages and risks?*

There are minimal identified risks to participating in this research. The exercise tests are designed to measure your endurance and you may experience some breathlessness during and after for a small amount of time. There will be no lasting affects following this testing. You will be required to make two visits to hospital, which may be an inconvenience, however we are happy to reimburse travel expenses or provide a taxi where appropriate.

## *What are the possible benefits of taking part?*

Participants involved in the study will be provided with the Aerosure device and manual that will be yours to keep after the study has ended. The information we get from this study may help us to reduce breathlessness in patients with COPD in the future.

## *What if something goes wrong?*

If you have a concern about any aspect of this study, you should call the researchers on the direct line that will do their best to answer your questions during office hours, or alternatively leave a message and someone will return your call (01162502758). There are no special compensation arrangements in the unlikely event that you are harmed through taking part in the research project. If you are harmed due to someone's negligence you may have grounds for legal action but may also have to pay costs for such action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study the normal National Health Service complaints mechanisms would be available to you. Advice can be sought from the Patient Information and Liaison Service (PILS). Their contact number is 08081788337 (available Monday to Friday 10-4) and email address pils.complaints@uhl-tr.nhs.uk

## *Will my taking part be kept confidential?*

Procedures for handling, processing, storage and destruction of your data are compliant with the Data Protection Act 1998. All information which is collected about you during the course of the research will be kept strictly confidential. With your consent we will contact your GP for relevant reports. Only authorised persons will routinely have access to your medical records and personal data. Regulating authorities will have access to data only for the purpose of monitoring the quality of the research and ensuring patient safety. Data will be retained for 5 years within University Hospitals of Leicester NHS Trust, and only non-identifiable data will leave the site and be stored

indefinitely by Actegy Ltd., for regulatory purposes. Data will be electronically stored, securely, in an encrypted format. By signing the consent form, you will acknowledge and authorise these procedures.

## *What if I withdraw from the study?*

If you withdraw from the study, any data already collected may be retained in non- identifiable form and used in the research. In the unlikely event that you become unable to make decisions for yourself whilst taking part in the research ("loss of capacity"), the research team will retain data collected and continue to use it confidentially in connection with the purposes for which you gave consent. You may be withdrawn from the study by the researcher, in this instance you will be given a reason and your GP will be informed.

## *What happens to the results of the study?*

The results of this study will be disseminated in peer and lay journals, professional publications and in presentations at conferences. Results will be reported to respect confidentiality. No identifiable information will be published. All participants will receive a summary of the results and are invited to attend a dissemination discussion in which participants can contribute ideas surrounding the design of the study and results of the study will be shared.

## *Who has reviewed this study?*

All research that involved NHS patients and staff, information from medical records or uses NHS premises must be granted a favourable opinion from the NHS research ethics committee prior to commencement. A favourable opinion does not mean that you will not come into harm during the study, however it means that the committee is satisfied that your rights will be respected and that the risks are reduced to a minimum. This study has been reviewed and given favourable opinion by the National Health Service ethics committee.

## *Who is organising and funding this research?*

This study is sponsored by the University Hospitals of Leicester. This study is being funded by Actegy LTD whom makes the Aerosure device.

## *Contact details for further information:*

For further information please contact:
Professor Sally Singh
Enya Daynes MSc
Centre of Exercise Rehabilitation Science (CERS), University Hospitals of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP.
Tel: 0116 250 2758
E-mail: enya.daynes@uhl-tr.nhs.uk

Thank you very much for considering taking part in this project.

University Hospitals of Leicester NHS
NHS Trust

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Groby Road
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## *What is the purpose of this study?*

Patients with Chronic Obstructive Pulmonary Disease (COPD) often experience breathlessness at rest or on exertion. The aim of this study is to investigate whether airflow oscillation (vibration) can assist in the reduction of breathlessness and increase exercise capacity in COPD, alongside sputum clearance. The airflow oscillation will be delivered using a device called Aerosure.

This is a pilot study that has been designed to test whether the use of the Aerosure device is a feasible and acceptable device for COPD patients who are suffering with breathlessness. We are asking for participants to return for an additional measure that will be used to inform a main randomised control trial.

## *Why have I been chosen?*

We are re-inviting participants who took part in the pilot study to return to complete some breathing tests that will inform some of the results and aid the development of the main study.

## *Do I have to take part?*

It is your decision whether or not you take part. If you agree to participate you will be given this information sheet to keep and once you have had suitable time (at least 24 hours) to consider your involvement and discuss with your family or GP if necessary you will be asked to sign consent form.

standard of care you receive. The data collected to the point of withdrawal may still be used. You may be withdrawn from the study by the researcher, in this instance you will be given a reason and your GP will be informed.

## *What will happen if I take part?*

A member of the medical research team in the Respiratory Biomedical Research Unit at Glenfield Hospital will contact you to explain the purpose of the additional measure and arrange a convenient time and date for you to come to the Respiratory Biomedical Research Unit, at Glenfield Hospital for your breathing tests. You will have a follow up visit after 8 weeks. During the visit(s) you will be expected to complete the below test:

Lung Clearance Index: this test is used to assess the small airways throughout your lungs and assess how air travels through your lungs. This test is performed in a seated position and you will be required to breathe in an inert gas and perform normal breathing through a mouthpiece. This test is easy to perform and is not effortful. We will measure the time it takes for this to be washed out of your lungs. This is a safe procedure used widely across research studies globally. This test will take approximately 20 minutes and will be repeated after adequate rest during the same visit. This test will be performed once more on a different visit, 8 weeks later

## *What are the possible disadvantages and risks?*

There are minimal identified risks to participating in this research. There will be no lasting affects following this testing. You will be required to make two visits to hospital, which may be an inconvenience, however we are happy to reimburse travel expenses or provide a taxi where appropriate.

## *What are the possible benefits of taking part?*

Participants involved in the study will gain a deeper understanding of their lung function and have access to healthcare support. The information we get from this study may help us to reduce breathlessness in patients with COPD in the future.

## *What if something goes wrong?*

If you have a concern about any aspect of this study, you should call the researchers on the direct line that will do their best to answer your questions during office hours, or alternatively leave a message and someone will return your call (01162502758). There are no special compensation arrangements in the unlikely event that you are harmed through taking part in the research project. If you are harmed due to someone's negligence you may have grounds for legal action but may also have to pay costs for such action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study the normal National Health Service complaints mechanisms would be available to you. Advice can be sought from the Patient Information and Liaison Service (PILS). Their contact number is 08081788337 (available Monday to Friday 10-4) and email address pils.complaints@uhl-tr.nhs.uk

## *Will my taking part be kept confidential?*

Procedures for handling, processing, storage and destruction of your data are compliant with the

Data Protection Act 1998. All information which is collected about you during the course of the research will be kept strictly confidential. With your consent we will contact your GP for relevant reports. Only authorised persons will routinely have access to your medical records and personal data. Regulating authorities will have access to data only for the purpose of monitoring the quality of the research and ensuring patient safety. Data will be retained for 5 years within University Hospitals of Leicester NHS Trust, and only non-identifiable data will leave the site and be stored indefinitely by Actegy Ltd., for regulatory purposes. Data will be electronically stored, securely, in an encrypted format. By signing the consent form, you will acknowledge and authorise these procedures.

## *What happens to the results of the study?*

The results of this study will be disseminated in peer and lay journals, professional publications and in presentations at conferences. Results will be reported to respect confidentiality. No identifiable information will be published. All participants will receive a summary of the results and are invited to attend a dissemination discussion in which participants can contribute ideas surrounding the design of the study and results of the study will be shared.

## *Who has reviewed this study?*

All research that involved NHS patients and staff, information from medical records or uses NHS premises must be granted a favourable opinion from the NHS research ethics committee prior to commencement. A favourable opinion does not mean that you will not come into harm during the study, however it means that the committee is satisfied that your rights will be respected and that the risks are reduced to a minimum. This study has been reviewed and given favourable opinion by the National Health Service ethics committee.

## *Who is organising and funding this research?*

This study is sponsored by the University Hospitals of Leicester.

## *Contact details for further information:*

For further information please contact:
Professor Sally Singh
Enya Daynes MSc
Centre of Exercise Rehabilitation Science (CERS), University Hospitals of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP.
Tel: 0116 250 2758
E-mail: enya.daynes@uhl-tr.nhs.uk

Thank you very much for considering taking part in this project.

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road
Leicester
LE3 9QP
Tel: 01162502758
Fax: 0116 258 3950

# PATIENT INFORMATION SHEET

## Training to Improve Dyspnoea (TIDe)

## A Randomised Controlled Trial to Investigate the Use of High Frequency Airway Oscillations as Training to Relieve Dyspnoea in COPD.

Principle Investigator: Professor Sally Singh
Study Lead: Enya Daynes MSc
Contact number: 01162502758
Email: enya.daynes@uhl-tr.nhs.uk

Leicester Biomedical Research Centre

CERS Centre for Exercise and Rehabilitation Science

Supported by NIHR

## *Invitation*

You are being invited to take part in the above research study conducted by the respiratory research team. We are inviting people with COPD who are suffering with breathlessness and who feel limited by this during daily tasks. Before agreeing to the research, please take time to read the following information carefully and discuss it with friends, relatives and your Respiratory Consultant if you wish. Ask a member of the research team if you have any questions or need further information. Take time to decide whether or not you wish to take part. This research will be contributing to an educational qualification. Thank you for reading this information sheet.

## *What is the purpose of this study?*

Patients with Chronic Obstructive Pulmonary Disease (COPD) often experience breathlessness at rest or on exertion. This study will investigate whether airflow oscillation (vibration) can reduce breathlessness and increase exercise capacity in COPD. The airflow oscillation will be delivered using a device. This study has been designed to test whether the use of this device is superior to an alternate device and acceptable for COPD patients who are suffering with breathlessness.

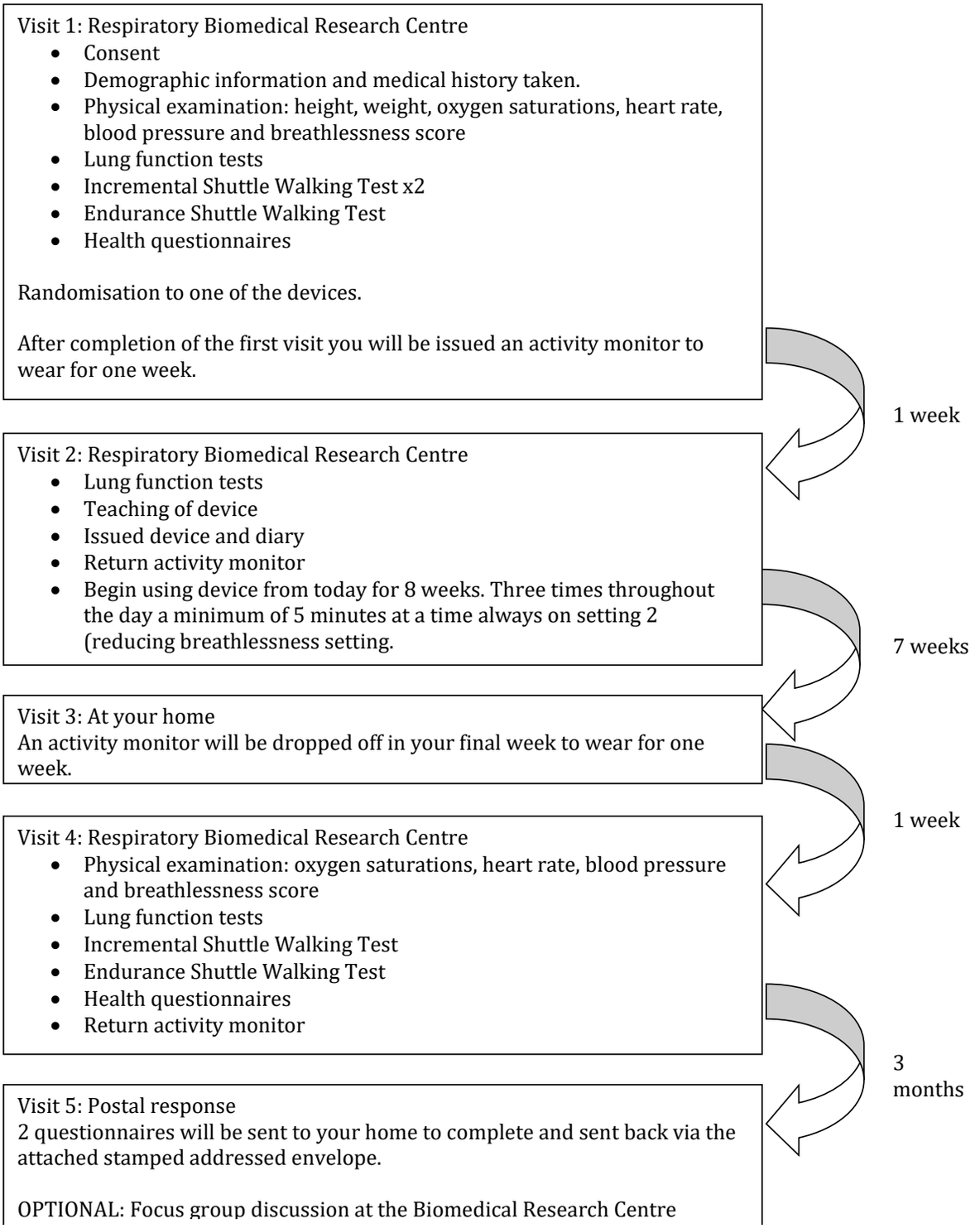
## *Do I have to take part?*

No, it is up to you to decide whether or not to take part. If you decide to take part you will be given this information sheet to keep and asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw, or a decision not to take part, will not affect the standard of care you receive. The data collected to the point of withdrawal may still be used. If you are currently undergoing exercise based research then you may need to wait until you have completed this study before we can continue.

Whilst we appreciate our volunteers, you may not be able to take part if you meet the following criteria: has significant disease other than COPD causing breathlessness, have uncontrolled bleed pressure or cardiovascular disease, have current or recent rib fractures or pneumothorax, are pregnant, have been coughing up blood or have participated in pulmonary rehabilitation in the last 6 months. The researcher will discuss this with you prior to enrolment to check eligibility. However if any of these change throughout the trial you must alert your researcher immediately.

## *What will happen if I take part?*

A member of the research team in the Respiratory Biomedical Research Unit at Glenfield Hospital will contact you to explain the study, answer any questions that you may have and ask whether or not you would like to take part. A convenient appointment at the Respiratory Biomedical Research Centre, at Glenfield Hospital for your initial visit, will be arranged. Below is an explanation of what will happen on your visits throughout the duration of the trial.


Visit 1: Respiratory Biomedical Research Centre
• Consent
• Demographic information and medical history taken.
• Physical examination: height, weight, oxygen saturations, heart rate, blood pressure and breathlessness score
• Lung function tests
• Incremental Shuttle Walking Test x2
• Endurance Shuttle Walking Test
• Health questionnaires
Randomisation to one of the devices.
After completion of the first visit you will be issued an activity monitor to wear for one week.
1 week
Visit 2: Respiratory Biomedical Research Centre
• Lung function tests
• Teaching of device
• Issued device and diary
• Return activity monitor
• Begin using device from today for 8 weeks. Three times throughout the day a minimum of 5 minutes at a time always on setting 2 (reducing breathlessness setting.
7 weeks
Visit 3: At your home
An activity monitor will be dropped off in your final week to wear for one week.
1 week
Visit 4: Respiratory Biomedical Research Centre
• Physical examination: oxygen saturations, heart rate, blood pressure and breathlessness score
• Lung function tests
• Incremental Shuttle Walking Test
• Endurance Shuttle Walking Test
• Health questionnaires
• Return activity monitor
3 months
Visit 5: Postal response
2 questionnaires will be sent to your home to complete and sent back via the attached stamped addressed envelope.
OPTIONAL: Focus group discussion at the Biomedical Research Centre

**Lung function:** You will be required to perform breathing tests to assess your lung capacity and respiratory muscle strength.

**Exercise capacity:** There are two different tests that need to be completed to gage your exercise tolerance. These are called the Incremental Shuttle Walking Test and the Endurance Shuttle Walking Test. This will involve walking between two cones, 10 meters apart at a set pace (recorded as bleeps on CD) until you feel you need to stop. These may take up to 20 minutes each dependent on your walking ability. One of these tests (the Incremental Shuttle Walking Test, is performed twice on your first visit and once on your second visit to account for learning of the test). Your breathlessness score will be taken before and after performing the tests and your heart rate and oxygen saturations will be monitored throughout. If you require oxygen then you will be required to use this at your prescribed rate. You will rest for 20 minutes between each exercise test.

**Questionnaires:** You will be asked to complete some questionnaires regarding your quality of life, anxiety and depression, and symptoms related to your COPD.

**Randomisation:** Once you have completed these tests you will be randomly allocated to one of the two device groups. The allocation of participants to the groups is in a 1:1 ratio and is done using an automated system. You will then be taught how to use the device.

**Activity monitor:** You will be asked to wear a physical activity monitor for one week at the start and one week at the end of the trial. This will explore how much you do day-to-day and will not interfere with your normal daily tasks.

**The Device:** You will be asked to use a device for 8 weeks three times throughout the day for a minimum of 5 minutes at a time. This device is a High Frequency Airway Oscillating device (HFAO) which provides a resistance to your breathing and vibrates the air as you breathe. This was developed by Actegy LTD. You may also be randomised to a mock device but you or your healthcare professional will not know which group you are in until after the trial period. These devices will look and feel the same and will give us an idea as to whether the working device provides therapeutic benefit over the mock device. You will be required to fill in the diary after every use. You may receive messages weekly to remind you to use the device and to provide a contact if you need to report any issues. You may keep the device after the study however this will no longer be maintained by the study team.

## *What are the possible disadvantages and risks?*

There are minimal identified risks to participating in this research. The exercise tests are designed to measure your endurance and you may experience some breathlessness during and after for a small amount of time. There will be no lasting affects following this testing. You will be required to make three visits to hospital, which may be an inconvenience, however we are happy to reimburse travel expenses or provide a taxi where appropriate.

## *What are the possible benefits of taking part?*

Participants involved in the study will be provided with the device and manual, this will be yours to keep after the study has ended. If you are randomised to the alternative device group you will receive the original device on completion of the study. As this study is exploring the benefits of this device, we do not yet know if this is effective and therefore we cannot guarantee any direct benefits to you. The information we get from this study may help us to reduce breathlessness in patients with COPD in the future.

## *What if something goes wrong?*

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions (**01162502758**). There are no special compensation arrangements in the unlikely event that you are harmed through taking part in the research project. If you are harmed due to someone's negligence you may have grounds for legal action but may also have to pay costs for such action. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been treated during the course of this study the normal National Health Service complaints mechanisms would be available to you. Advice can be sought from the Patient Information and Liaison Service (PILS). Their contact number is **08081788337** and email address pils.complaints@uhl-tr.nhs.uk

## *Will my taking part be kept confidential?*

All information which is collected about you during the course of the research will be kept strictly confidential. With your consent we will contact your GP for relevant reports. Only authorised members of the research team will routinely have access to your medical records and personal data. Contact details will be stored for the duration of the study to manage appointments and share the study results with you. By signing the consent form, you will acknowledge and authorise these procedures.

## *What if I withdraw from the study?*

If you withdraw from the study, any data already collected may be retained in non-identifiable form and used in the research. In the unlikely event that you become unable to make decisions for yourself whilst taking part in the research ("loss of capacity"), the research team will retain data collected and continue to use it confidentially in connection with the purposes for which you gave consent. You may be withdrawn from the study by the researcher, in this instance you will be given a reason and your GP will be informed.

## *What happens to the results of the study?*

Procedures for handling, processing, storage and destruction of your data are compliant with the Data Protection Act 2018. Regulating authorities will have access to anonymous data only for the purpose of monitoring the quality of the research and ensuring patient safety. Anonymous data will be retained for 5 years within University Hospitals of Leicester NHS Trust, and indefinitely by the funding company, for regulatory purposes. Any information about you which leaves the hospital will have your name, date of birth and address removed so that you cannot be recognised from it. Data will be electronically stored, securely, in an encrypted format.

The results of this study will be disseminated in peer and lay journals, professional publications and in presentations at conferences. Results will be reported to respect confidentiality. No identifiable information will be published. All participants will receive a summary of the results and are invited to attend a dissemination discussion in which participants can contribute ideas surrounding the design of the study and results of the study will be shared. This will occur at UHL at the end of the study in 2019. Notes will be taken at this event but the discussion will not be shared, this is primarily an opportunity to understand the study results. You are entitled to see any results or information about you under the Freedom of Information Act 2000.

## *Who has reviewed this study?*

All research that involves NHS patients and staff, information from medical records or uses NHS premises must be granted a favourable opinion from the NHS research ethics committee prior to commencement. A favourable opinion does not mean that you will not come into harm during the study, however it does mean that the committee is satisfied that your rights will be respected and that the risks are reduced to a minimum. This study has been reviewed and given favourable opinion by the Leicester South Research Ethics Committee.

## *Who is organising and funding this research?*

This study is sponsored by the University Hospitals of Leicester. This study is being funded by Actegy Ltd. who makes the original device.

## *Contact details for further information:*

For further information please contact:
Professor Sally Singh or Enya Daynes MSC MCSP
Centre of Exercise Rehabilitation Science (CERS), University Hospitals of Leicester, Glenfield Hospital, Groby Road, Leicester, LE3 9QP.
Tel: 0116 250 2758
E-mail: enya.daynes@uhl-tr.nhs.uk

Thank you very much for considering taking part in this project.

# Appendix 5

# Informed Consent Form for feasibility study and TIDe

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road

Leicester
LE3 9QP

Tel: 01162502758
Fax: 0116 258 3950

Patient Identification Number:

# PATIENT CONSENT FORM

**An eight week pilot study to investigate the effect of high-frequency airway oscillation on breathlessness in patients with chronic obstructive pulmonary disease**

Principal Investigator: Professor Sally Singh

*Patient to initial*

1. I confirm that I have read and understand the patient information sheet sub study dated 05-01-2017 version 1 for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected and that all data collected up until withdrawal will be retained. ☐

3. I understand that relevant sections of my medical notes and/or study data may be looked at by individuals from the study team, the sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I give permission for these individuals to access my records. ☐

4. I agree for my GP to be informed of my participation in this study. ☐

5. I agree to undergo baseline assessments and tests as described in the participant information sheet. The natures of these tests and investigations, along with any associated risks have been explained. ☐

6. I understand that the study researchers will contact me by telephone or post to remind me to complete questionnaires and ask me questions over the phone. ☐

7. I understand that I will be ask to visit the hospital 8 weeks after I enter the study for a follow up appointment. ☐

8. I would like to be considered to be invited to attend the dissemination event after the project is complete. Yes ☐ No ☐



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

| _____ | _____ | _____ |
|---|---|---|
| **Name of Patient** | **Date** | **Signature** |
| _____ | _____ | _____ |
| Researcher | Date | Signature |

1 for patient; 1 for researcher; 1 to be kept with hospital notes

University Hospitals of Leicester NHS
NHS Trust

Glenfield Hospital
Groby Road

Leicester
LE3 9QP
Tel: 01162502758
Fax: 0116 258 3950

Patient Identification Number:

# PATIENT CONSENT FORM

**A Randomised Controlled Trial to Investigate the Use of High Frequency Airway Oscillations as Training to Relieve Dyspnoea in COPD.**

Principal Investigator: Professor Sally Singh

*Patient to initial*

1. I confirm that I have read and understand the patient information sheet dated **23/11/2017 version 4** for the above study and have had the opportunity to ask questions. ☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected and that all data collected up until withdrawal will be retained. ☐
3. I understand that relevant sections of my medical notes and/or study data may be looked at by individuals from the study team, the sponsor, NHS Trust or from regulatory authorities where it is relevant to my taking part in the research. I understand that anonymised data will be shared with the funder. I give permission for these individuals to access my records. ☐
4. I agree for my GP to be informed of my participation in this study. ☐
5. I agree to undergo baseline assessments and tests as described in the participant information sheet. The natures of these tests and investigations, along with any associated risks have been explained. ☐
6. I understand that the study researchers will contact me by telephone, text message or post to remind me to use the device or complete questionnaires and ask me questions over the phone. ☐
7. I understand that I will be ask to visit the hospital 8 weeks after I enter the study for a follow up appointment. ☐
8. I would like to be considered to be invited to attend a focus group. Yes ☐ No ☐
9. I agree to take part in the above study. ☐

| _____ | _____ | _____ |
|---|---|---|
| **Name of Patient** | **Date** | **Signature** |
| _____ | _____ | _____ |
| Researcher | Date | Signature |

1 for patient; 1 for researcher; 1 to be kept with hospital notes

# Appendix 6

# Daily diary for TIDe

Patient Id:

# Eight Week Patient Diary

## Clinical study

Training to Improve Dyspnoea (TIDe)

## Summary

We would like you to use the Aerosure device 3 times a day for a minimum of 5 minutes, 7 days a week, for 8 weeks. You can do this at any time during the day that suits you. If you are unable to achieve 5 minutes at a time you can split this up further into manageable time slots. Please record duration that you used the device and number of breaths.

An explanation comes in every device box about the correct way to use the device, and this should have been demonstrated to you when you signed up for the trial.

Please use the scale on the next page to rate how difficult you found using the device. Write a number out of ten in the box after each exercise session. For example 0 would be like sitting in a chair and 10 would be how you feel after a very difficult activity.

If you have any concerns please contact Enya Daynes.
Tel: 01162502758
Email: enya.daynes@uhl-tr.nhs.uk

## Usage scale rating

| | |
|---|---|
| 0 | Nothing at all |
| 0.5 | Just noticeable |
| 1 | Very light |
| 2 | Light |
| 3 | Moderate |
| 4 | Somewhat difficult |
| 5 | Difficult |
| 6 | |
| 7 | Very difficult |
| 8 | |
| 9 | |
| 10 | Extremely difficult |

## Next Appointment

Please return the diary to us at your follow-up appointment:

Date: D D M M Y Y At: : am/pm

| | Date | Duration | Level of exertion | Notes |
|---|---|---|---|---|
| | Example 01/01/2017 | 5 mins | Score | Anything additional you wish to note, for example use of Mucus Relief mode, how you felt after use etc. |
| | | 5 mins | Score | |
| | | 5 mins | Score | |

| | | | | |
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## Contact Details

Respiratory BRU, Glenfield Hospital.
Enya Daynes
Tel: 01162502758
Email: enya.daynes@uhl-tr.nhs.uk

# Appendix 7

# Text message reminder

Dear <<name>>

This is a reminder to continue with the use of your device. You should be using this three times per day and recording in your paper diary. If you have been unable to do this or need to discuss this further, please contact Enya Daynes <<telephone number>>

# Appendix 8

# Three months follow up survey-TIDe

## A Randomised Controlled Trial to Investigate the Use of High Frequency Airway Oscillation as Training to Relieve Dyspnoea in COPD.

## Follow up questionnaire

1. Are you currently using the device issued by the research team?

☐ Yes ☐ No

*If no skip to question 3*

2. How often are you using the device issued by the research team?

☐ A few times per week ☐ Daily ☐ 2-3 times per day ☐ Other (please state):……

3. Do you find the device useful?

☐ Yes ☐ No

Explain:……
……
……

4. Any other comments:

……
……
……
……

**Thank you for completing this questionnaire. Please remember to complete the COPD Assessment Test and send in the attached stamped addressed envelope.**

# Appendix 9

# Evidence of service and calibration of INNOCOR

innovision

Leicester University
Clinical Sciences Building
Glenfield Hospital
Groby Road
GB- LE3 9QP Leicester
United Kingdom

# Order Confirmation

| | |
|---|---|
| Order No. | SO-3543 |
| External Document No. | |
| Salesperson | Jette Kurup |
| Date | 24-08-18 |
| Shipment Date | 18-07-18 |
| Prices incl. VAT | No |
| Currency Code | GBP |
| Page 1 | |

Customer No. 25278
VAT Registration No. GB-916583894

| Part No. | Description | QTY | Unit | Unit Price | Disc. % | Line Amount Excl. VAT |
|---|---|---|---|---|---|---|
| | enya.daynes@uhl-tr.nhs.uk | | | | | |
| CAL00002 | FACTORY CALIBRATION INNOCOR (SN: 1005250)<br>Calibration of gas analyser in Denmark<br>Change of Nafion tube, inlet filter and fan filter<br>Zero-point and gain calibration of all gases<br>Calibration of air and bolus filling flows<br>Flowmeter calibration (incl. linearisation table)<br>Zero calibration of cylinder pressure sensor<br>- Performance test<br>- Multi-point calibration of photoacoustic gas analyser (if needed)<br>- Calibration of SpO2<br>- Calibration of optional NIBP<br>[The calibration timer is reset] | 1 | pcs. | 935,00 | | 935,00 |
| HDD00101 | Harddisk 32GB SSD - Cactus | 1 | pcs. | 887,50 | | 887,50 |
| ADM1 | Administration fee | 1 | pcs. | 40,00 | | 40,00 |
| | Shipment and insurance from DK to GB | 1 | pcs. | 61,00 | | 61,00 |
| | Reverse Charge<br>The order is without VAT | | | | | |
| | | | **Total GBP** | | | **1.923,50** |

| | |
|---|---|
| **Payment terms** | 30 days net |
| **Shipment method** | DAP (to be invoiced) |
| **Warranty** | 12 months on parts and workmanship excluding consumable items. |
| **Terms of delivery** | Please read carefully the standard conditions of sale attached. |

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